

Report on the Deliberation Results

September 16, 2008
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Glaspia Tablets 200 mg
[Non-proprietary name]	Pirfenidone (JAN)*
[Applicant]	Shionogi & Co., Ltd.
[Date of application]	March 12, 2007

[Results of deliberation]

In the meeting held on August 29, 2008, the First Committee on New Drugs concluded that the product may be approved and decided to place the results of the deliberation before the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council. In addition, the following conclusions were reached: the product is not classified as a biological product or a specified biological product; re-examination period is 10 years; and both the drug substance and the drug product are classified as a powerful drug.

Furthermore, the brand name was changed from “Glaspia Tablets 200 mg” to “Pirespa Tablets 200 mg” in the interests of preventing medical accidents.

**Japanese Accepted Name (modified INN)*

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

Review Report (2)

September 8, 2008
Pharmaceuticals and Medical Devices Agency

[Brand name]	Pirespa Tablets 200 mg
[Non-proprietary name]	Pirfenidone
[Name of applicant]	Shionogi & Co., Ltd.
[Date of application]	March 12, 2007

[Results of Review]

The Pharmaceuticals and Medical Devices Agency (PMDA) asked the applicant to give appropriate consideration to the brand name “Glaspia Tablets 200 mg” in order to eliminate the risk of the product being mistaken for other pharmaceutical products with similar names. Subsequently, the applicant notified its intention to change the brand name to “Pirespa Tablets 200 mg.” PMDA found no particular concerns regarding this proposal.

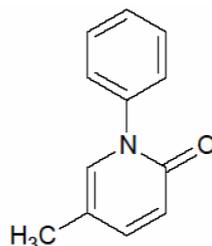
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Review Report

August 20, 2008
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	Glaspia Tablets 200 mg
[Non-proprietary name]	Pirfenidone
[Name of applicant]	Shionogi & Co., Ltd.
[Date of application]	March 12, 2007
[Dosage form/Strength]	Tablets containing 200 mg of Pirfenidone in one tablet
[Application classification]	Prescription drug (1) Drug with a new active ingredient
[Chemical structure]	



Molecular formula: C₁₂H₁₁NO
Molecular weight: 185.22
Chemical name:
5-Methyl-1-phenyl-1-*H*-pyridin-2-one

[Items warranting special mention]	Orphan drug
[Reviewing office]	Office of New Drug IV

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Review Results

August 20, 2008

[Brand name] Glaspia Tablets 200 mg
[Non-proprietary name] Pirfenidone
[Name of applicant] Shionogi & Co., Ltd.
[Date of application] March 12, 2007
[Results of review]

The Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the data and information submitted demonstrate the efficacy and safety of the product for use in the treatment of idiopathic pulmonary fibrosis.

PMDA has concluded that an acceptable level of clinical efficacy of this product has been demonstrated in the data from the Phase III studies, etc. With respect to safety, because a high incidence of photosensitivity has been observed, and which implies that Pirfenidone has a photocarcinogenic potential, the risks and benefits of treatment with this product should be adequately explained to, and fully understood by, the patient before starting the treatment. Moreover, because adverse drug reactions including gastrointestinal disorders and abnormal values for liver function tests have also been observed, the clinical course of the patient should be carefully monitored after the start of the Pirfenidone treatment. The occurrences of photosensitivity, skin cancer, etc. should be investigated further in the post-marketing surveillance.

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

[Indications]
Idiopathic pulmonary fibrosis

[Dosage and administration]
The usual initial dosage for an adult is an oral dose of 200 mg of Pirfenidone administered three times daily (600 mg/day) after a meal, which is increased in increments of 200 mg up to 600 mg (1800 mg/day) while observing the patient's condition. The dose may be increased or decreased according to the symptoms observed.

Review Report (1)

July 4, 2008

I. Product Submitted for Registration

[Brand name] Glaspia Tablets 200 mg
[Non-proprietary name] Pirfenidone
[Name of applicant] Shionogi & Co., Ltd.
[Date of application] March 12, 2007
[Dosage form/Strength] Tablets containing 200 mg of Pirfenidone in one tablet
[Proposed indications] Idiopathic pulmonary fibrosis
[Proposed dosage and administration]

The usual initial dosage for an adult is an oral dose of 200 mg of Pirfenidone administered three times daily (600 mg/day) after a meal. The dose is increased in increments of 200 mg up to 600 mg (1800 mg/day) while observing the patient's condition. The dose may be increased or decreased accordingly depending on the patient's age and the symptoms observed.

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

The data and information submitted by the applicant for the approval review of the product, as well as the responses to the inquiries made by the Pharmaceuticals and Medical Devices Agency (PMDA), are summarized below.

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

The active ingredient of Glaspia is Pirfenidone. Pirfenidone is a low molecular weight compound, which was first discovered by [REDACTED] (the US). In the early phase of product development, Pirfenidone was developed as an anti-inflammatory agent; however, after the anti-fibrotic effect of the drug was found in non-clinical studies, Pirfenidone has been developed as an antifibrotic drug.

In Japan, Pirfenidone was licensed to Shionogi & Co., Ltd., the applicant, and the clinical development of Pirfenidone began in Japan in 19[REDACTED] with an intended indication for treatment of "chronic idiopathic interstitial pneumonia," based on the efficacy of Pirfenidone reported in a pharmacological study in models of pulmonary fibrosis (Iyer SN, et al. *J Lab Clin Med.* 1995;125:779-85), and the efficacy of Pirfenidone suggested in patients with idiopathic pulmonary fibrosis in an open-label clinical study conducted in the US (5.3.5-06). The application for manufacturing approval of the drug product was filed in [REDACTED] 20[REDACTED], based on the data from a placebo-controlled Japanese Phase II study. However, substantive issues including a deficiency in the evidence supporting the efficacy of Pirfenidone, were identified during the approval review and; as a result, the application for manufacturing approval was withdrawn in [REDACTED] 20[REDACTED]. Subsequently, additional studies including a Japanese Phase III study were conducted, and because new evidence was obtained to support the efficacy and safety of Pirfenidone in patients with idiopathic pulmonary fibrosis¹, another application for marketing approval of this product was filed.

¹ As the "Clinical Diagnostic Criteria for Idiopathic Interstitial Pneumonia (fourth edition, 2001)" was established by the MHLW research group for diffuse lung diseases, and in which idiopathic interstitial pneumonia is classified into the categories of idiopathic pulmonary fibrosis, acute interstitial pneumonia, and other unexplained interstitial pneumonias, the name of the proposed indication was changed from "chronic idiopathic interstitial pneumonia" to "idiopathic pulmonary fibrosis."

Pirfenidone is not approved in other countries, but as of [REDACTED] 20[REDACTED], a clinical study involving patients with idiopathic pulmonary fibrosis is currently being conducted by [REDACTED] in the US and the EU.

Idiopathic pulmonary fibrosis (IPF) is an intractable disease with poor prognosis, which leads to a clinical course of chronic and progressive nature, and results in the formation of dense fibrosis that eventually develops into the irreversible formation of honeycomb lung (The median survival is said to be 2.5 to 5 years; Bjoraker JA, et al. *Am J Respir Crit Care Med.* 1998;157:199-203, Nagai S, et al. *Sarcoidosis Vasc Diffuse Lung Dis.* 1999;16:209-214, etc.). There are a limited number of effective treatments available for IPF. In Japan, the estimated number of patients with IPF is approximately 14 000 (Kondo A, et al. FY1992 Research Report—the MHW research group for the specified diseases: diffuse lung diseases. 1993;11-18, etc.). Thus, this product received orphan drug designation in September 1998 (Designation number [10-Drug-A] No.113 [September 4, 1998]).

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

Pirfenidone (drug substance) is registered in the Drug Master File (DMF) under No. 220MF10130 by Signa S. A. de. C.V. (Mexico). The summary of submitted data pertaining to the manufacturing process of the drug substance, etc., and an outline of the review by PMDA are presented in the Appendix.

Pirfenidone is white to slightly yellowish white crystalline powder. The following physicochemical properties were investigated: physical description, solubility, hygroscopicity, thermal analysis, melting point, pH, dissociation constant, partition coefficient, optical rotation, isomerism, and crystalline polymorphism. Crystalline polymorphism of Pirfenidone was not detected, and there are no optical or geometrical isomers of Pirfenidone.

The chemical structure of Pirfenidone was determined by elementary analysis, ultraviolet (UV) spectrum, infrared (IR) spectrum, nuclear magnetic resonance spectrum (¹H-NMR, ¹³C-NMR), mass spectrum, and crystal x-ray diffraction. Related substances, residual solvents, and inorganic compounds were investigated as impurities.

The drug substance specifications are set for physical description, identification (UV-VIS spectrum, IR spectrum), water content, purity (heavy metals, [REDACTED], related substances [HPLC]), residue on ignition, and assay (HPLC). Initially, the set limits for each related substance was not more than [REDACTED]%, and the set acceptance criteria for the total amount of all related substances was not more than [REDACTED]%; however, these acceptance criteria were changed during the approval review process [see “Outline of the Review by PMDA”].

With respect to the stability of the drug substance, the long-term testing (25°C, 60% RH, shielded from light, [REDACTED] months), another long-term testing ([REDACTED]°C, [REDACTED], shielded from light, [REDACTED] months), and the accelerated testing (40°C, 75% RH, shielded from light, 6 months) were conducted using 3 batches of drug substance that were manufactured at a commercial scale, packaged in double polyethylene bags, and placed in a fiber drum. In these tests, the physical description, identification (IR), purity (related substances), water content ([REDACTED]°C [REDACTED]), and content of Pirfenidone² were determined. Furthermore, the physical

² These attributes were evaluated based on the specifications for release testing that have been set by the DMF holder.

description, identification, related substances, water content, and content of Pirfenidone³ were investigated in the following stress tests: heated (■°C, ■■■■■, shielded from light, ■■■■■, ■ months); humidified (■°C, ■% RH, shielded from light, ■■■■■, ■ months); exposure to light (25°C, petri dish covered with plastic wrap, 1.2 million lx·hr and 200 W·hr/m²); and ■■■■■ (■°C, ■% RH, ■■■■■, ■■■■ lx·hr and ■ W·hr/m²). Because no marked changes in the quality of the drug substance were observed for any of the attributes tested in these stability tests, the re-test period for the drug substance was determined to be ■ years when stored at room temperature in the packaging conditions described above.

2.A.(2) Drug Product

The drug product is a film-coated tablet comprising the drug substance, vehicle, disintegrant, binder, lubricant, colorant, and coating agent. The proposed drug product contains 200 mg of Pirfenidone. The excipients used in the tablets are listed either in the Japanese Pharmacopoeia (JP) or in the Japanese Pharmaceutical Excipients (JPE), and none of the excipients used are new. Although the formulation of the pharmaceutical product used in the Phase I single dose study differs from that of the proposed drug product, the bioequivalence of these two products has been demonstrated through a dissolution test conducted in accordance with the “Guideline for bioequivalence studies for formulation changes of oral solid dosage forms” (PMSB/ELD Notification No.67, dated February 14, 2000) and “Partial revision to the guidelines for bioequivalence of generic drugs” (PMSB/ELD Notification No.786, dated May 31, 2001).

The manufacturing process consists of the first step (■■■■■), the second step (■■■■■), the third step (■■■■■), the fourth step (packaging and labeling), and the fifth step (testing and storage). The ■■■■ step is regarded as the critical step, for which process control items and control values are predetermined.

The specifications for the drug product are set for physical description (appearance), identification (TLC), mass variation test, dissolution test, and assay (HPLC). Initially, a purity test (related substances) was considered; however, because neither an increase in the amount of related substances nor any generation of new degradation products was observed during manufacturing, a purity test was excluded from the specifications. Moreover, based on the content of active ingredient and the mass ratio of the product, the mass variation test is used for uniformity of dosage units.

Regarding the stability of the drug product, the long-term testing (25°C, 60% RH, shielded from light, 36 months) and the accelerated testing (40°C, 75% RH, shielded from light, 6 months) were conducted using the pilot scale batches that were packaged in either a PTP sheet or a polyethylene bottle. Furthermore, the stress testing (exposure to light [25°C, petri dish, 1.2 million lx·hr and 200 W·hr/m²]) was conducted. In these tests, the physical description, identification (TLC), mass variation, related substances, dissolution test, ■■■■■, and contents were investigated. No marked changes on the quality of the drug product were observed in any of the attributes tested in these stability tests, and thus, the stability of the drug product stored for 36 months was confirmed.

2.B Outline of the review by PMDA

2.B.(1) Drug substance

PMDA asked the applicant to reconsider the set acceptance criteria for related substances of the drug substance that read as follows “the set limits for each related substance are not more than

³ These attributes were evaluated based on the specifications for acceptance testing that have been set by the applicant.

█%" because the proposed limits, based on the maximum clinical dose of Pirfenidone (1800 mg/day), are higher than the identification threshold (1.0 mg/day) and qualification threshold (1.0 mg/day) that are given in the "Impurities in New Drug Substances" (PFSB/ELD Notification No.1216001, dated December 16, 2002).

The applicant responded that the company would change the acceptance criteria for related substances of the drug substance to "the limits for each related substance are not more than █%."

With regard to the fact that the specifications proposed by the applicant differ in part from the specifications registered in the Drug Master File, PMDA asked the applicant to provide the rationale for the difference and explain its validity.

The applicant explained as follows:

The specifications for release testing conducted by the drug substance manufacturer are set for physical description, identification, water content, the residue on ignition, analysis for heavy metals, related substances (HPLC), content of Pirfenidone (HPLC), and loss on drying. The set limits for related substances were no more than █% for related substance A, no more than █% for related substance B, no more than █% for related substance C, no more than █% for related substance D, and no more than █% for the most abundant species of unidentified related substances (The acceptance criteria for the release testing of the related substances A, B, D, and the most abundant species of unidentified related substances were changed from "no more than █%" during the abovementioned review period), and no more than █% for the total amount of all related substances. There are differences in the specifications between the release testing and the acceptance testing proposed by the applicant, as presented in the table below, and the differences arise from the following facts:

- a. the applicant and the drug substance manufacturer possess different analytical equipment and use a different pharmacopeia as their reference. Consequently, they use a different set of testing methods (specifications) that are easily manageable with the equipment they possess and the pharmacopeia they use as a reference;
- b. that because the related substance contents observed in actual measurements of the acceptance criteria items, and in the long-term testing, accelerated testing, and stress testing were less than █% and because █, separate acceptance criteria for individual related substances were not set;
- c. and that although loss on drying was included in the specification for the release testing in order to control █, it is considered unnecessary to include loss on drying in the specification for the acceptance testing because the results of the batch analysis showed █. The specifications for the acceptance testing were appropriately validated, and the differences in the testing methods between the acceptance testing and the release testing do not influence the quality control of the drug substance.

Table. Differences from the DMF in specifications for the drug substance

Test item	Release testing for drug substance	Acceptance testing before the product manufacturing process
Identification (1)	The United States Pharmacopeia is used as a reference for the general test procedures	The Japanese Pharmacopoeia is used as a reference for the general test procedures
Identification (2)	The United States Pharmacopeia is used as a reference for the general test procedures	The Japanese Pharmacopoeia is used as a reference for the general test procedures
Related substances	The related substance content is determined using previously identified related substances as a reference standard and compared with the acceptance criteria for individual related substances	The acceptance criteria are not predetermined for individual related substances. In addition, HPLC is performed under different conditions.
Water content	Volumetric titration	Coulometric titration
Content of Pirfenidone		HPLC is performed under different conditions.
Loss on drying	Specified.	Not specified

2.B.(2) Drug product

PMDA asked the applicant to explain what investigations were carried out with regard to the stability of the drug product under high temperature and high humidity conditions.

The applicant explained as follows:

Stability tests were performed under conditions of high heat (■■■■, ■°C■■■■, ■ months) and high humidity (■■■■, ■°C■■%RH, ■ months); but no changes were observed in physical description, dissolution rates, and the content of Pirfenidone nor was any increase observed in the content of related substances. The product quality can be thus guaranteed if the drug product is distributed in Japan.

PMDA accepted the above-stated responses, and concluded that the proposed specifications, storage conditions, and re-test period for the drug substance, and the proposed specifications, storage conditions, and expiration period for the drug product are appropriate.

3. Non-clinical data

3.(i) Summary of pharmacology studies

The efficacy of Pirfenidone was investigated in a bleomycin (BLM)-induced pulmonary fibrosis model and in an endotoxin shock model as the primary pharmacodynamic studies. In addition, *in vitro* studies of the effects of Pirfenidone on fibroblast proliferation, collagen production, TGF-β [■] production, and TNF-α were conducted. As the secondary pharmacodynamic studies, the inhibitory effects of Pirfenidone on humoral immunity, and cellular immunity were investigated. As the safety pharmacology studies, the effect of Pirfenidone on the central nervous system, cardiovascular system, respiratory system, and gastrointestinal system was investigated in accordance with the guidelines for general pharmacology studies and safety pharmacology studies for human pharmaceuticals. Pharmacological drug interaction studies have not been conducted.

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

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

3.(i).A.(1).1 The effect of Pirfenidone in a BLM-induced pulmonary fibrosis model

a. Prophylactic administration (4.2.1.1-01)

The effect of Pirfenidone was assessed using the following procedures. Pulmonary fibrosis was induced in ICR mice by intravenously administering BLM for 5 days. Pirfenidone was orally administered to the mice three times daily at doses of 3.3, 10, or 33.3 mg/kg (10, 30, or 100 mg/kg/day) for 6 weeks. Administration of BLM and the Pirfenidone treatment started on the same day. The administration of Pirfenidone inhibited both the BLM-induced increases in the wet and dry weights of the left lung and the increase in the hydroxyproline content of the lung tissue (an index for the amount of collagenous fibers), in a dose-dependent manner. The ED₅₀ value for inhibition of the increase in hydroxyproline content was 24.6 mg/kg/day.

Histopathological examination of the right lung of BLM-treated control mice showed the thickening of the basal regions near the blood vessels and the bronchi and diffuse fibrotic lesions occurring mostly along with the outer edges of the lung, typical of BLM-induced fibrosis. These changes in the lung tissue were dose-dependently inhibited by Pirfenidone treatment. The fibrosis score was 1.2 in normal mice. The fibrosis score increased to 5.0 in the BLM-treated control group (the 0.5% CMC group). Fibrosis scores of 5.2, 4.4, and 3.4 were observed in the 10, 30 and 100 mg/kg/day Pirfenidone-treated groups, respectively. The percentage of fibrotic area in the lung measured under a light microscope was 18.7% in normal mice; whereas in the BLM-treated control group (the 0.5% CMC group), the percentage increased to 27.7%. The percentages of fibrotic area in the Pirfenidone treated groups were 25.0%, 22.5%, and 21.1% in the 10, 30, and 100 mg/kg/day Pirfenidone-treated groups, respectively.

With regard to the changes in the plasma concentration of the unchanged drug following the administration of the last dose of Pirfenidone, the C_{max} values were 3.93 and 9.48 µg/mL, and AUC_{0-6hr} values were 2.50 and 5.82 µg·hr/mL in the 30 and 100 mg/kg/day Pirfenidone-treated groups, respectively. In all dose groups, the trough plasma concentrations were below the quantification limits (0.1 µg/mL).

Based on the data presented above, the applicant explained that the anti-fibrotic effect of Pirfenidone is attainable within a clinical dose range, because the C_{max} value was approximately 10 µg/mL (5.3.3-08) when a dose of 1800 mg/day, which is the maximum daily dose in clinical settings, was administered repeatedly to healthy Japanese adult men.

b. Therapeutic administration (4.2.1.1-02)

The effect of Pirfenidone was assessed using the following procedures. Pulmonary fibrosis was induced in ICR mice by intravenously administering BLM for 5 days. Pirfenidone treatment began two weeks after the start of the BLM treatment. Pirfenidone was orally administered to the mice three times daily at doses of 3.3, 10, or 33.3 mg/kg (10, 30, or 100 mg/kg/day) for 4 weeks. In the BLM-treated control group an increase in the wet weight, dry weight, and hydroxyproline content of the left lung tissue was observed two weeks after the start of BLM treatment, and a further increase was observed at the sixth week. These increases were dose-dependently inhibited by the Pirfenidone treatment. The ED₅₀ value for inhibition of the increase in hydroxyproline content of the lung tissue was 58.3 mg/kg/day. In the 100 mg/kg/day Pirfenidone group, the hydroxyproline content of the lung tissue stayed at approximately the same level after the Pirfenidone treatment started. Thus, the applicant interpreted this observation as a suggestion that Pirfenidone does not have a therapeutic effect on already formed fibrotic lesions, but can inhibit the progression of fibrosis during the time Pirfenidone is

administered.

Histopathological examination of the right lung of BLM-treated control mice showed a fibrotic thickening of the basal regions near the blood vessels and the bronchi, and typical diffuse fibrotic lesions occurring mostly along the outer edges of the lung. These changes in the lung tissue were dose-dependently inhibited by Pirfenidone treatment. The fibrosis score was 1.6 in normal mice. The fibrosis score increased to 6.2 in the BLM-treated control group (the 0.5% CMC group). The fibrosis scores for the Pirfenidone treatment groups were 5.8, 5.5, and 5.1 in the 10, 30 and 100 mg/kg/day Pirfenidone-treated groups, respectively. The percentage of fibrotic area in the lung measured under a light microscope was 24.5% in normal mice, whereas in the BLM-treated control group (the 0.5% CMC group), the percentage increased to 33.5%. The percentages of fibrotic area for the 10, 30, and 100 mg/kg/day Pirfenidone-treated groups were 30.1%, 27.1%, and 25.1%, respectively.

With regard to the changes in the plasma concentration of the unchanged drug following the administration of the last dose of Pirfenidone, the C_{max} values were 3.65 and 8.97 $\mu\text{g/mL}$, and AUC_{0-6hr} values were 2.53 and 4.83 $\mu\text{g}\cdot\text{hr/mL}$ in the 30 and 100 mg/kg/day Pirfenidone-treated groups, respectively. In all dose groups, the trough plasma concentrations were below the quantification limits (0.1 $\mu\text{g/mL}$).

c. Comparison of effects with steroids (4.2.1.1-03)

The effects of Pirfenidone and Prednisolone were compared using the following procedures. Pulmonary fibrosis was induced in ICR mice by intravenously administering BLM for 5 days. Pirfenidone was orally administered three times daily at a dose of 33.3 mg/kg (100 mg/kg/day) for 6 weeks. Prednisolone was orally administered once daily at a dose of 3 or 15 mg/kg for 6 weeks. Administration of BLM and the treatments with Pirfenidone or Prednisolone started on the same day. The BLM-induced increases in the wet and dry weights of the left lung, and the increase in the hydroxyproline content of the lung tissue were inhibited by the Pirfenidone treatment, whereas no such inhibition was observed with either of the Prednisolone doses.

With regard to the histopathological examination of the right lung, the fibrosis score was 2.5 in normal mice. The fibrosis score increased to 5.6 in the BLM-treated control group (the 0.5% CMC group). The fibrosis scores for the 100 mg/kg/day Pirfenidone-treated group was 4.2; whereas the fibrosis scores in the 3 and 15 mg/kg/day Prednisolone-treated groups were 5.4 and 5.3, respectively. The percentage of fibrotic area in the lung measured under a light microscope was 19.2% in normal mice; whereas in the BLM-treated control group (the 0.5% CMC group), the percentage increased to 27.7%. The percentage of fibrotic area in the 100 mg/kg/day Pirfenidone-treated group was 21.5%. The percentages in the 3 and 15 mg/kg/day Prednisolone-treated groups were 25.2 and 23.4%, respectively.

d. Effect on the changes in the concentration of cytokines in the lung (4.2.1.1-04)

The effect of Pirfenidone on the changes in the concentrations of IL-1 β , IL-4, IL-6, IL-12p70, IFN- γ , MCP-1, TNF- α , SDF-1 α , IL-12p40, IL-18, TGF- β 1, and b-FGF in the left lung was assessed using the following procedures. Pulmonary fibrosis was induced in ICR mice by intravenously administering BLM for 5 days. Pirfenidone was orally administered three times daily at a dose of 10 or 33.3 mg/kg (30 or 100 mg/kg/day) for 4 weeks. Prednisolone was orally administered once daily at a dose of 15 mg/kg for 4 weeks. Administration of BLM and treatment with Pirfenidone or Prednisolone started on the same day. BLM induced inflammatory edema in the right lung, which peaked at the tenth day (Day 10) after the BLM administration, and an increase in the hydroxyproline content of the lung tissue, which peaked at the 28th day (Day 28). The Pirfenidone treatment inhibited the inflammatory edema and the increase in the hydroxyproline content of the lung tissue. Prednisolone treatment inhibited only the

inflammatory edema. In this experimental model, the increase in the concentration of inflammatory cytokines IL-1 β and IL-6 peaked at the fourth day (Day 4) after the start of BLM administration, and the increase in the concentration of the chemokine MCP-1 peaked at the tenth day (Day 10), and both increases were inhibited by Pirfenidone and Prednisolone. Although no BLM-induced changes in the concentration of TNF- α were observed in this experimental model, TNF- α production was inhibited by both Pirfenidone and Prednisolone. In this experimental model, the increase in the concentration of b-FGF, which is thought to be involved in fibrosis formation, peaked at the tenth day (Day 10) after the start of BLM administration, and the increase in the concentration of TGF- β 1 peaked at the 28th day (Day 28). An increase in the concentration of IL-12p40 and a decrease in the concentration of IFN- γ were observed at the tenth day (Day 10) and 28th day (Day 28). Pirfenidone inhibited the changes in the concentration of b-FGF, TGF- β 1, IL-12p40, and IFN- γ in a dose-dependent manner. On the contrary, Prednisolone inhibited only the increase in the concentration of IL-12p40. Compared with the control group of normal mice, an increase in the concentration of IL-12p70 was observed at the fourth day in BLM-treated mice, but neither Pirfenidone nor Prednisolone treatment showed any effect on the increase. In addition, there was an increase in the concentrations of IL-18 and SDF-1 α which peaked at the tenth day. This increase was inhibited by Pirfenidone, but only in the 100 mg/kg/day dose group. No BLM-induced changes in the concentration of IL-4 were observed in this experimental model, and neither Pirfenidone nor Prednisolone treatment had any effect on IL-4 concentration. Based on the data presented above, the applicant speculated that both Pirfenidone and Prednisolone inhibit the production of inflammatory cytokines and chemokines, which in turn inhibits inflammatory edema; and, because only Pirfenidone can inhibit the increases in the concentration of b-FGF and TGF- β 1 as well as the decrease in the concentration of IFN- γ , only Pirfenidone can exert an inhibitory effect against the increase in the hydroxyproline content of the lung tissue.

3.(i).A.(1).2 Effect on endotoxin shock model

a. Effect on mortality rate (4.2.1.1-05)

The effect of Pirfenidone on mortality rates was assessed using the following procedures. Acute inflammation was induced in C57BL/6 mice by intraperitoneally administering E. coli LPS and D-galactosamine (D-gal). Pirfenidone was orally administered 15 minutes before the LPS/D-gal administration, at doses of 100, 300, or 500 mg/kg. The mortality rate 72 hours post-administration was 100% in the control group (treated with 0.5% CMC); whereas in the Pirfenidone-treated groups, the mortality rate decreased in a dose-dependent manner. All mice survived in the 500 mg/kg dose group, and half of the mice survived in the 100 mg/kg dose group. Moreover, when a 500 mg/kg dose of Pirfenidone was orally administered 1, 2, 3, 4, or 5 hour(s) after the LPS/D-gal administration, the mortality rate decreased as the interval between the LPS/D-gal administration and Pirfenidone administration became shorter. Half of the mice treated with Pirfenidone within 4 hours were alive 120 hours after the LPS/D-gal administration.

b. Effect on liver injury (4.2.1.1-06)

The effect of Pirfenidone on liver injury was assessed using the following procedures. Acute inflammation was induced in C57BL/6 mice by intraperitoneally administering LPS/D-gal. A 500 mg/kg dose of Pirfenidone was orally administered 5 minutes before or 4 hours after the LPS/D-gal administration. The livers were removed 6 hours after the LPS/D-gal administration. In the control group (treated with 0.5% CMC), the removed livers showed DNA ladder formation indicative of hepatocyte apoptosis, hemorrhagic necrosis of the tissue, and apoptosis-positive cells. In both Pirfenidone-treated groups, the removed livers were nearly normal.

c. Effect on cytokine production (4.2.1.1-06)

The effect of Pirfenidone on the changes in the serum concentration of TNF- α , IL-12, IFN- γ and

IL-10 was assessed using the following procedures. Acute inflammation was induced in C57BL/6 mice by intraperitoneally administering LPS/D-gal. A 500 mg/kg dose of Pirfenidone was orally administered 5 minutes before the LPS/D-gal administration. In the control group (treated with 0.5% CMC), an increase was observed in the concentrations of TNF- α , IL-12, and IFN- γ , which peaked at 1.25, 3, and 4.5 hours after the LPS/D-gal administration, respectively. In the Pirfenidone-treated groups, these increases in the cytokine concentrations were inhibited. With regard to IL-10, the control group (treated with 0.5% CMC) showed a biphasic production of IL-10 with concentration peaks at 1.25 and 4.5 hours after the LPS/D-gal administration. In the Pirfenidone-treated groups, a greater increase in the IL-10 production was observed with a concentration peak at 3 hours after the LPS/D-gal administration.

d. Dose-dependence of the drug effect on cytokine production (4.2.1.1-05, 4.2.1.1-06)

The effect of Pirfenidone on the serum concentration of cytokines was assessed using the following procedures. Acute inflammation was induced in C57BL/6 mice by intraperitoneally administering LPS/D-gal. Pirfenidone was orally administered 5 minutes before the LPS/D-gal administration at doses of 30, 100, 300, or 500 mg/kg. Pirfenidone dose-dependently inhibited the increase in the concentration of TNF- α at 1.25 hours after the LPS/D-gal administration, and the increases in the concentration of IL-12 and IFN- γ at 5 hours after the LPS/D-gal administration. The minimum effective dose was 30-100 mg/kg. Moreover, Pirfenidone dose-dependently enhanced the increase in the concentration of IL-10 at 3 hours after the LPS/D-gal administration.

e. Effect on TGF- β 1 production in the liver tissue (4.2.1.1-07)

The effect of Pirfenidone on TGF- β 1 production in liver tissue at 6 hours after the LPS/D-gal administration was assessed using the following procedures. Acute inflammation was induced in C57BL/6 mice by intraperitoneally administering LPS/D-gal. A 500 mg/kg dose of Pirfenidone was orally administered 5 minutes before or 4 hours after the LPS/D-gal administration. An increase in the liver tissue concentration of TGF- β 1 was observed in the control group (treated with 0.5% CMC). The administration of Pirfenidone 5 minutes before the LPS/D-gal administration resulted in an 82.5% inhibition of the increase in the tissue concentration of TGF- β 1; while, the administration of Pirfenidone 4 hours after the LPS/D-gal administration resulted in an 81.5% inhibition of the increase.

f. Effect of the drug and drug metabolites on TNF- α production (4.2.1.1-08)

The inhibitory effect of Pirfenidone on the increase in the TNF- α production at 1.25 hours after the LPS/D-gal administration was compared with that of 5-hydroxymethyl and 5-carboxylic acid metabolites of Pirfenidone using the following procedures. Acute inflammation was induced in C57BL/6 mice by intraperitoneally administering LPS/D-gal. Pirfenidone, or its 5-hydroxymethyl or 5-carboxylic acid metabolites were orally administered 10 minutes before the LPS/D-gal administration, at doses of 100, 300, or 500 mg/kg. Pirfenidone and its 5-hydroxymethyl metabolite showed a dose-dependent inhibitory effect, and the estimated ED₅₀ values were 148 mg/kg and 281 mg/kg, respectively. On the other hand, the 5-carboxylic acid metabolite did not show any inhibitory effect.

3.(i).A.(1).3 *In vitro* effect

a. Effect on proliferation of human fibroblasts (4.2.1.1-09)

The effect of Pirfenidone on the proliferation of human lung fibroblasts, WI-38, was investigated using [³H] thymidine incorporation as a marker of cell proliferation. Addition of 1 to 300 μ g/mL Pirfenidone resulted in concentration-dependent inhibition of the proliferation of WI-38 cells. The IC₅₀ value was 230 μ g/mL, and the minimum effective dose was 10 μ g/mL. No cytotoxic effect was observed in doses up to 300 μ g/mL.

b. Effect on collagen production in human fibroblasts (4.2.1.1-10)

Collagen production was induced by adding TGF- β 1 to human lung fibroblasts, WI-38. The effect of Pirfenidone on collagen synthesis was investigated using [3 H] proline incorporation as a marker of collagen production. Addition of 1 to 300 μ g/mL Pirfenidone resulted in concentration-dependent inhibition of collagen production. The IC₅₀ value was 110 μ g/mL, and the minimum effective dose was 30 μ g/mL.

c. Effect on TGF- β 1 production in human monocytic cells (4.2.1.1-11)

Production of TGF- β 1 was induced by adding LPS to human monocytic THP-1 cells, and the effect of Pirfenidone on the TGF- β 1 production was investigated. Addition of 0.1 to 300 μ g/mL Pirfenidone resulted in concentration-dependent inhibition of TGF- β 1 production. The IC₅₀ value was 44.3 μ g/mL, and the minimum effective dose was 6 μ g/mL.

d. Effect on TNF- α production in human monocytic cells (4.2.1.1-12)

Production of TNF- α was induced by adding LPS to human monocytic THP-1 cells, and the effect of Pirfenidone on the TNF- α production was investigated. Addition of 0.1 to 300 μ g/mL Pirfenidone resulted in concentration-dependent inhibition of TNF- α production. The IC₅₀ value was 30.7 μ g/mL, and the minimum effective dose was 6 μ g/mL.

e. Effect of the drug and drug metabolites on TNF- α production in human monocytic cells (4.2.1.1-13)

Production of TNF- α was induced by adding LPS to human monocytic THP-1 cells, and the effect of Pirfenidone and its 5-hydroxymethyl and 5-carboxylic acid metabolites on the TNF- α production was investigated. Addition of 10 to 300 μ g/mL Pirfenidone as well as addition of 10 to 300 μ g/mL of the 5-hydroxymethyl metabolite of Pirfenidone resulted in concentration-dependent inhibition of TNF- α production. The IC₅₀ values for Pirfenidone and its 5-hydroxymethyl metabolite were 48.3 μ g/mL and 108.6 μ g/mL, respectively. With regard to the 5-carboxylic acid metabolite of Pirfenidone, only the addition of 300 μ g/mL showed a tendency of inhibition.

3.(i).A.(2) Secondary pharmacodynamics

3.(i).A.(2).1 Effect on humoral immunity (4.2.1.2-01)

Sheep red blood cells (SRBC) were intravenously administered to C3H mice to induce anti-SRBC antibody-producing cells in the spleen, and the effect of Pirfenidone and cyclosporine on the anti-SRBC antibody-producing spleen cells was determined by enumerating plaque-forming cells. Pirfenidone was orally administered at a dose of 250 mg/kg twice daily (500 mg/kg/day) for 4 days, and cyclosporine was orally administered at a dose of 100 mg/kg once daily for 4 days. The administration of cyclosporine resulted in an 82% inhibition in the number of plaque-forming cells, whereas the administration of Pirfenidone resulted in an 11% inhibition in the number of plaque-forming cells. The increase in serum antibody titer was checked using an agglutination method. The results showed that whereas cyclosporine inhibited the increase in anti-SRBC antibody titer to normal (baseline) levels, the Pirfenidone treatment had no inhibitory effect on anti-SRBC antibody production.

3.(i).A.(2).2 Effect on cellular immunity (4.2.1.2-01)

BDF1 mice were sensitized by subcutaneously injecting methylated bovine serum albumin (mBSA), and the effect of Pirfenidone and cyclosporine against the DTH reaction induced by the mBSA injection into the foot pad was investigated by measuring the foot pad thickness. Pirfenidone was orally administered at a dose of 250 mg/kg twice daily (500 mg/kg/day) for 10 days. Cyclosporine was orally administered at a dose of 100 mg/kg once daily for 10 days. The

administration of cyclosporine resulted in a 92% inhibition of foot pad swelling at the time point 24 hours after mBSA injection, whereas the administration of Pirfenidone resulted in a 19% inhibition of foot pad swelling at the same time point.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effect on central nervous system

a. Effect on general symptoms and behaviors in mice (4.2.1.3-01)

The effect of Pirfenidone on general symptoms and behaviors following a single dose of Pirfenidone administered orally at 30, 100, or 300 mg/kg was investigated. In the 30 mg/kg group, sedation and ptosis were observed in 1 of 4 mice. In the 100 mg/kg group, sedation was observed in all mice; in addition, abnormal body position, ptosis, and hypothermia were observed. In the 300 mg/kg group, in addition to the symptoms found in the 100 mg/kg dosed group, abnormal positioning of the limbs and a staggering gait were observed. These symptoms disappeared 2 hours after the Pirfenidone administration. No effect was observed on the number of fecal pellets, urine volume, body weight, or food consumption at all doses tested (from 30 mg/kg to 300 mg/kg).

b. Effect on general symptoms and behaviors in dogs (4.2.1.3-02)

The effect of Pirfenidone on general symptoms and behaviors in dogs was investigated. Three escalating single doses of Pirfenidone, 30 mg/kg, 100 mg/kg, and 300 mg/kg, were orally administered successively at 7-day intervals. Vomiting was seen in 1 of 4 dogs after the administration of the 100 mg/kg dose, and in all dogs after the administration of the 300 mg/kg dose. Increased ambulation was noted in all dogs after the administration of 100 and 300 mg/kg doses. Moreover, increased water-drinking behavior was noted in 3 of 4 dogs after the administration of the 100 mg/kg dose, and in all dogs after the administration of the 300 mg/kg dose.

c. Study on the onset mechanism of vomiting in dogs (4.2.1.3-03)

In order to investigate the mechanism of Pirfenidone in causing vomiting, dogs were treated with either a serotonin 5-HT₃ receptor antagonist (azasetron hydrochloride) or a dopamine D₂ receptor antagonist (metoclopramide hydrochloride) before receiving a 200 mg dose of Pirfenidone. The number of vomiting episodes and latency to vomiting were measured. However, neither the serotonin 5-HT₃ receptor antagonist nor the dopamine D₂ receptor antagonist showed any antiemetic effect.

d. Effect on locomotor activity in mice (4.2.1.3-01)

The effect of Pirfenidone on locomotor activity following the oral administration of single doses of 30, 100, or 300 mg/kg was investigated. The total locomotor activity over a 30-minute period after the administration of a 100 or 300 mg/kg dose of Pirfenidone decreased to 33.7% and 28.4%, respectively, of those of the control group (treated with 0.5% CMC).

e. Effect on pentobarbital anesthesia in mice (4.2.1.3-01)

The effect of Pirfenidone on the duration of deep anesthesia induced by intravenous administration of pentobarbital was assessed. Pirfenidone was administered orally at a dose of 30, 100, or 300 mg/kg. The administration of Pirfenidone dose-dependently increased the duration of deep anesthesia induced by pentobarbital. The duration of deep anesthesia was 36.5 minutes in the control group (treated with 0.5% CMC), whereas in the group given the 300 mg/kg dose of Pirfenidone, the duration of deep anesthesia was increased to 55.1 minutes.

f. Effect on electrically induced convulsion in mice (4.2.1.3-01)

The effect of Pirfenidone on the threshold current needed to cause tonic extensor convulsions

(convulsive threshold current) was assessed. Pirfenidone was administered orally at a dose of 30, 100, or 300 mg/kg. Pirfenidone dose-dependently increased the convulsive threshold current. The threshold current was 12.3 mA in the control group (treated with 0.5% CMC), whereas in the 300 mg/kg Pirfenidone group, the threshold current was increased to 19.3 mA.

g. Effect on pentylenetetrazol (PTZ)-induced convulsion in mice (4.2.1.3-01)

The effect of Pirfenidone on the threshold dose of PTZ needed to cause clonic convulsions (convulsive threshold dose) was assessed. Pirfenidone was administered orally at a dose of 30, 100, or 300 mg/kg while PTZ was administered by continuous intravenous infusion. Pirfenidone dose-dependently increased the convulsive threshold dose. The threshold dose was 40.1 mg/kg in the control group (treated with 0.5% CMC), whereas in the 300 mg/kg Pirfenidone group, the threshold dose was increased to 56.5 mg/kg.

h. Effect on acetic acid-induced writhing (pain response) in mice (4.2.1.3-01)

The effect of Pirfenidone on the number of writhing movements induced by intraperitoneal administration of acetic acid was investigated. Pirfenidone was administered orally at a dose of 30, 100, or 300 mg/kg. Pirfenidone dose-dependently decreased acetic acid-induced writhing. The number of writhing movements was 19 in the control group (treated with 0.5% CMC), whereas in the 300 mg/kg Pirfenidone group, the number of writhing movements decreased to 3.

i. Effect on body temperature in mice (4.2.1.3-01)

The effect of Pirfenidone on rectal temperature was investigated. Pirfenidone was administered orally at a dose of 30, 100, or 300 mg/kg. Compared with the control group (treated with 0.5% CMC), the rectal temperature was decreased by 1.6°C in the 100 mg/kg Pirfenidone group 15 to 30 minutes after Pirfenidone was administered, and by 1.3°C to 3.3°C in the 300 mg/kg Pirfenidone group 15 to 60 minutes after the administration.

j. Effect on extracellular dopamine concentration in the rat hypothalamus (4.2.1.3-04)

Since it was suspected that the central dopamine-mediated inhibition of prolactin secretion was involved in the onset mechanism for the uterine adenoma and uterine cancer observed in rats in a carcinogenicity study, the effect of Pirfenidone on the extracellular dopamine concentration in the hypothalamus was investigated using a microdialysis technique. Pirfenidone was administered orally at a dose of 30, 100, or 300 mg/kg. No Pirfenidone-related changes were observed in the 30 mg/kg dose group. However, in the 100 and 300 mg/kg dose groups, an increase in the dopamine concentration was observed 20 to 80 minutes and 20 to 120 minutes, respectively, after the administration. In the 100 and 300 mg/kg dose groups, the maximum percentage increase from the pre-dose concentration reached 270% and 1203%, respectively.

k. Effect on extracellular dopamine concentration in the rat striatum (4.2.1.3-05)

In order to confirm the site-specificity of Pirfenidone in increasing the extracellular concentration of dopamine, the effect of Pirfenidone on the extracellular dopamine concentration in the rat striatum was investigated using a microdialysis technique. Pirfenidone was administered orally at a dose of 30, 100, or 300 mg/kg. The results showed an approximately 8% decrease in the 300 mg/kg dose group; however, no other effect was noted.

3.(i).A.(3).2) Effect on cardiovascular system

a. Effect on blood pressure, heart rate, blood flow, and ECG in anesthetized rats (4.2.1.3-01)

The effect of Pirfenidone on blood pressure, heart rate, abdominal aortic blood flow, and ECG was investigated. Pirfenidone was intraduodenally administered at a dose of 10, 30, 100, and 300 mg/kg. In the 10 mg/kg dose group, no effect of Pirfenidone was observed on any of the above parameters; however, at dose rates of 30 mg/kg and above, a decreased blood pressure and an increased abdominal aortic blood flow were observed. In addition, an increased heart rate was observed in the 100 and 300 mg/kg dose groups. With regard to the ECG, isolated ventricular extrasystoles were observed in 2 of 6 rats in the control group (treated with 0.5% CMC); whereas in the 10, 30, 100, and 300 mg/kg Pirfenidone groups, isolated ventricular extrasystoles were observed in 3 of 6, 3 of 6, 4 of 6, and 5 of 6 rats, respectively. Moreover, in the 300 mg/kg Pirfenidone group, consecutive ventricular extrasystoles were observed in 2 rats, and a flattening of the T wave was observed in 1 rat.

b. Effect on blood pressure, heart rate, and ECG in unanesthetized rats (4.2.1.3-06)

The effect of Pirfenidone on blood pressure, heart rate, and ECG was investigated in unanesthetized rats. Pirfenidone was intraduodenally administered at a dose of 30, 100, or 300 mg/kg. In the 30 mg/kg dose group, blood pressure and heart rate did not show any Pirfenidone-related changes; however, increased heart rate was observed in the 100 and 300 mg/kg dose groups, and decreased blood pressure was observed in the 300 mg/kg dose group. With regard to the ECG, isolated ventricular extrasystoles were observed in 2 of 6 rats in the control group (treated with 0.5% CMC), whereas in the 30, 100, and 300 mg/kg Pirfenidone groups, isolated ventricular extrasystoles were observed in 2 of 6, 6 of 6, and 6 of 6 rats, respectively. Moreover, in the 300 mg/kg Pirfenidone group, ventricular couplets/triplets were observed in 2 rats. In the 100 and 300 mg/kg Pirfenidone groups, atrioventricular block was observed in 1 of 6 and 2 of 6 rats, respectively.

c. Effect on blood pressure, heart rate, and ECG in unanesthetized dogs (4.2.1.3-02)

Three escalating single doses of Pirfenidone 30 mg/kg, 100 mg/kg, and 300 mg/kg were orally administered successively at 7-day intervals, and the effect of Pirfenidone on blood pressure, heart rate, and the ECG was assessed using telemetry and a Holter ECG system. Pirfenidone did not show any effect on blood pressure at any of the doses tested; however, increased heart rate was observed in the 100 mg/kg and 300 mg/kg dose groups at 1 hour after the administration and at 1 to 4 hours after the administration, respectively. In the ECGs, QTc prolongation (7.6% at 2 hours after administration) was observed in the 100 mg/kg dose group, and shortened QTc was observed in the 300 mg/kg dose group. Moreover, 1 dog in the 100 mg/kg dose group and all dogs in the 300 mg/kg dose group experienced transient bradycardia accompanied by baseline drift on the ECG; this appeared to be associated with vomiting.

d. Effect on blood pressure, heart rate, and ECG in anesthetized dogs (4.2.1.3-07)

The effect on the ECGs observed in the unanesthetized dogs was investigated further using the following procedures. Dogs were anesthetized using inhaled isoflurane, and the effect of 30, 100, and 300 mg/kg doses of intraduodenally administered Pirfenidone on blood pressure, heart rate, and the ECG was assessed. In addition, the plasma concentration of Pirfenidone was measured. The administration of 100 and 300 mg/kg doses resulted in decreased blood pressure (the maximum percentage reductions in mean blood pressure were 37.7% and 70.1%, respectively) and increased heart rate (the maximum percentage increases were 23.5% and 27.0%, respectively). The ECGs were not influenced by the administration of Pirfenidone at any of the doses tested. The plasma concentration of unchanged drug increased in a dose-dependent manner, and the C_{max} and $AUC_{0-240min}$ values obtained with the 30, 100, and 300 mg/kg doses of

Pirfenidone were 39.89, 100.90, and 207.99 $\mu\text{g/mL}$ for C_{max} , and 5077, 18307, and 43648 $\mu\text{g}\cdot\text{min/mL}$ for $\text{AUC}_{0-240\text{min}}$, respectively.

e. Effect on action potential in the isolated guinea pig papillary muscle (4.2.1.3-08, 4.2.1.3-09, 4.2.1.3-10)

The effects of 1 to 1000 $\mu\text{mol/L}$ of Pirfenidone and 10 to 1000 $\mu\text{mol/L}$ of the 5-carboxylic acid metabolite of Pirfenidone on the action potential durations, APD_{50} and APD_{90} , and resting membrane potential, amplitude, and the maximum upstroke velocity were assessed while electrically stimulating the isolated guinea pig papillary muscle. Pirfenidone showed a tendency to shorten the APD_{50} at a concentration of 1000 $\mu\text{mol/L}$; however, no other parameters (including APD_{90}) were influenced by Pirfenidone. The 5-carboxylic acid metabolite did not influence the action potential parameters at any of the concentrations tested.

f. Effect on ionic currents in hERG channel-endowed cells (4.2.1.3-11, 4.2.1.3-12)

The effect of 10 to 1000 $\mu\text{mol/L}$ of Pirfenidone and 10 to 1000 $\mu\text{mol/L}$ of the 5-carboxylic acid metabolite of Pirfenidone on the hERG current was investigated. At concentrations of 100 $\mu\text{mol/L}$ or below, Pirfenidone did not influence the hERG currents; however, at a concentration of 1000 $\mu\text{mol/L}$ (185.2 $\mu\text{g/mL}$), a 20% and 26% inhibition of the peak of the tail current was observed at 20 mV and 60 mV, respectively. The 5-carboxylic acid metabolite did not influence the hERG currents at any of the concentrations tested.

3.(i).A.(3).3 Effect on the respiratory system

a. Effect on respiratory rate and respiratory volume in anesthetized rats (4.2.1.3-01)

The effect of Pirfenidone administered intraduodenally at doses of 10, 30, 100, or 300 mg/kg on respiratory rate per minute and respiratory minute volume was investigated. Compared with the control group (treated with 0.5% CMC), the respiratory rate decreased in the 100 mg/kg dose group, whereas, there was no difference in the respiratory rate between the control group and the 300 mg/kg dose group. Moreover, compared with the control group (treated with 0.5% CMC), the respiratory minute volume increased in the Pirfenidone groups treated with doses of 30 mg/kg or greater.

b. Effect on respiratory rate and blood gas parameters in unanesthetized dogs (4.2.1.3-02)

Three escalating single doses of Pirfenidone, 30 mg/kg, 100 mg/kg, and 300 mg/kg, were orally administered successively at 7-day intervals, and the effect of Pirfenidone on respiratory rate per minute, arterial blood pH, arterial oxygen partial pressure, arterial carbon dioxide partial pressure, and hemoglobin oxygen saturation was investigated. Compared with the vehicle control (0.5% CMC), an increase in the arterial oxygen partial pressure was observed after the 100 mg/kg of Pirfenidone was administered; in addition, increased respiratory rate and increased arterial blood pH were observed after the administration of the 300 mg/kg of Pirfenidone. Hemoglobin oxygen saturation was not influenced by Pirfenidone at any of the doses tested.

3.(i).A.(3).4 Effect on the gastrointestinal system

a. Effect on spontaneous motility of the isolated rabbit ileum (4.2.1.3-13)

Pirfenidone was added to the isolated rabbit ileum at concentrations of 1 to 100 $\mu\text{mol/L}$, and the effect of Pirfenidone on muscle tone and the frequency and amplitude of contractions during spontaneous motility was assessed. Pirfenidone did not influence the frequency and amplitude of contractions in spontaneous motility at any of the concentrations tested; however, addition of 100 $\mu\text{mol/L}$ (18.5 $\mu\text{g/mL}$) of Pirfenidone resulted in an 11.8% decrease in muscle tone.

b. Effect on gastric emptying and small intestinal transport in rats (4.2.1.3-13)

The effect of 3 oral doses of Pirfenidone, 30, 100, and 300 mg/kg, on gastric emptying and small intestinal transport was assessed based on the amount of dye remaining in the stomach and the distance traveled by the dye in the isolated small intestine after the dye was orally administered to rats. Pirfenidone dose-dependently inhibited gastric emptying. The gastric emptying rate was 84.8% in the control group (treated with 0.5% CMC), whereas in the 30, 100, and 300 mg/kg Pirfenidone groups, the gastric emptying rates were 49.9%, 22.3%, and 18.6%, respectively. Pirfenidone inhibited small intestinal transport at doses of 100 mg/kg and 300 mg/kg. The rate of small intestinal transport was 68.7% in the control group (treated with 0.5% CMC), whereas in the 100 and 300 mg/kg Pirfenidone groups, the rates of small intestinal transport were 36.8% and 34.2%, respectively.

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

PMDA asked the applicant to explain their opinion on the action mechanism of Pirfenidone because the effective concentration observed in the *in vitro* study, in which the action mechanism of Pirfenidone was investigated, was incompatibly higher than both the effective blood concentration observed in the BLM-induced pulmonary fibrosis models and the C_{max} (approximately 10 $\mu\text{g/mL}$) obtained after repeated administration of Pirfenidone at 1800 mg/day (the maximum daily dose for humans in clinical settings).

The applicant explained as follows:

At this point, it is not clear what molecules are directly targeted by Pirfenidone, because, although, there is a published report (other than the study data submitted) that Pirfenidone inhibits ICAM-1 expression and cell-cell adhesion mediated by ICAM-1 in IL-1-stimulated cultured human synovial fibroblasts at the minimum effective doses of 1.85 $\mu\text{g/mL}$ and 18.5 ng/mL, respectively (Kaneko M, et al. *Clin Exp Immunol.* 1998; 113: 72-76), the preliminary study showed that Pirfenidone has no inhibitory effect on ICAM-1 expression in the IL-1 β -stimulated human lung fibroblast line (CCL134) derived from patients with pulmonary fibrosis. Furthermore, although other effects of Pirfenidone, specifically, an antioxidative effect (Misra HP, et al. *Mol Cell Biochem.* 2000; 204:119-126), an inhibitory effect on Map Kinase p38 γ (Ozes ON, et al. *GTCbio's Protein Kinases in Drug Discovery.* May 8-9,2006), and an inhibitory effect on HSP47 expression (Hisatomi K, et al. *J Jpn Respir Soc.* 2006; 44:186), have previously been reported, the IC_{50} value or the minimum effective concentration reported in each of the abovementioned papers was extremely high. Because the study data concerning the effect of Pirfenidone on various cytokines and growth factors, obtained using a mouse model of BLM-induced pulmonary fibrosis (*in vivo* test system), show the parallel existence of the antifibrotic effect and the other effects of Pirfenidone associated with the progression of fibrosis, such as the inhibition of a decrease in IFN- γ concentration, inhibition of b-FGF production, and inhibition of TGF- β 1 production, these co-existing effects are considered to be the crucial effects by which Pirfenidone exerts the antifibrotic effect.

With regard to the fact that the effective dose range for Pirfenidone observed in the safety pharmacology studies overlaps the therapeutic dose range that was determined in the primary pharmacodynamic studies, PMDA asked the applicant to explain, in relation to the adverse events that occurred in the clinical studies, what of the pharmacological effects of Pirfenidone, observed in the safety pharmacology studies, may occur at the clinical doses for humans.

The applicant explained as follows:

In the studies of the effect of Pirfenidone on the gastrointestinal system, inhibition of gastric emptying was observed at 30 mg/kg and higher doses in rats, and the C_{max} obtained after

administration of the 30 mg/kg dose was 7.2 µg/mL. This suggests that the inhibitory effect on gastric emptying may occur near the clinically achievable plasma concentration range, and that the inhibitory effect of Pirfenidone on gastric emptying is probably associated with the adverse events of stomach discomfort and anorexia, which were relatively common in the clinical studies of Pirfenidone. Because the administration of the 100 mg/kg dose resulted in the inhibition of small intestinal transport in rats, this effect of Pirfenidone may also be a factor in causing stomach discomfort and anorexia. Moreover, because administration of Pirfenidone at 100 mg/kg increased extracellular dopamine concentrations in rat hypothalamus, it is possible that Pirfenidone causes the release of dopamine, and dopamine in turn stimulates the dopamine receptor in the chemoreceptor trigger zone, which induces vomiting (Mitchelson F. *Drugs*. 1992; 43:295-315); thus, this may be related to the reported adverse events of queasy, nausea, stomach discomfort, and anorexia. Although CNS adverse events, such as somnolence, malaise, and dizziness, were reported in the clinical studies of Pirfenidone, only mild sedation and ptosis were observed in mice after administration of the 30 mg/kg dose; thus, the causal relationships between Pirfenidone and these adverse events are not clear. In addition, although ventricular extrasystoles, decreased blood pressure, and increased blood flow were observed in rats after administration of a 10 or 30 mg/kg dose in the studies of Pirfenidone's effect on the cardiovascular system, no adverse events that are possibly linked to the observed effect of Pirfenidone on the cardiovascular system have been reported in the clinical studies.

PMDA concluded that although the direct mode of action of Pirfenidone is not yet elucidated, the pharmacological effect of Pirfenidone against idiopathic pulmonary fibrosis is explainable based on the data presented above and the information supplied by the applicant, including study results and inquiry responses. Since it was shown that Pirfenidone exerts an effect not only on the gastrointestinal system, but also on the central nervous system and cardiovascular system at doses near the pharmacological dose range in the safety pharmacology studies, and although no adverse events clearly linked to these effects of Pirfenidone have been reported in the clinical studies, PMDA considers that this matter needs to be carefully monitored and investigated in the post-marketing surveillance.

3.(ii) Summary of pharmacokinetic studies

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

The pharmacokinetic data submitted included the data from rats and dogs given oral and intravenous doses of Pirfenidone and the data from mice and guinea pigs given oral administration of Pirfenidone. The concentrations of unchanged Pirfenidone (unchanged drug), pirfenidone-5-carboxylic acid (5-carboxylic acid metabolite), and 5-hydroxymethyl-pirfenidone (5-hydroxymethyl metabolite) in mice, rat, and dog plasma, and in rat and dog urine and bile, as well as the concentration of unchanged drug in mice lung, were measured by HPLC using a validated method. After the sample was subjected to alkaline hydrolysis, the amounts of the glucuronic acid conjugate of the 5-carboxylic acid metabolite in urine and bile were calculated, based on the increase in the amount of the 5-carboxylic acid metabolite. The amount of ¹⁴C-labeled compounds (Pirfenidone and its metabolites) was measured using a liquid scintillation counter. The pharmacokinetic parameters are presented as mean or mean ± standard deviation, unless otherwise specified.

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

3.(ii).A.(1).1 Single-oral and single-intravenous administration

After a single 100 mg/kg dose of ¹⁴C-Pirfenidone was orally administered to male rats (n = 4), plasma Pirfenidone levels reached a peak at 0.17 ± 0.10 hours after the administration (C_{max}; 30.8 ± 9.3 µg/mL) (hereinafter, the radioactivity concentration is converted into and presented as the concentration of Pirfenidone), this was followed by a rapid elimination until 2 hours after

the administration; after which plasma levels plateaued until 8 hours after administration. From 8 hours and onward after the administration, the concentration declined rapidly again, and the $t_{1/2}$ was 4.5 ± 2.2 hours. After a single 100 mg/kg dose of unlabeled Pirfenidone was orally administered to male rats ($n = 4$), the plasma levels of unchanged drug reached the C_{max} ($21.0 \pm 6.6 \mu\text{g/mL}$) at 0.12 ± 0.09 hours after the administration, and the unchanged drug was eliminated with a $t_{1/2}$ of 2.9 ± 0.5 hours. Moreover, when a single 20 mg/kg dose of Pirfenidone was intravenously administered to male rats ($n = 4$), the $t_{1/2}$ for the unchanged drug in plasma was 0.3 ± 0.1 hours. With regard to the difference in the $t_{1/2}$ values between the oral and intravenous administration, the applicant explained that this difference arises from the fact that Pirfenidone is absorbed through a large portion of the gastrointestinal tract, and thus sustained absorption of Pirfenidone continued after the oral administration. The bioavailability (BA) of orally administered Pirfenidone was 77.1%, based on the calculations made using the AUC values obtained for the unchanged drug after the intravenous and oral administration of Pirfenidone (4.2.2.2-01, 02).

After a single 30 mg/kg dose of ^{14}C -Pirfenidone was orally administered to male dogs ($n = 3$), the plasma radioactivity reached C_{max} ($43.4 \pm 3.8 \mu\text{g/mL}$) at 0.5 ± 0.0 hours after the administration, and was then eliminated with a $t_{1/2}$ of 3.8 ± 0.1 hours. After a single 30 mg/kg dose of unlabeled Pirfenidone was orally administered to male dogs, the plasma concentration of the unchanged drug reached C_{max} ($24.3 \pm 8.0 \mu\text{g/mL}$) at 0.7 ± 0.3 hours after the administration, and was then eliminated with a $t_{1/2}$ of 0.9 ± 0.3 hours. Moreover, when a single 20 mg/kg dose of Pirfenidone was intravenously administered to male dogs ($n = 3$), the observed $t_{1/2}$ was 1.2 ± 0.3 hours, which is nearly the same elimination rate as for orally administered Pirfenidone. The BA of orally administered Pirfenidone was 56.3%, based on the calculations made using the AUC values obtained for the unchanged drug after the intravenous and oral administration of Pirfenidone (4.2.2.2-04, 05).

3.(ii).A.(1.2) Repeated oral administration

After a single 100 mg/kg dose of ^{14}C -Pirfenidone was orally administered to male rats ($n = 5$), the observed plasma radioactivity parameters, T_{max} , C_{max} , $t_{1/2}$, and $\text{AUC}_{0-24\text{hr}}$, were 0.15 ± 0.09 hours, $29.95 \pm 5.25 \mu\text{g/mL}$, 3.2 ± 1.1 hours, and $137.9 \pm 22.9 \mu\text{g}\cdot\text{hr/mL}$, respectively; whereas, the values of the same parameters observed after the last dose of 14 days of repeated oral dosing at the same dose were 0.22 ± 0.07 hours, $24.71 \pm 4.07 \mu\text{g/mL}$, 8.6 ± 2.1 hours, and $116.8 \pm 14.7 \mu\text{g}\cdot\text{hr/mL}$, respectively. After a single dose administration, the observed T_{max} , C_{max} , $t_{1/2}$, and $\text{AUC}_{0-24\text{hr}}$ for the plasma concentration of the unchanged drug were 0.08 ± 0.0 hours, $19.9 \pm 5.5 \mu\text{g/mL}$, 3.9 ± 1.4 hours, and $63.8 \pm 22.9 \mu\text{g}\cdot\text{hr/mL}$, respectively; whereas, after the last dose of 14 days of repeated dosing, the observed values for the same parameters were 0.18 ± 0.09 hours, $10.3 \pm 1.0 \mu\text{g/mL}$, 6.1 ± 4.7 hours, $39.5 \pm 6.4 \mu\text{g}\cdot\text{hr/mL}$, respectively. With regard to the reason for the decrease in the plasma concentration of the unchanged drug that was observed after repeated dosing, the applicant explained that it was possible that Pirfenidone metabolism was accelerated with the induction of metabolic enzymes (4.2.2.2-03).

3.(ii).A.(1.3) Dose relationship

After 3 single doses of Pirfenidone, 30, 100, 300 mg/kg, were orally administered to male rats ($n = 4$), the observed C_{max} values for the plasma concentration of the unchanged drug were 7.24 ± 2.31 , 21.0 ± 6.6 , and $56.3 \pm 27.9 \mu\text{g/mL}$, and the AUC values were 8.2 ± 1.2 , 36.0 ± 6.4 , and $121.4 \pm 39.7 \mu\text{g}\cdot\text{hr/mL}$, respectively, showing that the C_{max} and AUC values increased in a manner nearly proportional to the administered doses (4.2.2.2-02).

3.(ii).A.(1.4) Percentage absorption

After a single 100 mg/kg dose of ^{14}C -Pirfenidone was orally administered to bile duct-

cannulated male rats (n = 4), the total percentage of radioactivity excreted in the urine and bile over 48 hours was $91.3 \pm 2.1\%$ of the administered dose. After a single 30 mg/kg dose of ^{14}C -Pirfenidone was intraduodenally administered to bile duct-cannulated male dogs (n = 3), the total percentage of radioactivity excreted in the urine and bile over 48 hours was $95.8 \pm 1.8\%$ of the administered dose. These observations indicate that orally administered Pirfenidone is almost completely absorbed through the gastrointestinal tract (4.2.2.4-02, 4.2.2.4-06).

3.(ii).A.(1).5) Site of absorption

After a 20 mg/kg dose of ^{14}C -Pirfenidone was administered to male rats (n = 3 for each group) under fasting conditions by direct injection into the stomach, duodenum, jejunum, ileum, and the colon, the rate of Pirfenidone absorption in each section of the gastrointestinal tract was analyzed based on the elimination half-life of radioactivity in the each section of the tract. The results showed that Pirfenidone was most quickly absorbed through the duodenum ($t_{1/2} = 2.03$ minutes) and jejunum ($t_{1/2} = 2.28$ minutes), followed by the ileum ($t_{1/2} = 5.97$ minutes) and colon ($t_{1/2} = 6.19$ minutes), whereas the absorption through the stomach ($t_{1/2} = 34.33$ minutes) was slowest (4.2.2.2-06).

3.(ii).A.(1).6) Food effects

After a single 100 mg/kg dose of Pirfenidone was orally administered to fasting male rats (n = 3) or to fed male rats (n = 4), the observed plasma C_{\max} and AUC values for the unchanged drug showed a tendency to be higher in the fasted group (C_{\max} of 35.3 ± 9.0 $\mu\text{g/mL}$, and AUC of 58.5 ± 19.8 $\mu\text{g}\cdot\text{hr/mL}$) than in the fed group (C_{\max} of 21.0 ± 6.6 $\mu\text{g/mL}$, and AUC of 36.0 ± 6.4 $\mu\text{g}\cdot\text{hr/mL}$) (4.2.2.2-02).

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

3.(ii).A.(2).1) Tissue concentration

After a single 100 mg/kg dose of ^{14}C -Pirfenidone was orally administered to male rats (n = 4), the radioactivity levels in most organs and tissues reached maximum concentrations 5 to 30 minutes after the administration. Pirfenidone was then eliminated with a $t_{1/2}$ of 4 to 7 hours; however, the $t_{1/2}$ (approximately 15 hours) observed in the preputial gland was longer than that in any other tissues. Moreover, whole-body autoradiographs (whole-body ARG) obtained using the same dosing conditions showed that the highest radioactivity levels over the entire body were observed 15 to 30 minutes after the administration and, although the radioactivity had decreased in most of the tissues 6 hours after the administration, radioactivity was still detectable in the kidney, nasal cavity, preputial gland, and liver. Twenty-four hours after the administration, the radioactivity had disappeared from most organs and tissues but was still present in the nasal cavity and preputial gland.

Whole-body ARGs taken after 14-day repeated oral administration of ^{14}C -Pirfenidone to male rats at 100 mg/kg/day showed no major difference in the tissue distribution of radioactivity between the single-dose and repeated-dose administration; however, the slow elimination of radioactivity from the nasal cavity and preputial gland observed after the single-dose administration intensified into a stronger tendency for radioactivity to remain in the nasal cavity and preputial gland after the repeated-dose administration (4.2.2.3-01, 4.2.2.3-02, 4.2.2.2-03).

3.(ii).A.(2).2) Distribution into the placenta and fetus

After a single 100 mg/kg dose of ^{14}C -Pirfenidone was orally administered to female rats (n = 4) at 19 days of gestation, the radioactivity concentration in the organs and tissues of the dams reached maximum values 5 to 30 minutes after the administration, and the radioactivity concentration in the entire body of the fetus and its organs and tissues reached maximum values (approximately one-half of the plasma concentration of radioactivity observed in the dam) 30

minutes after the administration. Subsequently, the radioactivity elimination patterns observed in the dam and fetus were nearly the same. The percentage distribution of the drug to each fetus 30 minutes after the administration was approximately 0.1% of the administered dose. Whole-body ARGs obtained using the same dosing conditions showed that the distribution of radioactivity was not specific to particular organs or tissues in the fetus, but was nearly uniform; thus, it is inferred that although Pirfenidone passes through the placenta and into the fetus, Pirfenidone does not accumulate in the fetus (4.2.2.3-03).

3.(ii).A.(2).3 Serum protein binding

The *in vitro* percentage protein binding rates of ¹⁴C-Pirfenidone in serum samples from male mice, male rats, male dogs, and humans (healthy adult men and women) were determined and were, at a serum concentration of 10 µg/mL, 33.0 ± 1.5%, 32.8 ± 2.1%, 52.8 ± 0.4%, and 58.1 ± 4.0%, respectively, but were slightly lower at a serum concentration of 100 µg/mL. The percentage protein binding rates of Pirfenidone to purified human proteins were, at the concentration of 10 µg/mL, 34.8 ± 0.4% for serum albumin, 3.5 ± 1.1% for γ-globulin, and 4.2 ± 1.4% for α₁-acidic glycoprotein, indicating that Pirfenidone binds mainly to albumin in human serum (5.3.2.1-01).

3.(ii).A.(2).4 Percentage distribution in blood cells

The *in vivo* percentage distribution of Pirfenidone in blood cells was determined after a single 100 mg/kg dose of ¹⁴C-Pirfenidone was orally administered to male rats (n = 4), and after a single oral dose of 30 mg/kg or a single intravenous dose of 20 mg/kg was administered to male dogs (n = 3). In rats, the percentage distribution of Pirfenidone in blood cells stayed in the range of 20% to 35% over the 8 hours following the administration, and most of the radioactivity was found in the plasma; however, 12 and 24 hours after the administration, the percentage distribution of Pirfenidone in the blood cells increased (approximately 40% and 87%, respectively). In dogs, the percentage distribution of Pirfenidone in blood cells, for both routes of administration, stayed in the range of 14% to 26% during the first 2 hours after the administration; subsequently, the percentage distribution of Pirfenidone in blood cells became lower still, and most of the radioactivity was found in the plasma (4.2.2.3-01, 4.2.2.2-04).

3.(ii).A.(2).5 Lung concentrations of unchanged drug in the mouse model of BLM-induced pulmonary fibrosis

After a single 10 or 33.3 mg/kg dose of Pirfenidone was orally administered to mice with BLM-induced pulmonary fibrosis (male, n = 4), the observed lung concentrations of the unchanged drug for both dose rates were in the same range as the observed plasma concentration for the unchanged drug; thus, Pirfenidone is considered to have a good distribution into the lung (4.2.2.3-04).

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

3.(ii).A.(3).1) Metabolic pathway

Metabolites of Pirfenidone in plasma, urine, and feces of male rats and male dogs, as well as in the bile of male rats, were studied. As a result, the metabolic pathway for Pirfenidone was assumed to be as shown in the figure on the right: oxidation of the 5-methyl group on the pyridone ring yields the 5-hydroxymethyl metabolite, which is further oxidized to give the 5-carboxylic acid metabolite (4.2.2.4-01).

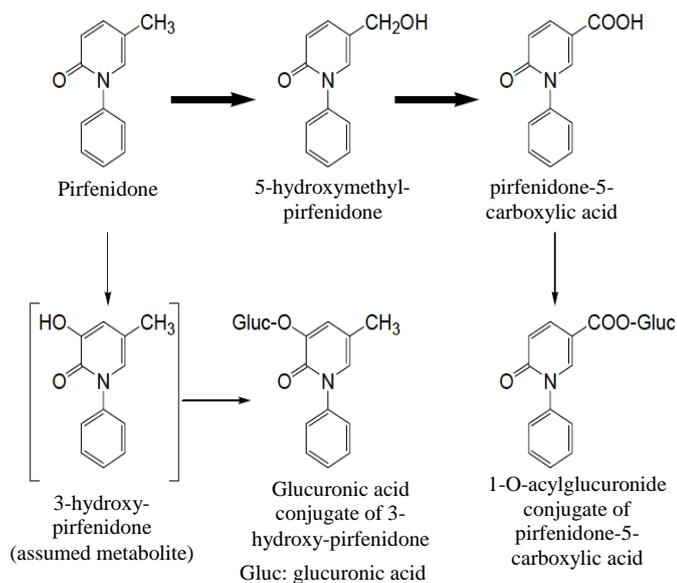


Figure Estimated metabolic pathway of Pirfenidone

3.(ii).A.(3).2) Metabolites in plasma

After a 100 mg/kg dose of ¹⁴C-Pirfenidone was orally administered to male rats (n = 5) as a single-dose or as repeated-doses for 14 days, the unchanged drug, 5-hydroxymethyl metabolite, and 5-carboxylic acid metabolite were found in plasma. After the single-dose administration, the observed plasma AUC_{0-∞} values for the unchanged drug, 5-hydroxymethyl metabolite, and 5-carboxylic acid metabolite were 59.5 ± 24.8, 13.0 ± 6.7, and 54.4 ± 6.8 µg·hr/mL, respectively, indicating that the 5-carboxylic acid metabolite and the unchanged drug of Pirfenidone show similar changes in their concentration over time. After the last dose of the repeated-dose administration, the observed plasma AUC_{0-24hr} values for the unchanged drug, 5-hydroxymethyl metabolite, and 5-carboxylic acid metabolite were 39.5 ± 6.4, 9.3 ± 2.2, and 48.8 ± 6.0 µg·hr/mL, respectively, indicating that the repeated dosing did not cause a significant change in the concentrations of metabolites over time.

After Pirfenidone was administered to male dogs (n = 4) as a single oral dose at 30 mg/kg or a single intravenous dose at 20 mg/kg, the observed plasma AUC_{0-24hr} values for the unchanged drug and 5-carboxylic acid metabolite were 74.5 ± 11.7 and 54.0 ± 4.9 µg·hr/mL after the oral dose, and 74.3 ± 10.5 and 38.5 ± 1.7 µg·hr/mL after the intravenous dose, respectively. The 5-hydroxymethyl metabolite was not detected after administration by either route. After a single 100 or 300 mg/kg dose of Pirfenidone was orally administered to male dogs (n = 4), the observed plasma AUC_{0-24hr} values for the unchanged drug and the 5-carboxylic acid metabolite were 209 ± 77 and 249 ± 104 µg·hr/mL for the 100 mg/kg dose, and 548 ± 227 and 411 ± 277 µg·hr/mL for the 300 mg/kg dose, respectively. The 5-hydroxymethyl metabolite was not detected even when a high dose of Pirfenidone was administered.

After a single 100 or 500 mg/kg dose of Pirfenidone was orally administered to male ICR mice (n = 3), the observed plasma AUC values for the unchanged drug, 5-hydroxymethyl metabolite and 5-carboxylic acid metabolite were 40.4, 27.6, and 40.0 µg·hr/mL for the 100 mg/kg dose, and 241, 123, and 257 µg·hr/mL for the 500 mg/kg dose, respectively. Similarly, after a single 100 or 500 mg/kg dose of Pirfenidone was orally administered to female C57BL/6 mice (n = 3), the observed plasma AUC values for the unchanged drug, 5-hydroxymethyl metabolite and 5-carboxylic acid metabolite were 44.3, 14.7, and 50.9 µg·hr/mL for the 100 mg/kg dose, and 296, 65.7, and 299 µg·hr/mL for the 500 mg/kg dose, respectively. Thus, the mice and rats showed

similar metabolic patterns (4.2.2.2-03, 4.2.2.4-02, 03, 04).

3.(ii).A.(3.3) Metabolites in plasma and the auricles of guinea pigs

In the phototoxicity test in guinea pigs, an inflammatory change was observed when the auricles of the guinea pigs were irradiated with UV light immediately after the oral administration of a 160 mg/kg dose of Pirfenidone; whereas, the degree of inflammatory change was milder when the auricles of the guinea pigs were irradiated with UV light 4 hours after the administration, and no inflammatory change was observed when the auricles were irradiated 6 hours after the administration. Based on the above observations, a single 160 mg/kg dose of ^{14}C -Pirfenidone was orally administered to female guinea pigs ($n = 3$), and the changes over time in radioactivity concentration and the concentration of the unchanged drug and metabolites in plasma and the auricles were determined. The result showed that although the radioactivity concentrations in the auricle (48.1, 6.62, and 3.64 $\mu\text{g/g}$ at 1, 4, and 6 hours after the administration, respectively) were lower than the radioactivity concentrations in plasma (55.8, 12.2, and 9.00 $\mu\text{g/mL}$ at 1, 4, and 6 hours after the administration, respectively), they showed similar patterns of change over time. The unchanged drug, 5-carboxylic acid metabolite, and the glucuronic acid conjugate of 3-hydroxy-pirfenidone were found in the auricles, and the unchanged drug accounted for the major fraction of the total radioactivity up to 4 hours after the administration ($86 \pm 2\%$, $57 \pm 11\%$, and $37 \pm 9\%$ at 1, 4, and 6 hours after the administration, respectively); thus, it is inferred that the concentration of the unchanged drug in the skin is associated with skin phototoxicity (4.2.2.4-05).

3.(ii).A.(3.4) Metabolites in urine and bile

After a single 100 mg/kg dose of ^{14}C -Pirfenidone was orally administered to male rats ($n = 4$), only the 5-carboxylic acid metabolite was found in the urine, and the cumulative urinary excretion during the first 48 hours after the administration was $92.8 \pm 4.4\%$ of the administered dose. After a single 100 mg/kg dose of Pirfenidone was orally administered to bile duct-cannulated male rats ($n = 4$), the unchanged drug, 5-carboxylic acid metabolite, and 1-O-acylglucuronide of 5-carboxylic acid metabolite were found in the bile, and the cumulative biliary excretion during the first 48 hours after the administration were, respectively, $0.1 \pm 0.1\%$, $5.1 \pm 2.5\%$, and $2.6 \pm 1.5\%$ of the administered dose. As in the uncannulated rats, only the 5-carboxylic acid metabolite was found in the urine of the cannulated rats, and $85.0 \pm 3.8\%$ of the administered dose was excreted in the urine within 48 hours after the administration.

After a single oral dose at 30 mg/kg or a single intravenous dose at 20 mg/kg of ^{14}C -Pirfenidone was administered to male dogs ($n = 4$), only the 5-carboxylic acid metabolite was found in the urine after both routes of administration, and the cumulative urinary excretion during the first 48 hours after the administration were, respectively, $85.8 \pm 1.9\%$ and $83.2 \pm 4.5\%$ of the administered dose. After a single 30 mg/kg dose of ^{14}C -Pirfenidone was intraduodenally administered to bile duct-cannulated male dogs ($n = 3$), the 5-carboxylic acid metabolite and 1-O-acylglucuronide of the 5-carboxylic acid metabolite were found in the bile, and the cumulative biliary excretion during the first 48 hours after the administration were, respectively, $7.6 \pm 1.4\%$ and $0.5 \pm 0.4\%$ of the administered dose. In the urine, the 5-carboxylic acid metabolite only was found, and the cumulative urinary excretion during the first 48 hours after the administration was $70.6 \pm 5.0\%$ of the dose administered (4.2.2.4-06, 02).

3.(ii).A.(3.5) Metabolic enzymes, enzyme inhibition, and enzyme induction in humans

An antibody-addition inhibition assay was carried out by adding antisera against various CYP isoforms to human liver microsomes. The production of 5-hydroxymethyl metabolite was used as a marker for inhibition. The assay results confirmed that several CYP isoforms (CYP1A2, 2C9, 2C19, 2D6, and 2E1) are involved in the earliest stage of oxidative metabolism of

Pirfenidone.

The inhibitory activity of Pirfenidone on the activity of CYP isoforms (CYP1A, 2A6, 2C9, 2C19, 3A4, 2D6, and 2E1) was assessed using human liver microsomes and model substrates for the CYP isoforms. The results showed that Pirfenidone has a weak inhibitory activity on CYP1A, 2A6, 2C9, 2C19, and 3A4, and no inhibitory activity on 2D6 and 2E1.

In addition, the inhibitory activity of the 5-carboxylic acid metabolite on the activity of the CYP isoforms (CYP1A, 2A6, 2C8/9, 2C19, 3A4, 2D6, and 2E1) was assessed; and the results showed that the 5-carboxylic acid metabolite has no inhibitory activity on any of the CYP isoforms tested.

The enzyme induction activity of Pirfenidone and its 5-carboxylic acid metabolite on human liver CYP isoforms was assessed using an *in vitro* human hepatocyte culture system. The result showed that although Pirfenidone induces human liver CYP3A4/5 and 2C19 at a high concentration (250 $\mu\text{mol/L}$, approximately 46 $\mu\text{g/mL}$), the degree of enzyme induction by Pirfenidone was weaker than that of rifampicin (a typical inducer of CYP3A4/5 and 2C19). The 5-carboxylic acid metabolite did not show an enzyme induction activity on any of the CYP isoforms tested (5.3.2.2-01, 02, 03, 04).

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

3.(ii).A.(4.1) Excretion into urine, feces, and bile

After a single 100 mg/kg dose of ^{14}C -Pirfenidone was orally administered to male rats ($n = 4$), the cumulative excretions of radioactivity in urine and feces during the first 48 hours after the administration were, respectively, $89.6 \pm 3.5\%$ and $5.5 \pm 1.3\%$ of the administered dose. After a single 100 mg/kg dose of ^{14}C -Pirfenidone was orally administered to bile duct-cannulated male rats ($n = 4$), the cumulative excretions of radioactivity in bile, urine, and feces during the first 48 hours after the administration were, respectively, $10.3 \pm 3.7\%$, $81.0 \pm 3.1\%$, and $0.6 \pm 0.2\%$ of the dose administered. When ^{14}C -Pirfenidone was repeatedly administered to male rats ($n = 5$) at 100 mg/kg/day for 14 days, the cumulative excretions of radioactivity in urine and feces ($89.5 \pm 0.6\%$ and $5.5 \pm 0.5\%$, respectively) during the first 24 hours after the last dose were approximately the same as observed after the single-dose administration; thus, there were no significant changes in the patterns of urinary and fecal excretions related to the repeated dosing. In addition, the total excretion of radioactivity in the 120 hours after the last dose was $95.8 \pm 0.3\%$, and no sign of significant accumulation of the administered radioactivity in the rats was found.

On the other hand, after a single 30 mg/kg dose of ^{14}C -Pirfenidone was orally administered to uncannulated male dogs ($n = 3$), the cumulative excretions of radioactivity in urine and feces during the first 120 hours after the administration were, respectively, $80.6 \pm 1.7\%$ and $8.9 \pm 3.5\%$ of the administered dose. Moreover, after a single 30 mg/kg dose of ^{14}C -Pirfenidone was intraduodenally administered to bile duct-cannulated male dogs ($n = 3$), the cumulative excretions of radioactivity in bile, urine, and feces during the 48 hours after the administration were, respectively, $14.6 \pm 2.6\%$, $81.3 \pm 2.6\%$, and $0.3 \pm 0.2\%$ of the dose administered (4.2.2.4-06, 4.2.2.2-03, 4.2.2.2-04, 4.2.2.4-02).

3.(ii).A.(4.2) Enterohepatic circulation

Male donor rats ($n = 4$) and male recipient rats ($n = 4$) were cannulated so that the bile of the donor flows into the duodenum of the recipient. After a 100 mg/kg dose of ^{14}C -Pirfenidone was orally administered to the donor rats, $11.1 \pm 2.2\%$ of the administered radioactivity was transported into the recipient rats via the bile, $7.4 \pm 1.5\%$ of which was reabsorbed and then

excreted into the urine and bile ($5.7 \pm 1.2\%$ and $1.6 \pm 0.5\%$, respectively).

Of the dose transferred into the recipient rat, $14.9 \pm 3.5\%$ was reabsorbed and recycled by the enterohepatic circulation (4.2.2.5-01).

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

After a single 100 mg/kg dose of ^{14}C -Pirfenidone was orally administered to post-partum female rats ($n = 5$) on the 12th day after the delivery, the plasma radioactivity reached C_{max} ($35.9 \pm 9.0 \mu\text{g/mL}$) at 0.33 ± 0.23 hours after the administration, and was then eliminated with a $t_{1/2}$ of 3.4 ± 1.3 hours. The radioactivity in milk reached C_{max} ($31.3 \pm 10.0 \mu\text{g/mL}$) at 0.42 ± 0.19 hours after the administration. The observed C_{max} values for milk and plasma were comparable. Subsequently, the radioactivity concentration in milk remained nearly constant from 2 to 8 hours after the administration (17 to $18 \mu\text{g/mL}$), and was then eliminated with a $t_{1/2}$ of 4.7 ± 1.4 hours. The $t_{1/2}$ values for radioactivity in milk and plasma were also similar. Based on the above observations, it became clear that Pirfenidone is excreted into milk (4.2.2.5-02).

3.(ii).A.(5) Pharmacokinetic drug interaction

No studies that correspond to pharmacokinetic drug interaction studies have been conducted.

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

PMDA asked the applicant to explain the safety of Pirfenidone in humans, especially in the organs (such as spleen, pancreas, kidney, and adrenal gland) in which a high radioactivity concentration was observed in rats in the distribution studies, and in the organs (such as nasal cavity and preputial gland) in which the repeated dosing of Pirfenidone showed a tendency to cause accumulation of radioactivity.

The applicant responded as follows:

a. Although a higher radioactivity concentration was observed in the spleen, pancreas, kidney, and adrenal gland in rats compared with that in plasma during the early phase after the administration in the distribution studies, the radioactivity concentration rapidly decreased over time, and the whole-body ARGs also did not show any sign of radioactivity accumulation in these organs. In addition, no findings indicating toxicity in these organs were reported in the repeated-dose toxicity studies in rats, and there have been no occurrences of particular adverse events related to these organs in Japanese clinical studies; **b.** With regard to the nasal cavity, the distribution of radioactivity was not uniform between the sites in the nasal cavity, and it is possible that the radioactivity is localized in the sites containing many granules. In the repeated-dose toxicity studies in rats, the gross pathological examination of the nasal tissues did not show any changes indicative of toxicity; and, although nasopharyngitis was reported as a related adverse event in the Japanese clinical studies, the incidence rate of nasopharyngitis was higher in the placebo group; **c.** Similarly, in the preputial gland, the distribution of radioactivity showed a tendency to concentrate in the vacuolated sites in the tissue, and it is possible that the localization of radioactivity is specific for secretory granules. Again, in the repeated-dose toxicity studies in rats, the gross pathological examination of preputial gland did not show any changes indicative of toxicity, and although the preputial gland also exists as one of the independent sebaceous glands in humans, the histological structure and function are thought to differ between human and rat. Moreover, in the Japanese clinical studies, asteatotic eczema was reported as a possibly related adverse event during the Phase III study, and the incidence of asteatotic eczema was higher in the low-dose group than the placebo group; however, asteatotic eczema was not reported in the high-dose group; thus, it is considered unlikely that Pirfenidone poses a risk to the safety of these organs.

PMDA asked the applicant to explain whether or not it is possible that long-term administration

of Pirfenidone will induce metabolic enzymes in humans, because although the applicant stated that in the human hepatic drug-metabolizing enzyme studies, induction of CYP3A4/5 and 2C19 enzymes was observed only after exposure to a high concentration (250 $\mu\text{mol/L}$, approximately 46 $\mu\text{g/mL}$) of the drug, the repeated oral dose studies in rats showed that the plasma concentration of the unchanged drug decreased after the repeated dosing even when the concentration was 20 $\mu\text{g/mL}$ or less, and the occurrence of metabolic enzyme induction was suggested at concentrations near the C_{max} (approximately 10 $\mu\text{g/mL}$) (5.3.3-08) obtained after the repeated administration of Pirfenidone in humans at 1800 mg/day (the maximum daily dose in clinical settings).

The applicant explained as follows:

Phenobarbital-type enzyme induction was observed at 100 mg/kg/day or higher doses (C_{max} value after the first dose was 16.0 $\mu\text{g/mL}$ for the 1-month study, and 14.8 $\mu\text{g/mL}$ for the 6-month study) in the 1-month and 6-month repeated-dose toxicity studies in rats, and at 10 mg/kg/day or higher doses (C_{max} value after the first dose was 0.78 $\mu\text{g/mL}$) in the 6-week TID repeated-dose toxicity study in mice, and at 20 mg/kg/day or higher doses (C_{max} value after the first dose was 16.1 $\mu\text{g/mL}$ for the 3-month study, and 19.1 $\mu\text{g/mL}$ for the 9-month study) in the 3-month and 9-month repeated-dose toxicity studies in dogs, but there are species differences in the plasma concentration of Pirfenidone that resulted in enzyme induction. Furthermore, although approximately a 2-fold higher induction of CYP3A4/5 and 2C19 activity was observed at the concentration of approximately 46 $\mu\text{g/mL}$ in the primary culture of human hepatocytes during the *in vitro* enzyme induction study, this was the result of a continuous 3-day exposure to Pirfenidone at a high concentration (approximately 46 $\mu\text{g/mL}$), and no enzyme-inducing activity resulted from 3-day exposure to Pirfenidone at the dose (100 $\mu\text{mol/L}$, approximately 19 $\mu\text{g/mL}$) close to the estimated drug concentration in the human liver (approximately 20 $\mu\text{g/mL}$), which was calculated based on the C_{max} value (approximately 10 $\mu\text{g/mL}$) obtained after repeated administration of Pirfenidone at 1800 mg/day in humans; thus, it is unlikely that Pirfenidone will cause enzyme induction in humans within the clinical dose range.

PMDA accepted the responses from the applicant; however, because the duration of treatment with Pirfenidone is expected to extend over a long period of time in patients with idiopathic pulmonary fibrosis, PMDA advises that the applicant should conduct a further investigation during the post-marketing surveillance in order to confirm the safety of the organs in which a high concentration of radioactivity or a tendency for radioactivity accumulation was observed in animal studies.

3.(iii) Summary of the toxicology studies

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

The results of the following toxicology studies were submitted: single-dose toxicity, repeated-dose toxicity, genotoxicity, carcinogenicity, reproductive and developmental toxicity, antigenicity, skin phototoxicity, skin photosensitization, and photogenotoxicity.

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

Single-dose toxicity was evaluated in rats (4.2.3.1-01) and dogs (4.2.3.1-02) given Pirfenidone by gavage. The approximate lethal dose was determined to be 1000 mg/kg for rats and >1000 mg/kg for dogs. Decreased activity and mydriasis were observed in both animal species. Noteworthy findings in rats included abnormal gait, lateral position, respiratory depression, ptosis, lacrimation, and hypothermia, while those in dogs included muscle weakness in the limbs, vomiting, salivation, shivering, and abnormal phonation. In addition, decreased levels of erythroid parameters (red blood cell count, hemoglobin concentration, and hematocrit), increased plasma AST and ALT levels and amylase activity, a decreasing trend in thymus weight, and cortex atrophy were detected in dogs. The approximate lethal dose was determined to be > 1000 mg/kg for non-fasting rats.

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

Repeated-dose toxicity was evaluated in rats (1- and 6-month dosing) and dogs (3- and 9-month dosing) given Pirfenidone by gavage. Pirfenidone was also administered in divided dose (three times a day) by gavage for 6 weeks to mice, an animal species used for drug efficacy assessment. This study showed inflammatory changes of the urinary tract and, as a result, an additional study was conducted to further investigate this observation. As common toxic findings, neurological symptoms due to the CNS-depressive action of the drug were noted. Also noted were decreases in erythroid parameters in rats, mucous submandibular gland hypertrophy accompanied by mucous feces and salivation in dogs, and inflammatory changes in the renal pelvis and bladder in mice. Increased activity of hepatic drug metabolizing enzymes (phenobarbital-type CYP induction) and related changes (increased liver weight, hepatocyte hypertrophy, hyperplasia of smooth endoplasmic reticulum, etc.) were also observed. All of these changes recovered after drug withdrawal. When the NOAELs (rats, 100 mg/kg/day; dogs, 20 mg/kg/day) in rats (6-month dosing) and dogs (9-month dosing) were compared with the human exposure (5.3.3-08) after repeated dosing of 1800 mg/day (maximum daily dose of Pirfenidone used in humans), the C_{max} in rats and dogs was 1.1 to 1.9 times and 2.1 to 2.3 times, respectively, that in humans, and the AUC_{0-24hr} in rats and dogs was 0.7 to 1.1 times and 0.3 to 0.4 times, respectively, that in humans.

3.(iii).A.(2).1) Repeated-dose toxicity studies in rats (4.2.3.2-01 to -03)

A 1-month study (0, 20, 100, or 500 mg/kg/day) and a 6-month study (0, 20, 100, 500, or 1000 mg/kg/day) were conducted. Both studies included recovery groups with a 1-month or 35-day post-dose recovery period.

In both studies decreased activity and respiratory depression (1-month study, 500 mg/kg; 6-month study, ≥ 500 mg/kg) were noted in the early phase of dosing. Other noteworthy findings included the following: abnormal gait and lacrimation in the 500 mg/kg group of the 1-month study; prolonged APTT in the 500 mg/kg and higher dose groups of the 6-month study; and decreased body weight gain associated with decreased food consumption and decreased food efficiency, and decreases in erythroid parameters (red blood cell count, hemoglobin concentration, and hematocrit) in the 1000 mg/kg group of the 6-month study. Salivation (1-month study, 500 mg/kg; 6-month study, ≥ 100 mg/kg, hereinafter the same) was also observed. Hepatic biochemistry detected decreased cholesterol (≥ 100 mg/kg; ≥ 100 mg/kg), decreased triglyceride (≥ 100 mg/kg; ≥ 500 mg/kg), and increased phospholipids (500 mg/kg; ≥ 500 mg/kg). Increased activity of phenobarbital-type hepatic drug metabolizing enzymes (≥ 100 mg/kg; ≥ 100 mg/kg) and increased hepatic CYP contents (500 mg/kg; ≥ 500 mg/kg) were detected. As changes related to the induction of the hepatic drug metabolizing enzymes, increased liver weight (no change; ≥ 500 mg/kg), hepatic centrilobular hypertrophy (no change; 1000 mg/kg), hyperplasia of smooth endoplasmic reticulum, and decreased glycogen (500 mg/kg; no electron

microscopy conducted) were noted. In addition, decreased pH and increased specific gravity of the urine (500 mg/kg; ≥ 100 mg/kg) were observed and abnormal crystals were also found in urinary sediments derived from the 500 mg/kg and higher dose groups of the 6-month study. These were all considered to be due to metabolites (5-carboxylic acid) excreted in urine. All of the changes observed at the end of the dosing period recovered post-dosing. The effect of Pirfenidone on the coagulation system (prolonged APTT and PT and increased platelet count) was observed in the 500 mg/kg post-dose recovery group of the 1-month study (in this study, a post-dose recovery group was not included for the lower dose levels of 20 or 100 mg/kg). To further investigate this finding, additional 1-month and 2-month repeated-dose studies were conducted at the same doses as used in the original 1-month study. No effect on the coagulation system was noted in any of the post-dose recovery groups for any of the dose levels (post-dose periods of 8, 15, 30, and 62 days for the 0, 20, 100, and 500 mg/kg/day groups, respectively) of the additional 1-month study or in any group in the additional 2-month study. On the basis of the above findings, the NOAEL in rats was determined to be 100 mg/kg/day in both the 1- and 6-month oral repeated-dose studies. As for toxicokinetics, the exposure (AUC_{0-24hr} and C_{max}) increased dose-dependently. However, the exposure decreased after repeated dosing in the 500 mg/kg and higher dose groups and was higher in females than in males in the 1000 mg/kg group.

3.(iii).A.(2).2) Repeated-dose toxicity studies in dogs (4.2.3.2-04 to -05)

A 3-month study and a 9-month study were conducted at the same doses (0, 20, 70, or 200 mg/kg/day). In both studies, 5-week post-dose recovery groups were included.

Common noteworthy findings in both studies included vomiting and salivation in the 70 mg/kg and higher dose groups and decreased activity, abnormal gait, abnormal phonation, stiffness and relaxation of limbs, dysstasia, abnormal breathing, head shaking, convulsion, sleep, mydriasis, and increased ALP in the 200 mg/kg group. In addition, mucous feces (3-month study, ≥ 70 mg/kg; 9-month study, ≥ 20 mg/kg, hereinafter the same), increased submandibular gland weight (≥ 20 mg/kg; 200 mg/kg), and hypertrophy of mucous glands (200 mg/kg; ≥ 70 mg/kg), and increased platelet count (200 mg/kg; ≥ 70 mg/kg) were noted. Other noteworthy findings included decreased prostate weight in the 20 mg/kg and higher dose groups of the 3-month study; diarrheal feces, ptosis, tremor, decreased food consumption, decreased uterus weight and uterine atrophy and prostatic atrophy in the 200 mg/kg group of the 3-month study; and decreased mean body weight gain (including body weight loss in a few animals) in the 70 mg/kg or higher dose groups of the 9-month study. Hepatic biochemistry revealed increased phospholipids (200 mg/kg; ≥ 20 mg/kg), increased activity of phenobarbital-type hepatic drug metabolizing enzymes (≥ 20 mg/kg; ≥ 20 mg/kg), and increased hepatic CYP contents (≥ 20 mg/kg; ≥ 70 mg/kg). As changes related to the induction of the hepatic drug metabolizing enzymes, increased liver weight (200 mg/kg; 200 mg/kg), hepatic centrilobular hypertrophy (200 mg/kg; 200 mg/kg), hyperplasia of smooth endoplasmic reticulum, and decreased glycogen (≥ 20 mg/kg; no electron microscopy conducted) were noted. On the basis of the frequencies and severity of the findings as well as their toxicological relevance, the NOAEL in dogs was determined to be 70 mg/kg/day in the 3-month repeated-dose study and 20 mg/kg/day in the 9-month repeated-dose study. As for toxicokinetics, the exposure (AUC_{0-24hr} and C_{24hr}) increased dose-dependently and there were no repeated-dose-related changes or gender differences.

3.(iii).A.(2).3) Oral divided-dose study in mice and its investigative study

a. Six-week TID dosing study in mice (4.2.3.2-06 to -07)

Pirfenidone was administered to mice, an animal species used for drug efficacy assessment, by gavage at daily doses of 0, 10, 30, 60, 100, or 500 mg/kg in three divided doses (TID) (0, 3.3, 10, 20, 33.3, or 167 mg/kg/dose) for 6 weeks. Decreased activity was observed in the 500 mg/kg group. Histopathological examinations detected mononuclear cell infiltration in the renal pelvic

mucosa and submucosa and in the Harderian glands in the 100 mg/kg and higher dose groups, and in the submucosa and muscle layers of the bladder in the 500 mg/kg group. The NOAEL was determined to be 60 mg/kg. Increased activity of phenobarbital-type hepatic drug metabolizing enzymes was noted in all treatment groups, and increased hepatic CYP contents were noted in the 500 mg/kg group. As changes related to these findings, increased liver weight and hepatic centrilobular hypertrophy were observed in the 500 mg/kg group. As for toxicokinetics, the exposure (AUC_{0-24hr} and C_{max}) increased dose-dependently but decreased after repeated dosing in the 30 mg/kg and higher dose groups.

b Two-week QD dosing study in mice (4.2.3.2-08)

Pirfenidone was administered to mice by gavage at a daily dose of 0, 100, 300, or 1000 mg/kg once a day (QD) for 2 weeks to evaluate whether the inflammatory renal pelvic changes noted in the 6-week TID dosing study in mice were dependent on the dosing frequency per day. Mononuclear cell infiltration was observed in the renal pelvic mucosa and submucosa in the 100 mg/kg and higher dose groups. The exposure (AUC_{0-24hr}) at a daily dose of 100 mg/kg was comparable to that in the 6-week TID dosing study in mice. These findings suggested that the inflammatory lesions in the renal pelvis depended not on the dosing frequency per day but on the exposure per day.

c. Two-week TID and QD dosing study in rats (4.2.3.2-09)

Pirfenidone was administered to rats by gavage for 2 weeks at a daily dose of 0, 100, 300, or 1000 mg/kg TID (0, 33.3, 100, or 333.3 mg/kg/dose) or at a daily dose of 1000 mg/kg once a day (QD) to evaluate whether a greater dosing frequency per day would cause rats to develop inflammatory renal pelvic changes as observed in the 6-week TID dosing study in mice. No animals developed renal pelvic lesions in any of the treatment groups and the exposure (AUC_{0-24hr}) at a daily dose of 1000 mg/kg, whether TID or QD, far exceeded the exposure at which lesions were noted in mice. These findings suggested that the inflammatory changes in the renal pelvis were specific to mice.

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

A bacterial reverse mutation test (4.2.3.3-01) and a chromosomal aberration test using cultured cells derived from Chinese hamster lungs (4.2.3.3-02) were conducted as *in vitro* tests, and an oral bone marrow micronucleus assay in mice (4.2.3.3-03) and an unscheduled DNA synthesis test using rat hepatic cells (4.2.3.3-04) were conducted as *in vivo* tests. All these tests produced negative results, demonstrating that Pirfenidone has no genotoxic activity.

3.(iii).A.(4) Carcinogenicity

A 104-week dietary carcinogenicity study was conducted in mice and rats. Increased frequencies of hepatocellular tumors in mice and of hepatocellular tumors and uterine tumors in rats were observed. When the non-carcinogenic doses in mice and rats (mice, <800 mg/kg/day; rats, 375 mg/kg/day) were compared with the human exposure after repeated dosing of 1800 mg/day (maximum daily dose of Pirfenidone used in humans) (5.3.3-08), the C_{max} and AUC_{0-24hr} in mice were less than 0.07 to 0.18 times and less than 0.11 to 0.29 times, respectively, those in humans. The exposure in rats was not calculated but, based on the results of other studies, was estimated to be smaller than the clinical exposure. The oncogenic mechanisms for these tumors were examined in investigative studies. The results of the studies suggested that the hepatocellular tumors observed in mice and rats were rodent-specific changes associated with the induction of phenobarbital-type hepatic drug metabolizing enzymes and also suggested that the uterine tumors observed in rats developed through a rat-specific mechanism attributable to an increase in the estradiol/progesterone ratio resulting from a higher extracellular dopamine concentration in the hypothalamus (4.2.1.3-04). Pirfenidone was thus considered to be unlikely

to pose a carcinogenic risk in humans.

3.(iii).A.(4).1) Carcinogenicity study in mice (4.2.3.4-01)

A 104-week carcinogenicity study was conducted in B6C3F₁ mice at planned doses of 0, 800, 2000, and 5000 mg/kg/day (mean actual doses of 0, 819.3, 2016.4, and 5025.7 mg/kg/day for males; 0, 832.7, 2015.4, and 5037.0 mg/kg/day for females). Significant increases were noted in frequency of hepatocellular adenoma in the male and female low dose and higher groups (16/50, 36/50, 47/50, and 46/50 for males; 8/50, 20/50, 38/50, and 45/50 for females), of hepatocellular carcinoma in the male moderate and higher dose groups and the female high dose group (7/50, 13/50, 35/50, and 45/50 for males; 8/50, 7/50, 15/50, and 28/50 for females), and of hepatoblastoma in the male low dose and higher groups (0/50, 7/50, 14/50, and 21/50). Non-neoplastic lesions included increased frequencies in eosinophilic altered hepatocellular foci in the male and female low dose and higher groups, in hepatic centrilobular hypertrophy in the male low and higher dose groups and the female high dose group, in “wear and tear” pigmentation of Kupffer cells in the male moderate and higher dose groups and the female high dose group, and in hepatic single-cell necrosis in the male moderate and higher dose groups. As for toxicokinetics, the plasma concentrations of the unchanged drug and its 5-carboxylic acid metabolite increased almost dose-dependently and there were no gender differences or accumulation.

3.(iii).A.(4).2) Carcinogenicity study in rats (4.2.3.4-02)

A 104-week carcinogenicity study was conducted in F344 rats at planned doses of 0, 375, 750, and 1500 mg/kg/day (mean actual doses of 0, 384.2, 767.6, and 1532.8 mg/kg/day for males; 0, 382.5, 775.5, and 1546.3 mg/kg/day for females). Significant increases were noted in frequency of hepatocellular adenoma in the male moderate and higher dose groups and the female high dose group (1/50, 5/50, 34/50, and 41/50 for males; 1/50, 3/50, 1/50, and 18/50 for females) and of uterine carcinoma in the female high dose group (2/50, 6/50, 8/50, and 13/50). Non-neoplastic lesions included increased frequencies in hepatic centrilobular hypertrophy in the male and female low dose and higher groups, eosinophilic altered hepatocellular foci and mixed-type altered hepatocellular foci in the male low and higher dose groups and the female high dose group, clear cell altered hepatocellular foci in the male and female high dose groups, endometrial cystic hyperplasia in the female moderate and higher dose groups, and endometrial glandular hyperplasia in the female high dose group. As for toxicokinetics, the plasma concentrations of the unchanged drug and its 5-carboxylic acid metabolite increased almost dose-dependently and there were no gender differences or accumulation.

3.(iii).A.(4).3) Investigative studies of oncogenic mechanisms

a. Investigative study of the induction of hepatic drug metabolizing enzymes in mice given dietary doses for 4 weeks (4.2.3.4-03)

In response to the finding that hepatocellular tumors increased in the carcinogenicity study in mice, a 4-week dietary dose study was conducted in B6C3F₁ mice given the same doses as used in the previous carcinogenicity study (the planned doses were 0, 800, 2000, and 5000 mg/kg/day; the mean actual doses were 0, 748.4, 1999.3, and 4773.1 mg/kg/day for males; 0, 779.8, 1969.5, and 4958.4 mg/kg/day for females) to investigate the capacity of Pirfenidone to induce hepatic CYP enzymes (CYP1A, 2B, 2D, and 3A). Phenobarbital-type induction of hepatic CYPs, mainly CYP2B and 3A, was noted, except testosterone 2 α -hydroxylase activity (CYP2D) in the female low dose group.

b. Investigative study of the induction of hepatic drug metabolizing enzymes in rats given dietary doses for 4 weeks (4.2.3.4-04)

In response to the finding that hepatocellular tumors increased in the carcinogenicity study in

rats, a 4-week dietary dose study was conducted in F344 rats given the same doses as used in the previous carcinogenicity study (the planned doses were 0, 375, 750, and 1500 mg/kg/day; the mean actual doses were 0, 430.1, 852.3, and 1647.2 mg/kg/day for males; 0, 413.9, 824.8, and 1554.2 mg/kg/day for females) to investigate the capacity of Pirfenidone to induce hepatic CYP enzymes (CYP1A, 2B, 2C11, and 3A). Phenobarbital-type hepatic CYP induction was noted in all treatment groups. CYP2B induction was more notable in males than in females.

c. Investigative study of the effect on the plasma hormone concentrations in rats given dietary doses for 4 weeks (4.2.3.4-05)

In response to the finding that uterine tumors increased in the carcinogenicity study in rats, a 4-week dietary dose study was conducted in F344 female rats given the same high dose as used in the previous carcinogenicity study (the planned doses were 0 and 1500 mg/kg/day; the mean actual doses on Days 7 and 29 were 0 and 1262.5 mg/kg/day each) to evaluate the effect of Pirfenidone on female hormones by measuring the plasma concentrations of estradiol (E), progesterone (P), and prolactin (PL) in animals showing diestrus 1 and 4 weeks after starting dose. In both measurements, high levels of E and low levels of P and PL were noted with a significantly elevated E/P ratio. This finding demonstrated that the plasma concentrations of these hormones changed with an upward trend for estrogen.

3.(iii).A.(5) Reproductive and developmental toxicity

In a previous dietary dose study of fertility and embryo-fetal development in rats (4.2.3.5-04), no direct effect was observed on either the parent animal's reproductive potential or embryo-fetal development. This time, a fertility and embryo-fetal development study in which the dosing of the female animals (which were employed in a study of fertility and early embryonic development) was continued until hard palate closure before examination of the fetuses, and a study of prenatal and postnatal development including maternal function were conducted in rats. An embryo-fetal development study was also conducted in rabbits. Pirfenidone showed no teratogenicity in any of these studies, whereas it affected pregnancy maintenance and child delivery by dams. Perinatal dosing also lowered the birth rate. When the NOAEL (30 mg/kg/day) for pregnancy maintenance in rabbits was compared with the human exposure (5.3.3-08) after repeated dosing of 1800 mg/day (maximum daily dose of Pirfenidone used in humans), the C_{max} in rabbits was 0.33-0.44 times that in humans and the AUC_{0-24hr} in rabbits was also far below that in humans. In rats, placental/fetal (4.2.2.3-03) and lacteal (4.2.2.5-02) transfers of Pirfenidone were noted.

3.(iii).A.(5).1 Fertility and embryo-fetal development study in rats (4.2.3.5-01)

Pirfenidone was administered by gavage at doses of 0, 50, 150, 450, or 1000 mg/kg/day to male rats from 4 weeks prior to mating through the day before autopsy (for approximately 9 weeks) and to female rats from 2 weeks prior to mating through 17 days of gestation. Noteworthy findings included ptosis (males, ≥ 150 mg/kg/day; females before mating, ≥ 50 mg/kg/day; pregnant females, 1000 mg/kg/day; hereinafter the same), decreased activity (≥ 450 mg/kg/day; ≥ 50 mg/kg/day; 1000 mg/kg/day), weakness of limbs and abnormal gait (≥ 450 mg/kg/day; ≥ 450 mg/kg/day; 1000 mg/kg/day), respiratory depression (1000 mg/kg/day; ≥ 450 mg/kg/day; none), decreased body weight gain (≥ 450 mg/kg/day; none; ≥ 150 mg/kg/day), decreased food consumption (≥ 450 mg/kg/day; ≥ 450 mg/kg/day [after 1 week of dosing]; 1000 mg/kg/day). While body weight gain and a prolonged estrous cycle were observed during the premating period in females given 450 mg/kg or higher doses, there were no abnormal findings in sperm examinations or pertaining to the mating rate, conception rate, number of corpora lutea, number of implantations, rate of preimplantation loss, or the survival and development of fetuses. The NOAELs determined in this study were as follows: for general toxicity, 50 mg/kg/day for males, <50 mg/kg/day for premating females, and 50 mg/kg/day for pregnant females; for reproductive

toxicity, 1000 mg/kg/day for males and 150 mg/kg/day for females; and 1000 mg/kg/day for embryo-fetal development toxicity.

3.(iii).A.(5).2) Embryo-fetal development study in rabbits (4.2.3.5-02)

Pirfenidone was administered by gavage at doses of 0, 30, 100, or 300 mg/kg/day to pregnant rabbits from 6 days of gestation through 18 days of gestation. Noteworthy findings related to general toxicity to dams included death in the 300 mg/kg group; respiratory distress, abdominal position, auricular vasodilation, dullness in the startle response, ptosis, drooping auricles, and decreased food consumption in the 100 mg/kg and higher dose groups; and deep respiration, salivation, lacrimation, decreased body weight gain in the 300 mg/kg group. Noteworthy findings related to reproductive toxicity included premature birth in the 100 mg/kg group and abortion and total resorption of the embryos in the 300 mg/kg group. There were no abnormal findings in fetal survival and development including external, visceral, and skeletal observations. The NOAEL in this study was determined to be 30 mg/kg/day for maternal general and reproductive toxicities and 300 mg/kg/day for embryo-fetal development toxicity. As for toxicokinetics, the exposure (AUC_{0-6hr} and C_{max}) increased dose-dependently and showed no changes associated with repeated dosing.

3.(iii).A.(5).3) Study of prenatal and postnatal development including maternal function in rats (4.2.3.5-03)

Pirfenidone was administered by gavage at doses of 0, 100, 300, or 1000 mg/kg/day to pregnant rats from 7 days of gestation through the 20th day after the delivery. Noteworthy findings related to general toxicity to dams included death (during pregnancy, 1000 mg/kg; during lactation, none; hereinafter the same), decreased activity (≥ 100 mg/kg; ≥ 300 mg/kg), respiratory depression (≥ 300 mg/kg; 1000 mg/kg), lacrimation (1000 mg/kg; none), salivation (≥ 300 mg/kg; ≥ 300 mg/kg), decreased body weight gain (≥ 300 mg/kg; ≥ 300 mg/kg), and decreased food consumption (≥ 100 mg/kg; ≥ 300 mg/kg). Noteworthy findings related to reproductive toxicity included a prolonged gestational period and a decreased birth rate in the 1000 mg/kg group. With respect to F1 animals, a decreasing trend in the mean number of pups per litter and the mean number of liveborn pups per litter, increased mean number of stillborn pups per litter, and decreased birth rate in the 1000 mg/kg; and a decreased body weight gain during lactation in the 300 mg/kg and higher groups. However, Pirfenidone did not affect developmental differentiation, reflex and sensory functions, external and skeletal morphologies, sexual maturation, estrous cycle, behavior, or reproductive function. The NOAEL in this study was determined to be <100 mg/kg/day for maternal general toxicity, 300 mg/kg/day for reproductive toxicity, and 100 mg/kg/day for prenatal and postnatal development toxicity. Since Pirfenidone was found to be transferred into milk (4.2.2.5-02), the decreased body weight gain observed in F1 animals during lactation may have been directly associated with Pirfenidone.

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

3.(iii).A.(6).1) Antigenicity study (4.2.3.7-01)

An active systemic anaphylaxis (ASA) test and a passive cutaneous anaphylaxis (PCA) test were conducted in guinea pigs. When Pirfenidone was administered by gavage or by subcutaneous injection with Freund's adjuvant (FA), the ASA and PCA reactions were negative, demonstrating the absence of immunogenicity. However, when a conjugate of Pirfenidone and bovine gamma-globulin was administered subcutaneously together with FA, the ASA reaction was negative, whereas the PCA reaction was positive, showing that Pirfenidone exhibited a weak allergenicity.

3.(iii).A.(6).2) Skin phototoxicity studies

a. Skin phototoxicity study in guinea pigs (4.2.3.7-02)

Pirfenidone was administered at a single gavage dose of 0, 40, or 160 mg/kg or by a single skin application of 0, 1, or 5% (w/v) solution (100 μ L) to female Hartley guinea pigs shaved on the shoulder area, and the animals were subsequently irradiated (0.18 J/cm²) simultaneously with ultraviolet-A (UVA) and ultraviolet-B (UVB), followed by UVA irradiation (14 J/cm²). Neither route of administration caused any changes in the shoulder skin. However, when UVA and UVB were simultaneously irradiated (10 J/cm²) after an oral dose of 160 mg/kg during a sensitization process for a subsequent skin sensitization study (4.2.3.7-02), erythema was noted in the skin of the auricles. This finding suggested that Pirfenidone had the potential to induce skin phototoxicity.

b. Additional skin phototoxicity study in guinea pigs (4.2.3.7-03)

As a result of the skin phototoxicity noted above, an additional skin phototoxicity study was conducted employing the skin of the auricles as the evaluation site. Pirfenidone was administered by gavage to female Hartley guinea pigs at a dose of 0, 2.5, 10, 40, or 160 mg/kg/day for 3 days. UVA and UVB were simultaneously irradiated (10 J/cm²) immediately after each gavage. Erythema was observed in the skin of the auricles after each treatment in the 160 mg/kg group. Histopathological examinations revealed inflammatory changes in the dermis in the 40 mg/kg and higher dose groups. These findings indicated that Pirfenidone induced skin phototoxicity. Erythema had almost disappeared and the inflammatory changes also ameliorated on the day after the last treatment, suggesting a good post-dose recovery.

c. Investigative study of the preventive effect of sunscreens against skin phototoxicity in guinea pigs (4.2.3.7-04)

The preventive effect of sunscreens on Pirfenidone-induced skin phototoxicity was evaluated. Various types of sunscreens with different dosage forms (emulsion and cream), sun protection factors (SPFs, a measure of protective effect against UVB), and protection grades for UVA (PAs, a measure of protective effect against UVA) were applied to the skin of the auricles of female Hartley guinea pigs (emulsion, 2 μ L/cm²; cream, 2 mg/cm²). A single 0 or 160 mg/kg dose of Pirfenidone was subsequently administered by gavage, immediately followed by simultaneous UVA and UVB irradiation (10 J/cm²). In this study, sunscreens reduced the erythema, as well as the histological findings including edema, inflammatory cell infiltration, and hyperemia, which were observed in animals unprotected by sunscreens. The sunscreens tested included Type 1 (emulsion, SPF 20, PA+), Type 2 (emulsion, SPF 32, PA++), Type 3 (emulsion, SPF 50+, PA+++), and Type 4 (cream, SPF 50+, PA+++). Sunscreens of Type 2 or greater protection significantly reduced erythema and those of Type 3 or greater protection significantly reduced histological changes, demonstrating that sunscreens with SPF 50+ and PA+++ had a preventive effect.

d. Investigative study of the onset of skin phototoxicity, the start time of ultraviolet irradiation, and irradiance levels in guinea pigs (4.2.3.7-05)

The relationships between the onset of Pirfenidone-induced skin phototoxicity and the start time of the ultraviolet irradiation and the irradiance levels were evaluated. Female Hartley guinea pigs received simultaneous UVA and UVB irradiation (10 J/cm²) 0, 2, 3, 4, 5, or 6 hours after a single gavage dose of 0 or 160 mg/kg Pirfenidone to evaluate the relationship between Pirfenidone-induced skin phototoxicity and the start time of ultraviolet irradiation. Erythema in the skin of the auricles was significantly reduced in animals irradiated at least 2 hours after gavage and was not observed in animals irradiated 4 or more hours after dosing. With respect to histology, inflammatory cell infiltration, edema, and hyperemia were noted in the dermis of animals irradiated immediately after gavage, whereas these conditions were significantly

reduced in animals irradiated 4 or more hours after dosing. Furthermore, skin phototoxicity was not noted after irradiation after a 6-hour interval. When female Hartley guinea pigs received simultaneous UVA and UVB irradiation at doses of 1.25, 2.5, 5, or 10 J/cm² after a single gavage dose of 0 or 160 mg/kg Pirfenidone to evaluate the relationship between Pirfenidone-induced skin phototoxicity and irradiance levels, erythema in the skin of the auricles was markedly reduced in severity with decreasing irradiance levels and was not observed in animals irradiated at 1.25 J/cm². Histological results showed a similar trend. However, marginal inflammatory changes were detected even after irradiation at 1.25 J/cm². When a single 160 mg/kg dose of ¹⁴C-Pirfenidone was administered by gavage (4.2.2.4-05), the radioactivity in the auricles showed a concentration-time profile similar to that in plasma (though the radioactive level in auricles was lower than that in plasma) and the unchanged drug accounted for a large part of radioactivity until 4 hours after gavage. These findings suggested that skin phototoxicity was associated with the concentration of the unchanged drug in the skin.

3.(iii).A.(6).3) Skin photosensitization study in guinea pigs (4.2.3.7-02)

Pirfenidone was administered by gavage to female Hartley guinea pigs shaved on the shoulder area at doses of 0, 40, or 160 mg/kg/dose or by a skin application of 0 or 5% (w/v) solution (100 µL) five times a week for 2 weeks. Immediately after each gavage or skin application, UVA and UVB were irradiated (10 J/cm²) simultaneously to sensitize the animals. Seventeen days after the last sensitization, Pirfenidone was again administered by gavage using the same dose as used in the sensitization or by a skin application of 0, 1, or 5% (w/v) solution (100 µL), immediately followed by UVA irradiation (14 J/cm²) to induce skin photoallergenicity. Neither route of administration caused any macroscopic skin abnormalities, demonstrating that Pirfenidone had no capability to photosensitize the skin.

3.(iii).A.(6).4) Photogenotoxicity studies

Photo-Ames tests using bacteria (4.2.3.7-06 and -08) and photo-chromosomal aberration tests using cultured cells derived from Chinese hamster lungs (4.2.3.7-07 and -09) were conducted to evaluate Pirfenidone and its major metabolite, pirfenidone-5-carboxylic acid. The photo-Ames tests of Pirfenidone and the 5-carboxylic acid metabolite and the photo-chromosomal aberration test of the 5-carboxylic acid metabolite produced negative results, while the photo-chromosomal aberration test of Pirfenidone showed a positive result, i.e., a dose-dependent increase in abnormal structures. A photo-chromosomal aberration test (4.2.3.7-10) of the photolyte (Photolyte-1) prepared using the same light irradiation conditions used in the previous photo-chromosomal aberration test of Pirfenidone produced a negative result. This indicated that the photolyte itself was unlikely to be involved in the induction of photo-chromosomal aberrations by Pirfenidone.

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

3.(iii).B.(1) Phototoxicity

In relation to the high frequencies of photosensitivity in clinical studies, PMDA asked the applicant to consider the necessity of conducting repeated-dose phototoxicity studies and to expand on the systemic effect of the phototoxicity-inducing substance.

The applicant responded that they would conduct a 4-week repeated-dose phototoxicity study with UV irradiation in hairless mice because both the skin outcomes after repeated dosing and UV irradiation and the systemic effect of the phototoxicity-inducing substance were still unknown.

Although the results of the study have not been provided yet, in consideration of the fact that repeated dosing and repeated exposure to light neither exacerbated skin lesions nor affected the

whole body in the preliminary studies, PMDA has no particular concerns about the cutaneous effect of the repeated onset of phototoxicity or the possible adverse systemic effect of the phototoxicity-inducing substance. The final results of the study are scheduled to be submitted before the Review Report (2) is prepared.

3.(iii).B.(2) Photogenotoxicity and photocarcinogenicity

Being aware of the likelihood that the phototoxic and photogenotoxic concentrations of Pirfenidone are close to each other, PMDA requested the applicant to consider (1) the possibility that photogenotoxicity is induced in the skin showing clinical photosensitivity, (2) the necessity of conducting a photocarcinogenicity study or an *in vivo* nonclinical study as an aid to the assessment of photocarcinogenicity, and (3) the need to include a cautionary statement in the package insert about photogenotoxicity and photocarcinogenicity.

The applicant responded as follows:

When the exposure levels were compared between the skin phototoxicity studies and the photo-chromosomal aberration test and the clinical studies, the C_{max} after the repeated dosing of 1800 mg/day (maximum daily dose) to humans was approximately 10 $\mu\text{g/mL}$, while the C_{max} in plasma at the dose at which inflammatory changes were observed in the dermis of the auricles in the phototoxicity study in guinea pigs was 11.9 $\mu\text{g/mL}$. In the photo-chromosomal aberration test using cultured cells derived from Chinese hamsters, cells with abnormal structures increased dose-dependently when the C_{max} was 16 $\mu\text{g/mL}$ or greater (the no observed effect level [NOEL] was <16 $\mu\text{g/mL}$). These findings suggested that the gap between the phototoxic and photogenotoxic concentrations was too small to rule out the possibility of gene damage at photoirradiated sites in humans. Based on these findings, the applicant considered the conduct of a photocarcinogenicity study and a skin photo-micronucleus assay as *in vivo* nonclinical studies. However, since it is clear that light damages genes and, therefore, the possibility of Pirfenidone exhibiting photocarcinogenicity cannot be ruled out, the applicant decided against the conduct of a photocarcinogenicity study or an *in vivo* nonclinical study as an aid to the assessment of photocarcinogenicity. The applicant instead plans to include as follows: **a.** a cautionary statement in the Important Precautions section of in the package insert to the effect that structural abnormalities of chromosomes were observed in a photogenotoxicity study and, therefore, the possibility of skin carcinogenicity associated with light exposure cannot be ruled out; and **b.** a cautionary statement in the Other Precautions section to the effect that photoirradiation induced structural abnormalities of chromosomes in a photo-chromosomal aberration test using cultured cells derived from Chinese hamster lungs and, therefore, the possibility of skin carcinogenicity associated with light exposure cannot be ruled out.

PMDA considers that the wording used in the cautionary statement should be changed to “light exposure has the potential to induce skin cancer,” based on the high probability of light exposure-related skin carcinogenicity.

3.(iii).B.(3) Melanin affinity

The risks of phototoxicity (skin irritation) and photogenotoxicity were discussed on the assumption that Pirfenidone is unlikely to be retained in the skin based on the results of tissue distribution and whole-body ARG studies in rats. However, the distribution of Pirfenidone was investigated only in albino animals and melanin affinity, a potentially important factor in the risk assessment of photosafety, was not considered. In view of this, PMDA asked the applicant to explain the appropriateness of the above discussion.

The applicant responded as follows:

The applicant conducted an additional whole-body ARG study in colored rats using ^{14}C -

Pirfenidone to evaluate melanin affinity of Pirfenidone. Radioactivity in the melanin-rich iris reached a peak 30 minutes post-dose, similar to that in the liver, and reduced thereafter. There was only a trace of radioactivity after 8 hours and no radioactivity observed after 24 hours. Furthermore, no difference was found in radioactivity transfer between the melanin-rich black skin and melanin-absent white skin. These findings indicated that Pirfenidone was unlikely to be accumulated in melanin-containing tissues.

3.(iii).B.(4) Carcinogenicity

In relation to the development of hepatocellular tumors in carcinogenicity studies, PMDA asked the applicant to give the rationale for regarding Pirfenidone's induction of hepatic drug metabolizing enzymes as phenobarbital-type.

The applicant responded that they had determined that the induction was phenobarbital-type by comparing the enzyme activity patterns as the markers for each CYP isozyme in rats and mice respectively, with data obtained from the literature (Parkinson A, et al. *Biochem Pharmacol.* 1992;43:2169-80, Nerurkar PV, et al. *Biochem Pharmacol.* 1993;46:933-43).

In the carcinogenicity study in mice, the pigmentation of Kupffer cells and hepatic single-cell necrosis were observed, suggesting the presence of continued liver damage. Also, it does not seem reasonable to attribute the development of hepatocellular tumors to the induction of drug metabolizing enzymes alone. For these reasons, PMDA asked the applicant to explain the possibility that continued hepatic damage causes hepatocellular tumors.

The applicant responded as follows:

The pigmentation of Kupffer cells was considered to be caused by unsaturated fatty acids generated through lipid peroxidation of cell membrane components. Single-cell necrosis was also noted in male animals. Based on these findings, the possibility that continued minor hepatocellular damage and subsequent reactive proliferation of cells contributed to the development of the hepatocellular tumors cannot be ruled out. In female animals, however, pigmentation was observed but single-cell necrosis was rare. Considering the results obtained from both genders, the hepatic drug metabolizing enzymes appeared to be a major contributor to the development of hepatocellular tumors.

PMDA asked the applicant to discuss the rationale for considering that the risk of hepatocellular tumors in humans is low, in relation to the finding that the human exposure levels largely exceeded the exposure at the non-carcinogenic doses in the carcinogenicity studies.

The applicant responded that although the human exposure levels largely exceeded the exposure at the non-carcinogenic doses in the carcinogenicity studies, the exposure levels appeared unlikely to induce drug metabolizing enzymes in humans and thus were unlikely to pose a risk of hepatocellular tumors in consideration of the following points: **a.** The increased incidence of hepatocellular tumors in mice and rats appeared to be attributable to the non-genetic damage effect associated with the induction of phenobarbital-type hepatic drug metabolizing enzymes. A human epidemiological study of phenobarbital reported that tumors did not develop even at dose levels suggesting enzyme induction (McLean EM, et al. *Bull Cancer.* 1990;77:505-8, Whysner J, et al. *Pharmacol Ther.* 1996;71:153-91). **b.** When the induction of human hepatic drug metabolizing enzymes was investigated using an *in vitro* human hepatocyte culture system (5.3.2.2-04), induction of CYP3A4/5 and CYP2C19 was noted only after exposure to a high Pirfenidone concentration (approximately 46 µg/mL), which exceeded the plasma concentration (C_{max} , approximately 10 µg/mL) obtained after repeated dosing of 1800 mg/day (maximum daily dose used in humans).

3.(iii).B.(5) Toxicity of metabolites

PMDA asked the applicant to explain whether they had fully evaluated the toxicity of the metabolites in humans based on the submitted toxicity study results.

The applicant responded that they believed that the toxicity of the metabolites had been sufficiently evaluated, giving the following information: The major metabolite was pirfenidone-5-carboxylic acid in all human studies and in the animal (rats and dogs) toxicity studies. The exposure to this metabolite in humans and animals was, respectively, approximately half and almost equivalent to the exposure to the unchanged drug. When the NOAELs (rats, 100 mg/kg/day; dogs, 20 mg/kg/day) in the repeated-dose toxicity studies in rats (6-month dosing) and dogs (9-month dosing) were compared with the human exposure to the 5-carboxylic acid metabolite after repeated dosing of 1800 mg/day (maximum daily dose of Pirfenidone used in humans) (5.3.3-08), the C_{max} in both animal species exceeded the clinical exposure and the AUC_{0-24hr} was comparable. In the repeated-dose toxicity studies, safety was evaluated up to 1000 mg/kg in rats and 200 mg/kg in dogs.

PMDA accepted the applicant's responses to the issues (1) to (5) above, with the proviso that cautionary statements about photogenotoxicity and photocarcinogenicity are included in the package insert as recommended. Phototoxicity, photogenotoxicity, photocarcinogenicity, and reproductive toxicity (an effect on pregnancy maintenance and child delivery of the dam, decreased birth rate, an effect on the development of pups) of Pirfenidone are significant clinical concerns. However, in light of the present situation that in the absence of established therapies for idiopathic pulmonary fibrosis which is a refractory disease with poor prognosis, PMDA concludes that Pirfenidone can be used in the treatment of humans, provided that the applicant takes appropriate measures to reduce those risks, including calling attention to such risks and ensuring that the patients are fully aware of them before the start of treatment.

4. Clinical data

4.(i) Summary of results of the clinical pharmacokinetic and pharmacodynamic studies

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

The results of four Japanese studies (5.3.2.1-01, 5.3.2.2-01 to 5.3.2.2-03) and one study conducted outside of Japan (5.3.2.2-04) evaluating the protein binding and metabolism of Pirfenidone in humans were submitted (these study results are presented in the section on non-clinical pharmacokinetics). In addition, as data for pharmacokinetic assessment, the results of a Phase I single dose study (5.3.3-04) and a multiple dose study (5.3.3-08) in healthy Japanese male adults, a food effect study (5.3.3-04), Phase II studies in patients with idiopathic interstitial pneumonia (5.3.3-09 and 5.3.5-01), and a Phase III study in patients with idiopathic pulmonary fibrosis (5.3.3-10) were submitted.

The concentrations of the unchanged drug, 5-carboxylic acid metabolite, and 5-hydroxymethyl metabolite in plasma, urine, serum, and serum ultrafiltrate after administration of Pirfenidone were determined using high performance liquid chromatography in accordance with validated procedures. The quantitation limits for plasma, serum ultrafiltrate, and urine concentrations of the unchanged drug were 0.100 µg/mL, 0.100 µg/mL, and 1.00 µg/mL, respectively. The quantitation limits for plasma and urine concentrations of 5-carboxylic acid metabolite were 0.100 µg/mL and 10.0 µg/mL, respectively. The quantitation limits for plasma and urine concentrations of 5-hydroxymethyl metabolite were 0.100 µg/mL and 2.00 µg/mL, respectively. In this report, pharmacokinetic parameters are expressed as the mean or mean ± standard deviation unless otherwise specified.

4.(i).A.1) Evaluation of pharmacokinetics in healthy adults

a. Single dose study in healthy Japanese adults (5.3.3-04, Study 1)

The plasma pharmacokinetics and urinary excretion of Pirfenidone were evaluated in 18 healthy Japanese male adults (excluding those given placebo) who received a single oral dose of 200, 400, or 600 mg under fasting conditions.

Plasma pharmacokinetic parameters are presented in the table below. As shown in the table, both the C_{max} and AUC_{0-48hr} of the unchanged drug and 5-carboxylic acid metabolite increased almost in proportion to the increase in the dose, and the T_{max} and $t_{1/2}$ were similar between dose levels. The urinary excretion rate of the unchanged drug up to 48 hours post-dose was lower than 1% at all dose levels (200 mg, $0.10 \pm 0.10\%$; 400 mg, $0.17 \pm 0.13\%$; 600 mg, $0.14 \pm 0.09\%$), while that of 5-carboxylic acid metabolite was approximately 90% at all dose levels (200 mg, $87.7 \pm 1.9\%$; 400 mg, $88.6 \pm 7.1\%$; 600 mg, $91.7 \pm 3.4\%$). This indicated that Pirfenidone was rapidly metabolized and excreted into urine primarily as 5-carboxylic acid metabolite.

Table. Pharmacokinetic parameters after a single dose in subjects under fasting conditions

	Dose (mg)	C_{max} ($\mu\text{g/mL}$)	T_{max} (hr)	AUC_{0-48hr} ($\mu\text{g}\cdot\text{hr/mL}$)	$t_{1/2}$ (hr)
Unchanged drug	200	3.88 ± 0.82	0.75 ± 0.27	13.97 ± 2.71	2.10 ± 0.45
	400	9.24 ± 1.74	0.58 ± 0.20	29.10 ± 11.77	1.96 ± 0.55
	600	10.57 ± 1.78	0.83 ± 0.26	37.03 ± 11.97	1.76 ± 0.40
5-Carboxylic acid metabolite	200	$2.99 \pm 0.97^{\text{a}}$	0.67 ± 0.26	$7.87 \pm 0.81^{\text{a}}$	1.80 ± 0.26
	400	$5.39 \pm 2.07^{\text{a}}$	0.58 ± 0.20	$14.88 \pm 1.81^{\text{a}}$	1.96 ± 0.67
	600	$7.00 \pm 1.44^{\text{a}}$	0.83 ± 0.26	$23.17 \pm 1.57^{\text{a}}$	1.93 ± 0.46

Mean \pm standard deviation, n = 6

a) The weight used for calculation is a value of Pirfenidone-5-carboxylic acid itself, not a value of Pirfenidone-equivalent weight.

b. Multiple dose study in healthy Japanese adults (5.3.3-08, Study 2)

The plasma pharmacokinetics and urinary excretion of Pirfenidone were evaluated in 12 healthy Japanese male adults who received multiple oral doses using a dose titration regimen (Period I, 200 mg/dose; Period II, 400 mg/dose; and Period III, 600 mg/dose) for 18 days in three 6-day periods. With the exception of Days 1 and 6 in each period, Pirfenidone was given three times daily after each meal. On Days 1 and 6 in each dosing period, Pirfenidone was given twice daily in the morning and afternoon and the pharmacokinetic parameters determined. Plasma pharmacokinetic parameters in each period are presented in the table below. As shown in the table, both C_{max} and AUC_{0-24hr} of the unchanged drug and 5-carboxylic acid metabolite increased in proportion to the increase in dose and there was no major difference in these parameters between Days 1 and 6 of each period. The urinary secretion rates of the unchanged drug and 5-carboxylic acid metabolite were also similar between Days 1 and 6 of each period, suggesting that multiple dosing had little effect on the pharmacokinetics of Pirfenidone.

Table. Pharmacokinetic parameters after post-meal repeated dose

	Dose (mg)	Date of dosing (aggregate)	C _{max0-4hr} ^{a)} (µg/mL)	T _{max0-4hr} ^{a)} (hr)	C _{max4-24hr} ^{b)} (µg/mL)	T _{max4-24hr} ^{b)} (hr)	AUC _{0-24hr} ^{c)} (µg·hr/mL)	t _{1/2} (hr)
Unchanged drug	200	1	2.71 ± 0.91	1.08 ± 0.47	2.83 ± 1.12	6.04 ± 1.05	19.17 ± 6.46	2.17 ± 0.30
		6	3.06 ± 1.28	1.08 ± 0.82	2.70 ± 0.51	6.29 ± 0.96	22.03 ± 5.47	2.25 ± 0.29
	400	1 (7)	4.94 ± 1.29	1.79 ± 0.89	6.22 ± 1.59	5.79 ± 1.36	46.13 ± 10.01	2.42 ± 0.48
		6 (12)	6.19 ± 1.89	1.17 ± 0.54	5.91 ± 2.09	6.38 ± 1.15	48.69 ± 11.21	2.36 ± 0.38
	600	1 (13)	8.20 ± 1.29	1.25 ± 0.45	9.21 ± 1.97	6.33 ± 1.15	77.22 ± 15.44	2.53 ± 0.42
		6 (18)	8.19 ± 1.54	1.71 ± 0.54	10.00 ± 1.70	6.13 ± 1.00	82.31 ± 16.50	2.55 ± 0.45
5-Carboxylic acid metabolite	200	1	1.85 ± 0.44 ^{d)}	1.17 ± 0.39	2.01 ± 0.42 ^{d)}	6.04 ± 1.05	12.63 ± 1.68 ^{d)}	2.15 ± 0.49
		6	1.78 ± 0.55 ^{d)}	1.17 ± 0.78	1.71 ± 0.36 ^{d)}	6.29 ± 0.96	12.73 ± 1.49 ^{d)}	2.33 ± 0.36
	400	1 (7)	2.78 ± 0.54 ^{d)}	1.67 ± 0.78	3.56 ± 1.07 ^{d)}	5.83 ± 1.32	24.88 ± 2.40 ^{d)}	2.47 ± 0.56
		6 (12)	3.28 ± 0.79 ^{d)}	1.33 ± 0.75	3.06 ± 0.57 ^{d)}	6.13 ± 1.09	25.54 ± 2.42 ^{d)}	2.55 ± 0.60
	600	1 (13)	4.10 ± 0.67 ^{d)}	1.25 ± 0.45	4.67 ± 1.03 ^{d)}	6.50 ± 1.17	38.09 ± 3.86 ^{d)}	2.80 ± 0.74
		6 (18)	3.84 ± 0.81 ^{d)}	1.75 ± 0.45	4.67 ± 0.75 ^{d)}	6.04 ± 1.05	38.65 ± 3.17 ^{d)}	2.81 ± 0.63

Mean ± standard deviation, n = 12

a) Value after dosing in the morning; b) Value after dosing in the afternoon; c) AUC_{0-24hr} after dosing twice a day;

d) The weight used for calculation is a value of Pirfenidone-5-carboxylic acid itself, not a value of Pirfenidone-equivalent weight.

c. *Ex vivo* protein binding rate (5.3.3-02)

When a single oral dose of 600 mg of Pirfenidone was given to healthy Japanese adults under fasting conditions, the serum protein binding rate of the unchanged drug at 1 and 3 hours post-dose was 56.36 ± 1.75% and 59.26 ± 2.50%, respectively.

4.(i).A.2) Food effect study (5.3.3-04: Study 1)

The effect of food intake on the plasma pharmacokinetics and urinary excretion of the unchanged drug and 5-carboxylic acid metabolite was evaluated in 6 healthy Japanese male adults who received a single 400 mg oral dose of Pirfenidone under fasting conditions or after a meal in a cross-over study. The T_{max}, C_{max}, t_{1/2}, and AUC_{0-48hr} of the unchanged drug in plasma after dosing under fasting conditions were 0.58 ± 0.20 hours, 9.24 ± 1.74 µg/mL, 1.96 ± 0.55 hours, and 29.10 ± 11.77 µg·hr/mL, respectively. Those after post-meal dosing were 1.83 ± 0.75 hours, 4.88 ± 1.72 µg/mL, 1.77 ± 0.55 hours, and 22.13 ± 10.63 µg·hr/mL, respectively. These results indicated that food intake significantly lowered C_{max} and AUC_{0-48hr} and significantly prolonged T_{max}. The urinary excretion rate of the unchanged drug and 5-carboxylic acid metabolite up to 48 hours post-dose was 88.74 ± 6.98% for dosing under fasting conditions and 84.67 ± 4.31% for post-meal dosing, demonstrating no significant difference.

4.(i).A.3) Evaluation of pharmacokinetics in patients

a. Phase II study (5.3.3-09 and 5.3.5-01, Study 3)

The plasma concentrations of the unchanged drug and 5-carboxylic acid metabolite were determined after the initial dose (200 mg) and during the multiple dose period in 15 Japanese patients⁴ with chronic idiopathic interstitial pneumonia who received Pirfenidone at a dose of 200 mg three times daily after each meal for 2 days, then at a dose of 400 mg three times daily after each meal for 2 days, and finally at a dose of 600 mg three times daily after each meal on consecutive days. As seen in the following table of pharmacokinetic parameters after the initial dose of 200 mg, changes in plasma concentrations in patients appeared to be comparable to those in healthy adults. After model analysis of the plasma concentration data for the unchanged drug and 5-carboxylic acid metabolite after the initial dose, the plasma concentrations for each patient for the time point immediately before the afternoon dosing on Day 3 in the multiple dose period, immediately before the afternoon dosing on Day 5 in the multiple dose period, and for 1 hour after the afternoon dosing on Day 7 in the multiple dose period were predicted using the model. There was only a small difference between the estimations and the actual measurements

⁴ Patients whose blood was collected over time at the initial dose

in subjects in whom the concentrations could be calculated. This suggested that multiple dosing had little effect on the pharmacokinetics of the unchanged drug and 5-carboxylic acid metabolite.

Table. Pharmacokinetic parameters after the initial dose

	Dose (mg)	C _{max} (µg/mL)	T _{max} (hr)	AUC _{0-last} (µg·hr/mL)	t _{1/2} (hr)
Unchanged drug	200	2.70 ± 0.70	1.76 ± 1.11	7.31 ± 1.58	3.53 ± 2.21 ^{a)}
5-Carboxylic acid metabolite	200	1.80 ± 0.55 ^{b)}	2.06 ± 0.96	4.85 ± 1.50 ^{b)}	3.74 ± 3.07 ^{c)}

Mean ± standard deviation, n = 15

a) n = 12; b) The weight used for calculation is a value of Pirfenidone-5-carboxylic acid itself, not a value of Pirfenidone-equivalent weight; c) n = 11

Logistic regression analysis was performed to evaluate the relationship between adverse drug reactions (ADRs) and C_{max} in Japanese patients with chronic idiopathic interstitial pneumonia (No. of patients analyzed for plasma pharmacokinetics: 73 receiving Pirfenidone + 35 receiving placebo = 108), by assuming the plasma concentration 1 hour after the afternoon dosing on Day 7 to be the C_{max} and assigning the presence or absence of ADRs occurring up to Day 7 to either of the following two values: 1 (present) or 0 (absent). The results showed that anorexia and queasy were significantly associated with C_{max} ($P = 0.011$ and $P = 0.038$, respectively).

b. Phase III study (5.3.3-10: Study 5)

Japanese patients with idiopathic pulmonary fibrosis assigned to the high dose treatment received Pirfenidone at a dose of 200 mg three times daily after each meal for 2 weeks, then at the dose of 400 mg three times daily after each meal for 2 weeks, and finally at a dose of 600 mg three times daily after each meal on consecutive days. Patients assigned to the low dose treatment received Pirfenidone at a dose of 200 mg three times daily after each meal for 4 weeks and subsequently at the dose of 400 mg three times daily after each meal on consecutive days (No. of patients analyzed for plasma pharmacokinetics: 93 receiving high doses + 50 receiving low doses + 98 receiving placebo = 241). The plasma concentrations of the unchanged drug and 5-carboxylic acid metabolite were determined immediately before the afternoon dosing in Week 12 (trough concentration) and 1-2 hours after the afternoon dosing (assumed to be the C_{max}). As shown in the table below, there was no significant difference between dose levels in the trough concentrations and C_{max} of the unchanged drug and 5-carboxylic acid metabolite per 100 mg of the drug administered.

Table. Plasma concentrations of the unchanged drug and 5-carboxylic acid metabolite in patients

	Dose level	Unchanged drug (µg/mL)	5-Carboxylic acid metabolite (µg/mL) ^{a)}
Trough	High	7.32 ± 3.60	3.83 ± 1.43
	Low	4.56 ± 3.14	2.38 ± 0.98
C _{max}	High	11.2 ± 5.6	5.60 ± 2.42
	Low	7.40 ± 3.58	3.96 ± 1.43

Mean ± standard deviation

a) The weight used for calculation is a value of Pirfenidone-5-carboxylic acid itself, not a value of Pirfenidone-equivalent weight.

Furthermore, logistic regression analysis was performed to evaluate the relationship between ADRs and C_{max}, by assigning the presence or absence of ADRs occurring up to Day 12 to either of the following two values: 1 (present) or 0 (absent). The results showed that C_{max} affected photosensitivity reaction, gamma-glutamyltransferase (GGTP) increased, and “anorexia +

decreased appetite” ($P < 0.001$, $P = 0.003$, and $P < 0.001$, respectively).

In consideration of these findings as well as the fact that food intake significantly lowers the C_{max} of Pirfenidone, it is planned that a cautionary statement to the effect that Pirfenidone must be taken after a meal will be inserted in the PRECAUTIONS section in the package insert to call users’ attention.

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

In light of the absence of studies to evaluate pharmacokinetic interactions, PMDA asked the applicant to explain the possibility of interactions with other drugs expected to be used concomitantly with Pirfenidone.

The applicant responded as follows:

Based on concomitant drugs used in Phase II and III studies, the most probable concomitant drugs include antitussives and expectorants as symptomatic treatments of the primary disease; vaccines to prevent infection, antibiotics, antipyretic analgesics, and cold remedies to treat infection because patients with idiopathic pulmonary fibrosis are prone to infection; and antiulcer drugs and antacids to treat gastrointestinal symptoms that would frequently develop after administration of Pirfenidone. In addition, Pirfenidone is unlikely to have pharmacokinetic interactions with other drugs for the following reasons: **a.** Pirfenidone is metabolized not by a particular CYP isoform but by multiple isoforms (CYP1A2, 2C9, 2C19, 2D6, and 2E1) and is therefore unlikely to be affected by CYP inhibition by concomitant drugs; **b.** Pirfenidone has a weak inhibitory effect on CYP1A, 2A6, 2C9, 2C19, and 3A4 but does not inhibit 2D6 or 2E1 and its major metabolite 5-carboxylic acid metabolite does not inhibit any of these CYP isoforms, either; **c.** Pirfenidone induces human hepatic CYP3A4/5 and 2C19 only after exposure to high concentrations and is therefore unlikely to cause such an induction at clinical doses; **d.** Pirfenidone has a low serum protein binding rate.

The applicant also explained that a foreign study to examine the pharmacokinetics of Pirfenidone in healthy adults who received Pirfenidone in combination with a liquid mixture of antacids (aluminum hydroxide, magnesium hydroxide, and simethicone) showed there was little likelihood of antacids affecting the pharmacokinetics of Pirfenidone.

Since ADRs such as photosensitivity reaction and gastrointestinal disorder occurred more frequently at greater exposure to Pirfenidone, PMDA asked the applicant to give their view on the impact of renal function on the occurrence of ADRs.

The applicant responded as follows:

In order to examine the relationship between creatinine clearance (Ccr) of the subjects and frequencies of adverse events (AEs) and ADRs associated with the administration of Pirfenidone, AEs and ADRs reported in Phase II and III studies were compiled for each term of AE/ADR and differences in the frequencies of those events/reactions were determined between subjects with impaired renal function ($Ccr < 80$ mL/min) and those with normal renal function ($Ccr \geq 80$ mL/min) by using Fisher’s exact test. The results showed that there was no significant difference for any term between the two groups [see the table below]. The safety of Pirfenidone in patients with severe renal disorder is unknown because such patients were excluded from the Phase II and III studies. Based on this, and in consideration of the renal involvement in the elimination of Pirfenidone, the inclusion of “patients with renal dysfunction” in the list of subjects in the Careful Administration section in the package insert is planned to call users’ attention to this potential problem.

Table. Relationship between Ccr and major adverse events in a Phase III study

Ccr (mL/min)	High dose		P value	Low dose		P value
	<80	≥80		<80	≥80	
No. of subjects analyzed	42	51		22	28	
Photosensitivity reaction	20 (47.6)	34 (66.7)	0.091	13 (59.1)	15 (53.6)	0.778
GGTP increased	11 (26.2)	12 (23.5)	0.812	6 (27.3)	6 (21.4)	0.743
Anorexia + decreased appetite	7 (16.7)	15 (29.4)	0.319	3 (13.6)	5 (17.9)	1.000

No. of subjects (%)

Although accepting the above response at present, the PMDA considers that the effect of concomitant drugs actually used in clinical settings needs to be evaluated in post-marketing surveillance. In addition, since only a limited number of patients with renal impairment were included in the clinical studies and since Pirfenidone may be used in patients with a more deteriorated renal function after product launch, the relationship of renal function with ADRs should be further investigated in post-marketing surveillance.

4.(ii) Summary of clinical efficacy and safety

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

In the application, data and information for efficacy and safety assessment derived from the results of a Japanese Phase II study (5.3.5-01, Study 3), an extended treatment study following a Japanese Phase II study (5.3.5-02, Study 4), and a Japanese Phase III study (5.3.5-03, Study 5) were submitted. The results of Phase I studies (5.3.3-01, Study 1; and 5.3.3-05, Study 2) were also submitted as data and information for safety assessment.

4.(ii).A.(1) Phase I studies (5.3.3-01: Study 1 [■■■■, 19■■ to ■■■■, 19■■]; 5.3.3-05: Study 2 [■■■■, 20■■ to ■■■■, 20■■])

4.(ii).A.(1).1 Study 1

A randomized, single-blind, placebo-controlled study (Steps 1 and 3) and a randomized, open-label, two-period, crossover study (Step 2, with a 1-week wash-out period) were conducted to evaluate the safety and pharmacokinetics of Pirfenidone in healthy Japanese male adults (target number of subjects, 22 [18 for Pirfenidone + 4 for placebo]) [for pharmacokinetics, see “(i) Summary of results of the clinical pharmacokinetic and pharmacodynamic studies”].

In Step 1, subjects received a single oral 200 mg dose of Pirfenidone or placebo under fasting conditions. In Step 2, subjects received a single oral 400 mg dose of Pirfenidone under fasting conditions or after a meal. In Step 3, subjects received a single oral 600 mg dose of Pirfenidone or placebo under fasting conditions.

Overall, 12 subjects experienced 18 AEs including abnormal laboratory values (AEs were compiled using Japanese Adverse Reaction Terminology [J-ART]). The events whose relationship with Pirfenidone could not be ruled out (adverse drug reactions [ADRs]) included one ADR of serum bilirubin increased in the 200 mg group; 2 ADRs of serum bilirubin increased, one ADR each of sleepiness and herpes labialis in the 400 mg group; 2 ADRs of serum bilirubin increased, one ADR each of queasy, heaviness of head, herpes zoster, white blood cell count increased, and monocyte count increased in the 600 mg group; and one ADR of sleepiness in the placebo group. No deaths or any other serious adverse events (SAEs) were reported.

4.(ii).A.(1).2 Study 2

A randomized, double-blind, placebo-controlled, intergroup comparison study was conducted to

evaluate the safety and pharmacokinetics of Pirfenidone in healthy Japanese male adults⁵ (target number of subjects, 15 [12 for Pirfenidone + 3 for placebo]) [for pharmacokinetics, see “(i) Summary of results of the clinical pharmacokinetic and pharmacodynamic studies”].

In the study, subjects received multiple oral doses using a dose titration regimen: 200 mg of Pirfenidone or placebo three times daily after each meal for 6 days in Period I; 400 mg of Pirfenidone or placebo three times daily after each meal for 6 days in Period II; 600 mg of Pirfenidone or placebo three times daily after each meal for 6 days in Period III, with the exception of Days 1 and 6 of each period, when the study drug was given twice daily in the morning and the afternoon).

Overall, 7 subjects given Pirfenidone and 1 subject given placebo experienced 15 and 5 AEs, respectively. The AEs (including abnormal laboratory values) were compiled using the MedDRA/J terminology. Adverse drug reactions included 3 ADRs of abnormal faeces, 1 ADR each of malaise and stomatitis in the 200 mg group; 2 ADRs of abnormal faeces and 1 ADR of stomatitis in the 400 mg group; 3 ADRs of somnolence and 1 ADR of abnormal faeces in the 600 mg group; and 1 ADR each of dizziness, nausea, asthenia, headache, and anorexia in the placebo group. One placebo-treated subject discontinued the study drug due to 5 AEs (dizziness, nausea, asthenia, headache, and anorexia). No death or any other SAEs were reported.

4.(ii).A.(2) Phase II study (5.3.5-01, Study 3 [REDACTED], 20[REDACTED] to [REDACTED], 20[REDACTED])

A randomized, double-blind, placebo-controlled, parallel-design study was conducted to evaluate the efficacy, safety and pharmacokinetics of Pirfenidone in patients with chronic idiopathic interstitial pneumonia⁶ (target number of subjects, 90 [60 for Pirfenidone + 30 for placebo]) [for pharmacokinetics, see “(i) Summary of results of the clinical pharmacokinetic and pharmacodynamic studies”].

The study consisted of a 7-day dose titration period and a 48-week treatment period. In the dose titration period, dose was titrated as follows: Subjects received Pirfenidone at a dose of 200 mg or placebo three times daily after each meal for 2 days (600 mg/day), then at a dose of 400 mg or placebo three times a day after each meal for 2 days (1200 mg/day), and finally at a dose of 600 mg or placebo three times daily after each meal for 3 days (1800 mg/day). If an adverse event developed, dose reduction was allowed and the dosage was individually determined for each subject. In the treatment period, subjects received Pirfenidone or placebo at the maintenance dose predetermined in the dose titration period three times a day after each meal. If an AE developed, dose reduction was allowed. If the investigator subsequently considered an increase in the dose to be acceptable, an increase in the dosage up to 1800 mg/day was allowed.

The safety analysis set consisted of all of the 109 treated subjects (73 given Pirfenidone and 36 given placebo). The full analysis set (FAS) for efficacy consisted of 107 subjects after excluding one subject given Pirfenidone who failed to meet the target disease criteria and 1 subject given placebo who failed to meet the severity criteria. The per protocol set (PPS) consisted of 93 subjects (60 given Pirfenidone and 33 given placebo) after excluding a further 14 subjects (9 subjects [7 given Pirfenidone and 2 given placebo] who discontinued the study drug less than 6 months of study medication due to AEs, and 2 subjects given Pirfenidone who violated the

⁵ This was an additional study conducted to examine the pharmacokinetics of Pirfenidone in detail in humans receiving multiple doses.

⁶ Patients who are 20 or more years old but younger than 75 years, diagnosed as having chronic idiopathic interstitial pneumonia based on the “Clinical Diagnostic Criteria for Idiopathic Interstitial Pneumonia (third edition)” by the MHW designated disease research group for diffuse lung diseases (high-resolution CT is essential but pathological examinations are optional), and have a PaO₂ at rest ≥ 70 Torr and SpO₂ during exercise $\leq 90\%$ within 1 month prior to enrollment.

protocol in terms of handling⁷, and 3 subjects excluded for other reasons.)

The Data and Safety Monitoring Board conducted an interim analysis⁸ on ■■■■■, 20■■■, based on data obtained after 6 months of study medication in all treated subjects excluding those who discontinued or dropped out of the study. The committee came to the following conclusions (■■■■■, 20■■■): (1) Although the values for arterial oxygen saturation (SpO₂) during exercise, the primary endpoint, in Pirfenidone-treated subjects suggested the efficacy of Pirfenidone, no significant difference was noted between them and placebo-treated subjects; (2) With respect to improvement in other parameters excluding vital capacity (VC), total lung capacity (TLC), diffusing capacity for carbon monoxide (DLco), and arterial O₂ pressure (PaO₂), a significant difference between the Pirfenidone groups and the placebo group or a trend suggesting superior efficacy of Pirfenidone was noted; (3) Acute exacerbation was observed disproportionately in placebo-treated subjects, indicating the necessity from an ethical point of view of terminating the study early and administering Pirfenidone to placebo-treated subjects. In response to the above recommendation, the double-blind study was terminated early⁹ (decoded on ■■■, ■■■■, 20■■■).

With respect to the primary endpoint¹⁰, SpO₂ during exercise in the FAS (primary parameter, SpO₂ area¹¹; secondary parameters, normalized SpO₂ area¹² and lowest SpO₂¹³), the mean SpO₂ area and the mean normalized SpO₂ area were adjusted by using baseline values as covariates. As shown in the following table of the adjusted means, there was no significant difference between the treatment groups for either parameter after 6 or 9 months of study medication. Likewise, no significant difference was noted between the treatment groups after either dosing period in the mean changes from baseline in SpO₂ area, normalized SpO₂ area, or lowest SpO₂.

⁷ A study drug with the wrong assignment number was prescribed.

⁸ In this study, for which two analyses (i.e., an interim analysis after 6 months of study medication and a final analysis after 12 months [at the end of the study]) were planned, the significance level for analysis of the primary endpoint was set at two-sided 0.025.

⁹ Data obtained after 9 months of medication was also analyzed because all subjects had completed the 9-month observations and examinations by the time of decoding.

¹⁰ Intergroup comparisons of primary and secondary endpoints were made only in subjects for whom data both at baseline and after 6 months of medication were available (if 6-month data were missing, the LOCF method was applied to replace missing data with data obtained at 3 months or later).

¹¹ Area enclosed between a straight line starting from the reference value (SpO₂ of 100%) on the longitudinal axis and running parallel to the horizontal axis and a curve connecting the data points for SpO₂ measured over time in a 6-minute walk test. For subjects in whom measurement of SpO₂ was terminated without completing a full 6-minute test, the value obtained at the time of termination was extrapolated parallel to the horizontal axis up to 6 minutes to determine the area.

¹² Area normalized by dividing the area up to the cessation of the walk by the duration time of the walk

¹³ The lowest SpO₂ obtained during a 6-minute walk test

Table. Comparison of SpO₂ area and normalized SpO₂ area

Parameter	Period	Pirfenidone (n = 66)	Placebo (n = 30)	P value ^{a)}
SpO ₂ area (logarithmic conversion)	6 months	8.13 ± 0.03	8.23 ± 0.05	P = 0.089
	9 months	8.12 ± 0.04	8.23 ± 0.06	P = 0.092
Normalized SpO ₂ area	6 months	9.04 ± 0.29	9.86 ± 0.43	P = 0.114
	9 months	8.79 ± 0.29	9.61 ± 0.44	P = 0.125

Adjusted mean ± standard error

a) Analysis of covariance with the baseline value as a covariate

Mean changes from baseline in VC, a secondary endpoint, in the FAS are presented in the table below. The VC change in subjects given Pirfenidone was significantly larger than that in those given placebo after 9 months of treatment, while there was no significant difference between the treatment groups after either the 6- or 9-month treatment periods in TLC, DLco, PaO₂ at rest, KL-6, or SP-D.

Table. Comparison of changes in VC

Parameter	Period	Pirfenidone (n = 67)	Placebo (n = 31)	Welch's t test
VC (L)	6 months	-0.01 ± 0.21	-0.08 ± 0.19	P = 0.100
	9 months	-0.03 ± 0.22	-0.13 ± 0.19	P = 0.037

Mean ± standard deviation

AEs (excluding abnormal laboratory values) compiled using J-ART were reported in 97.3% of subjects (71 of 73) given Pirfenidone and 88.9% of subjects (32 of 36) given placebo in the double-blinded period (dose titration period + treatment period). One subject given placebo died of interstitial pneumonia; this was considered to be unrelated to the study drug. SAEs other than death reported in the double-blinded period included 17 SAEs in 14 subjects given Pirfenidone (pneumonia in 3 subjects, abdominal distension/anorexia/common cold syndrome, common cold syndrome, vasculitis, interstitial pneumonia, ileus, cholangitis, pneumothorax/lower respiratory tract infection, viral infection, carcinoma hepatocellular, facial palsy, and epilepsy in 1 subject each) and 12 SAEs in 9 subjects given placebo (interstitial pneumonia in 3 subjects, pneumothorax, lower respiratory tract infection/chest pain/pleurisy, respiratory tract infection, pyrexia, pneumonia/interstitial pneumonia, and common cold syndrome in 1 subject each). Of these, 5 SAEs (abdominal distension, anorexia, cholangitis, facial palsy and epilepsy) in subjects given Pirfenidone and one SAE (pyrexia) in a subject given placebo were considered to be ADRs, all of which improved or resolved. AEs resulting in discontinuation of the study drug were 21 AEs (sun sensitivity [8 events], queasy [3 events], anorexia [2 events], pyrexia [2 events], and other AEs [1 each]) in the Pirfenidone group and 12 AEs (acute exacerbation of interstitial pneumonia [5 events], pyrexia [3 events] and other AEs [1 each]) in the placebo group.

Abnormal laboratory values were reported in 65.8% (48 of 73) of subjects given Pirfenidone and in 61.1% (22 of 36) of subjects given placebo in the double-blinded period. None of the abnormal laboratory values was serious. Abnormal laboratory values resulting in discontinuation of the study drug were 12 events (serum LDH increased [2 events] and other abnormal laboratory values [1 event each]) in the Pirfenidone group and 16 abnormal laboratory values (CRP increased [3 events], serum LDH increased [3 events], white blood cell count increased [2 events], and other abnormal laboratory values [1 event each]) in the placebo group.

ADRs were reported in 91.8% (67 of 73) of subjects given Pirfenidone and 47.2% (17 of 36) of subjects given placebo. ADRs associated with abnormal laboratory values were reported in 50.7% (37 of 73) of subjects given Pirfenidone and 27.8% (10 of 36) of subjects given placebo. The following table summarizes common ADRs.

Table. Common adverse drug reactions reported in the double-blinded period of Study 3 (frequencies $\geq 5\%$)

	Pirfenidone	Placebo
No. of subjects analyzed	73	36
Photosensitivity reaction	36 (49.3)	0 (0.0)
Anorexia	19 (26.0)	2 (5.6)
Nausea	17 (23.3)	2 (5.6)
Stomach discomfort	17 (23.3)	2 (5.6)
Malaise	12 (16.4)	1 (2.8)
Somnolence	11 (15.1)	5 (13.9)
Diarrhoea	11 (15.1)	2 (5.6)
Dyspepsia	10 (13.7)	1 (2.8)
Rash	6 (8.2)	2 (5.6)
Headache	6 (8.2)	1 (2.8)
Dizziness	5 (6.8)	1 (2.8)
Abdominal distension	6 (8.2)	1 (2.8)
Constipation	5 (6.8)	1 (2.8)
Vomiting	6 (8.2)	0 (0.0)
Pyrexia	4 (5.5)	1 (2.8)

	Pirfenidone	Placebo
Abnormal laboratory values		
GGTP increased	18 (24.7)	1 (2.8)
ALT increased	8 (11.0)	0 (0.0)
AST increased	6 (8.2)	1 (2.8)
Eosinophil count increased	6 (8.2)	1 (2.8)
ALP increased	4 (5.5)	1 (2.8)
Protein urine present	4 (5.5)	1 (2.8)
LDH increased	4 (5.5)	0 (0.0)

No. of subjects (%), compiled using MedDRA/J terminology

In response to the early termination of the double-blind study, the protocol of the study was revised as follows: After decoding, subjects assigned to placebo discontinued receiving placebo and those assigned to Pirfenidone could continue to receive Pirfenidone until the end of the study (i.e., Week 49) if they wished to do so. Subsequently, all subjects, including those originally assigned to placebo who wished to receive Pirfenidone, were able to continue to receive Pirfenidone; and the study period was extended to [REDACTED] 20 [REDACTED] (originally until [REDACTED] 20 [REDACTED]). A total of 68 subjects (42 subjects receiving continued doses of Pirfenidone and 26 subjects switching from placebo to Pirfenidone) enrolled in the extended treatment period. The longest total treatment duration (double-blinded period + extended treatment period) was approximately 95 weeks.

In the extended treatment period, death occurred in 3 subjects: 2 subjects switching from placebo to Pirfenidone (interstitial pneumonia and interstitial pneumonia/mediastinal emphysema/subcutaneous emphysema) and 1 subject receiving continued doses of Pirfenidone (pulmonary mycosis [invasive bronchopulmonary aspergillosis]). The pulmonary mycosis was considered to be related to Pirfenidone. SAEs, other than death, reported in the extended treatment period were 4 SAEs in 4 subjects switching from placebo to Pirfenidone (1 discrete SAE each) and 13 SAEs in 12 subjects (pneumonia [3 events], pneumothorax [2 events], and other SAEs [1 each]) receiving continued doses of Pirfenidone. Pneumonia, pyrexia, jaundice, and hepatic function disorder reported in subjects switching from placebo to Pirfenidone and interstitial pneumonia, gastric cancer, and renal cancer in subjects receiving continued doses of Pirfenidone were considered to be related to the study drug, all of which except gastric cancer improved or resolved. Nineteen AEs (sun sensitivity [3 events], anorexia [2 events], and other AEs [1 each]) and 22 abnormal laboratory values (CRP increased [2 events] and other abnormal laboratory values [1 event each]) resulted in discontinuation of the study drug during the extended treatment period.

Integrated analysis of the safety analysis set (99 subjects, 73 subjects receiving continued doses of Pirfenidone + 26 subjects switching from placebo to Pirfenidone) who received Pirfenidone throughout the study (double-blinded period + extended treatment period) showed that 98.0% of subjects (97 of 99) experienced AEs (including abnormal laboratory values). ADRs (excluding abnormal laboratory values) and abnormal laboratory values were observed in 88.9% (88 of 99) and 49.5% (49 of 99) of subjects, respectively, throughout the study. Common ADRs and

abnormal laboratory values included sun sensitivity (photosensitivity) in 50.5% (50 of 99) of subjects, anorexia in 29.3% (29 of 99), queasy in 22.2% (22 of 99), GGTP increased in 22.2% (22 of 99), stomach discomfort in 19.2% (19 of 99), sleepiness in 16.2% (16 of 99), malaise in 13.1% (13 of 99), heartburn in 11.1% (11 of 99), and GPT increased in 11.1% (11 of 99).

The applicant made the following claim: The findings above suggest that Pirfenidone prevents the deterioration of respiratory function associated with chronic idiopathic interstitial pneumonia and is thus expected to contribute to a better prognosis; and although ADRs including photosensitivity and gastrointestinal symptoms, were reported, if appropriate measures such as discontinuation/interruption of Pirfenidone and dose reduction were implemented the ADRs would improve or resolve.

4.(ii).A.(3) Extended treatment study following a Phase II study (5.3.5-02: Study 4 [REDACTED], 20[REDACTED] to [REDACTED], 20[REDACTED])

An open-label uncontrolled study was conducted following the Phase II study (Study 3) to evaluate the safety and efficacy of the continued administration of Pirfenidone in patients¹⁴ with chronic idiopathic interstitial pneumonia who wished to continue to receive doses of Pirfenidone.

In this study, subjects who had received Pirfenidone in Study 3 continued the dose regimen employed in Study 3, and those who had received placebo in Study 3 started receiving Pirfenidone at 600 mg/day and increased the dosage as appropriate up to 1800 mg/day. The treatment was scheduled to last until the end of March 2004 (the longest treatment period, approximately 92 weeks; the longest overall treatment periods including Study 3, 156 weeks or longer).

The safety and efficacy analysis set of Study 4 consisted of all the 49 subjects treated with Pirfenidone in Study 4 (34 from the Pirfenidone group and 15 from the placebo group in Study 3¹⁵). Of these, 26 subjects completed the treatment period and 23 subjects discontinued the study (16 subjects due to AEs, 5 due to the investigator's judgment, and 2 due to dropout or lost to follow-up).

In this study, death occurred in 8 subjects: interstitial pneumonia, myelodysplastic syndrome/infection MRSA, microscopic polyangiitis, interstitial pneumonia/respiratory failure, tension pneumothorax, severe pneumonia/sepsis, pulmonary embolism, and lung cancer in one subject each. The causal relationship of microscopic polyangiitis with the study drug could not be ruled out. One subject died (acute exacerbation of interstitial pneumonia) after post-study follow-up, and a causal relationship with the study drug could not be ruled out. Twenty-two subjects experienced 29 SAEs other than death (excluding abnormal laboratory values) compiled using J-ART. Common SAEs were pneumonia (7 events), pneumothorax (4 events), interstitial pneumonia (3 events), gastric cancer (2 events), lung cancer (2 events), and other SAEs (1 each). With respect to the 2 SAEs of lung cancer, 1 SAE each of gastric cancer, interstitial pneumonia, and vasculitis, a causal relationship with the study drug could not be ruled out; however, those SAEs except cancer improved or resolved. Nineteen AEs excluding

¹⁴ Subjects who were receiving systemic administration of a corticosteroid at a dose equivalent to more than 10 mg/day of prednisolone and those who had received steroid pulse therapy within 3 months prior to enrollment were excluded.

¹⁵ Of the 68 subjects (42 receiving continued doses of Pirfenidone and 26 switching from placebo to Pirfenidone) enrolled in the extended treatment period of Study 3, 48 subjects (35 receiving continued doses of Pirfenidone and 13 switching from placebo to Pirfenidone) who completed the extended treatment period of Study 3 and 2 subjects originally assigned to placebo in Study 3 who did not participate in the extended treatment period of Study 3 were enrolled in the Study 4 (the extended treatment study following the completion of the Phase II study). Of these, one subject who was in the Pirfenidone group in the Study 3 did not actually receive the study drug during the Study 4.

abnormal laboratory values (interstitial pneumonia [3 events], lung cancer [2 events], gastric cancer [2 events], pneumothorax [2 events], and other AEs [1 each]) resulted in the discontinuation of the study drug. There were 9 serious abnormal laboratory values: CRP increased, neutrophil count increased/lymphocyte count decreased/CRP increased, CRP increased/urine analysis abnormal (red blood cells urine)/cylindruria, white blood cell count increased/CRP increased (1 event each). Of these, CRP increased and CRP increased/urine analysis abnormal (red blood cells urine)/cylindruria were considered to be related to the study drug. One subject with CRP increased died (microscopic polyangiitis) and all other abnormal laboratory values improved or resolved. Eight abnormal laboratory values (CRP increased [2 events], urinary occult blood positive [2 events], cylindruria [2 events] and other abnormal laboratory values [1 event each]) resulted in the discontinuation of Pirfenidone.

In this study, an integrated analysis was performed combining data for the 50 subjects¹⁶ enrolled in the post-Study 3 extended treatment study with the findings obtained in Study 3. The mean cumulative treatment duration from Study 3 was 903 ± 273 days, the shortest durations were between 36 weeks and less than 48 weeks, and 42.0% of the subjects received the study drug for 156 weeks or longer. AEs (excluding abnormal laboratory values) and abnormal laboratory values were reported in 100.0% (50 of 50) and 86.0% (43 of 50) of treated subjects, respectively. ADRs (excluding abnormal laboratory values) were reported in 94.0% (47 of 50) and common ADRs (frequencies $\geq 10\%$) included sun sensitivity in 29 subjects (58.0%), queasy in 11 (22.0%), anorexia in 10 (20.0%), heartburn and stomach discomfort in 9 each (18.0%), sleepiness in 6 (12.0%), and diarrhoea and abdominal distension in 5 each (10.0%). ADRs associated with abnormal laboratory values were reported in 50.0% (25 of 50) of the subjects, and common ADRs associated with abnormal laboratory values included GGTP increased in 13 (26.0%), GPT increased and urinary occult blood positive in 7 each (14.0%), and ALP increased and CRP increased in 5 each (10.0%).

In light of the above, the applicant explained that although caution must be exercised due to the occurrence of ADRs including photosensitivity and gastrointestinal disorders, the fact that half of the subjects completed the scheduled treatment period suggested that the long-term administration of Pirfenidone was possible.

The applicant also explained that following the conclusion (based on the findings of Phase II studies, etc.) that the efficacy and safety of Pirfenidone had been confirmed; the applicant filed a new drug application in Japan in [REDACTED], 20[REDACTED]. The then Pharmaceuticals and Medical Devices Evaluation Center made the following points: **a.** Although the measurements of SpO₂ during exercise, the primary endpoint, suggested that Pirfenidone was effective, its efficacy was not sufficiently verified in the primary analysis population. **b.** Area of SpO₂ during exercise, the primary parameter, is not a widely recognized parameter and its appropriateness was not verified. **c.** Handling of the frequently developing photosensitivity, such as to what degree preventive measures can reduce the condition, needs to be studied. In response to these concerns, the applicant withdrew the application and decided to conduct a Phase III study additionally.

4.(ii).A.(4) Phase III study (5.3.5-03, Study 5 [REDACTED], 20[REDACTED] to [REDACTED], 20[REDACTED])

A randomized, double-blind, placebo-controlled, parallel-design study was conducted to evaluate the efficacy, safety, and pharmacokinetics of Pirfenidone in patients with idiopathic

¹⁶ The subject who did not receive the study drug in the Study 4 (extended treatment study following the Phase II study) was included.

pulmonary fibrosis¹⁷ (target number of subjects, 250 [100 for high doses of Pirfenidone + 50 for low doses of Pirfenidone + 100 for placebo]) [see “(i) Summary of results of the clinical pharmacokinetic and pharmacodynamic studies”].

The study consisted of a 4-week dose titration period and 48-week treatment period. In the dose titration period, subjects received Pirfenidone at a dose of 200 mg (low and high dose groups) or placebo three times a day after each meal for 2 weeks, then at a dose of 200 mg (low dose group) or 400 mg (high dose group) or placebo three times a day after each meal for 2 weeks. In the treatment period, subjects received Pirfenidone at a dose of 400 mg (low dose group) or 600 mg (high dose group) or placebo three times a day after each meal for 48 weeks. If an adverse event developed during the treatment period, appropriate dose reduction or interruption was allowed. Since the results of the Phase II study suggested that the lowest baseline SpO₂ affected the primary endpoint, subjects were stratified according to the level of the lowest baseline SpO₂ ($\leq 88\%$ and $\geq 89\%$).

The safety analysis set consisted of all the 271 treated subjects (109 given high doses, 55 given low doses, and 107 given placebo). The FAS for efficacy evaluation consisted of 267 subjects (108 given high doses, 55 given low doses, and 104 given placebo) excluding 4 subjects who failed to produce efficacy data due to AE-associated early discontinuation of the study medication. The PPS consisted of 234 subjects (86 given high doses, 47 given low doses, and 101 given placebo) excluding one ineligible subject, 13 subjects who discontinued the study before Week 27, 11 subjects who dropped out or was lost to follow-up before Week 27, 3 subjects who violated the protocol in terms of handling, and 5 subjects who failed to comply with the protocol in terms of handling.

At the initiation of the study, the lowest SpO₂ during exercise was used as the primary endpoint and progression-free survival and VC as key secondary endpoints. However, after reviewing blinded data from 208 subjects who were already scheduled to be included in the population for analysis with the aim of evaluating the impact of subjects who discontinued the study on efficacy assessment, the Data and Safety Monitoring Board concluded that VC was more appropriate as the primary endpoint than the lowest SpO₂. Following this conclusion, the protocol was revised so that VC was the primary endpoint and the lowest SpO₂ was a key secondary endpoint [see “Outline of the review by PMDA”].

The primary endpoint, mean changes in VC from baseline (adjusted by using the baseline VC as a covariate) at Week 52 (or at the final observation) in the FAS¹⁸ is presented in the table below. Comparison between the high dose and placebo groups, conducted as the primary analysis,¹⁹ revealed a significant difference between the two treatment groups. Likewise, comparison between the low dose and placebo groups, conducted as a secondary analysis, showed a significant difference between the two treatment groups.²⁰

¹⁷ Patients who are 20 or more years old but younger than 75 years, diagnosed as having idiopathic pulmonary fibrosis based on the Clinical Diagnostic Criteria for Idiopathic Interstitial Pneumonia (draft of the fourth edition) by the MHLW research group for diffuse lung diseases, and in whom a difference between SpO₂ at rest and SpO₂ during exercise in a 6-minute treadmill walk test is $\geq 5\%$ and the lowest SpO₂ during exercise is $\geq 85\%$.

¹⁸ Subjects for whom relevant data at Week 4 and thereafter were unavailable owing to the discontinuation of the study drug before Week 4 were excluded from the analysis of intergroup differences of the primary and secondary endpoints.

¹⁹ In this study, efficacy evaluation by comparing high doses of Pirfenidone and placebo was regarded as the primary analysis, and the evaluation of low doses was considered to be a secondary analysis to evaluate benefits and risks at reduced doses. Multiplicity was therefore not considered in comparison between the high dose and placebo groups and between other group combinations.

^{20, 22} On determining the necessary sample size based on the results of the Phase II study, the applicant considered the difficulties in recruiting a sufficient number of patients because this study targeted an orphan disease, and the statistical significance for efficacy was set at two-sided 0.1.

Table. Comparison of changes in VC (L)

	Adjusted mean ± standard error	Intergroup difference ± standard error (90% confidence interval [CI])	<i>P</i> value ^{a)}
High dose (n = 104)	-0.09 ± 0.02	0.07 ± 0.03 [0.01-0.13]	0.042
Low dose (n = 54)	-0.08 ± 0.03	0.09 ± 0.04 [0.02-0.16]	0.039
Placebo (n = 103)	-0.16 ± 0.02	-	-

(No. of subjects)

a) Analysis of covariance with the baseline value as a covariate

A secondary endpoint, mean changes from baseline in the lowest SpO₂ during exercise at Week 52 (or at the final observation) adjusted by using the lowest baseline SpO₂ during exercise as a covariate in the FAS is presented in the table below. There is no significant difference among treatment groups and the mean change in the high dose group was smaller than that in the placebo group.

Table. Comparison of changes in the lowest SpO₂ (%)

	Adjusted mean ± standard error	Intergroup difference ± standard error (90% CI)	<i>P</i> value ^{a)}
High dose (n = 99)	-1.70 ± 0.35	-0.17 ± 0.50 [-0.98 to 0.65]	0.739
Low dose (n = 53)	-0.84 ± 0.48	0.69 ± 0.59 [-0.29 to 1.67]	0.249
Placebo (n = 100)	-1.53 ± 0.35	-	-

(No. of subjects)

a) Analysis of covariance with the baseline value as a covariate

When cumulative progression-free rates were estimated by the Kaplan-Meier method (figure below) and the distribution of progression-free survival²¹ in the FAS was compared among treatment groups, a significant inhibition of disease progression was observed in the high dose group over the placebo group (*P* = 0.028, log rank test). There was also a significant difference between the low dose and placebo groups (*P* = 0.066, log rank test)²², while no significant difference was noted between the high and low dose groups (*P* = 0.911, log rank test).

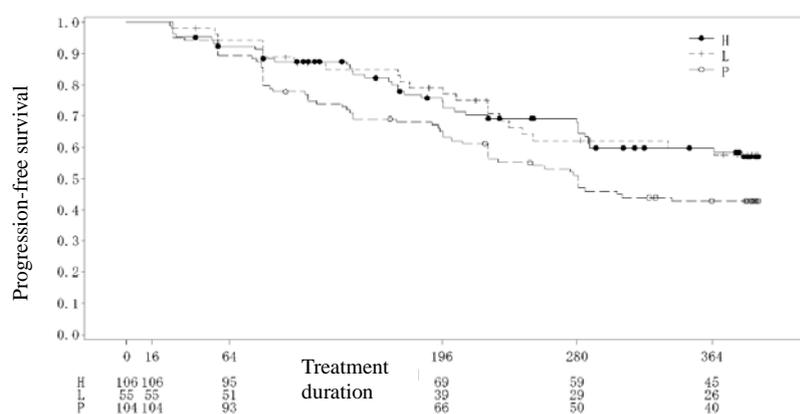


Figure. Distribution of progression-free survival by the Kaplan-Meier method

AEs (excluding abnormal laboratory values) compiled using the MedDRA/J terminology occurred in 100.0% (109 of 109) of subjects given high doses, 98.2% (54 of 55) of those given low doses, and 98.1% (105 of 107) of those given placebo. Death was reported in 3 subjects

²¹ Progression is defined as death or a ≥10% decrease in VC.

given high doses (idiopathic pulmonary fibrosis [2 subjects] and respiratory failure [1 subject]), 4 subjects given low doses (idiopathic pulmonary fibrosis [2 subjects], pneumonia bacterial [1 subject], and pneumonia [1 subject]), and 4 subjects given placebo (idiopathic pulmonary fibrosis [3 subjects] and completed suicide [1 subject]). Of these, 2 deaths in the high dose group (idiopathic pulmonary fibrosis [2 subjects]) and 2 deaths in the placebo group (idiopathic pulmonary fibrosis [1 subject] and completed suicide [1 subject]) were considered to be related to the study drug. Other SAEs were 28 SAEs (pneumonia [6 events], idiopathic pulmonary fibrosis [4 events], pyrexia [3 events], pneumothorax [2 events], acute bronchitis [2 events], and other SAEs [1 each]) in 23 subjects given high doses, 11 SAEs (pneumonia [3 events], pneumonia bacterial [2 events], and other SAEs [1 each]) in 8 subjects given low doses; and 31 SAEs (pneumothorax [5 events], respiratory tract infection [4 events], pneumonia [3 events], idiopathic pulmonary fibrosis [2 events], acute bronchitis [2 events], and other SAEs [1 each]) in 20 subjects given placebo. Of these, 9 SAEs (idiopathic pulmonary fibrosis [3 events], pyrexia [3 events], myalgia [1 event], gastric cancer [1 event], and lung neoplasm malignant [1 event]) in the high dose group, 1 SAE (lung neoplasm malignant) in the low dose group, and 4 SAEs (idiopathic pulmonary fibrosis [1 event], lung neoplasm malignant [1 event], squamous cell carcinoma of lung [1 event], and cerebral thrombosis [1 event]) in the placebo group were considered to be related to the study drug, and these SAEs except small cell carcinoma of the lung, gastric cancer, and lung neoplasm malignant in 1 subject each resolved or improved. AEs resulting in the discontinuation of the study medication were 20 AEs (idiopathic pulmonary fibrosis [4 events], photosensitivity reaction [3 events], pyrexia [2 events], respiratory failure [2 events], and other AEs [1 each]) in the high dose group, 13 AEs (idiopathic pulmonary fibrosis [2 events], photosensitivity reaction [2 events], and other AEs [1 each]) in the low dose group, and 13 AEs (idiopathic pulmonary fibrosis [4 events] and other AEs [1 each]) in the placebo group.

Abnormal laboratory values were reported in 62.4% (68 of 109) of subjects given high doses, 65.5% (36 of 55) of subjects given low doses, and 63.6% (68 of 107) of subjects given placebo. Three serious abnormal laboratory values (AST increased, ALT increased, and GGTP increased [1 event each]) were observed in one subject given high doses and a causal relationship with the study drug could not be ruled out. Abnormal laboratory values resulting in the discontinuation of the study medication included 2 abnormal laboratory values (AST increased and ALT increased [1 event each]) in the high dose group, 1 abnormal laboratory value (ALT increased) in the low dose group, and 1 abnormal laboratory value (MPO-ANCA increased) in the placebo group.

Adverse drug reactions (excluding abnormal laboratory values) were reported in 88.1% (96 of 109) of subjects given high doses, 78.2% (43 of 55) of subjects given low doses, and 68.2% (73 of 107) of subjects given placebo. ADRs associated with abnormal laboratory values occurred in 42.2% (46 of 109) of subjects given high doses, 36.4% (20 of 55) of subjects given low doses, and 20.6% (22 of 107) of subjects given placebo. Common ADRs associated with abnormal laboratory values are presented in the table below.

Table. Common adverse drug reactions in Study 5
(frequencies $\geq 5\%$ in at least one treatment group)

ADR	High dose	Low dose	Placebo
No. of subjects analyzed	109	55	107
Photosensitivity reaction	56 (51.4)	29 (52.7)	24 (22.4)
Anorexia	15 (13.8)	6 (10.9)	1 (0.9)
Stomach discomfort	11 (10.1)	6 (10.9)	9 (8.4)
Decreased appetite	9 (8.3)	2 (3.6)	1 (0.9)
Somnolence	3 (2.8)	4 (7.3)	3 (2.8)
Nausea	7 (6.4)	2 (3.6)	7 (6.5)
Dizziness	6 (5.5)	0 (0.0)	1 (0.9)
Rash	3 (2.8)	3 (5.5)	2 (1.9)

ADR	High dose	Low dose	Placebo
Abnormal laboratory values			
GGTP increased	18 (16.5)	8 (14.5)	6 (5.6)
CRP increased	13 (11.9)	4 (7.3)	5 (4.7)
ALT increased	9 (8.3)	2 (3.6)	6 (5.6)
LDH increased	8 (7.3)	1 (1.8)	3 (2.8)
AST increased	7 (6.4)	2 (3.6)	3 (2.8)
Cholesterol total increased	4 (3.7)	3 (5.5)	0 (0.0)

No. of subjects (%)

On the basis of the above, the applicant made the following claims: The findings that Pirfenidone reduced the deterioration of VC levels and prolonged progression-free survival suggest that Pirfenidone has the ability to inhibit the progression of idiopathic pulmonary fibrosis and that if any ADR develops, appropriate measures such as dose reduction and interruption can be taken to allow the continuation of treatment. Pirfenidone has thus been demonstrated to be useful.

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

4.(ii).B.(1) Reasons for and the appropriateness of the alteration of the primary endpoint in the Phase III study

PMDA asked the applicant to give the reasons for altering the primary endpoint during the conduct of the Phase III study in chronological detail because the alteration of the primary endpoint could have a significant impact on the interpretation of the study results.

The applicant responded as follows:

- When the Phase II study was conducted, efficacy parameters for idiopathic pulmonary fibrosis had not been established. The applicant therefore selected the lowest SpO₂ during exercise as the primary endpoint because this parameter seemed to most accurately reflect dyspnoea, a major cause of QOL deterioration, and also to be sensitive in responding to disease progression.
- Since the Phase II study showed a favorable result suggesting the efficacy of Pirfenidone, the lowest SpO₂ during exercise was again selected as the primary endpoint for the Phase III study. However, in consideration of the fact that the lowest SpO₂ during exercise was not an established parameter, the applicant selected VC and progression-free survival as key secondary endpoints to support the result of the primary endpoint.
- While the Phase III study was in progress, a validation study was also under way to evaluate the lowest SpO₂ during exercise in a 6-minute treadmill walk test in a research supported by Health and Labour Sciences Research Grants (a clinical study of an innovative therapy for idiopathic interstitial pneumonia). However, the validation study was not progressing smoothly and was unlikely to provide study results before the Phase III study was completed.
- In an in-house review of the interim data pooled from the Phase III study, the following concerns were raised: **a.** Numerous subjects discontinued the study, which may affect the assessment of the study drug. **b.** Although progression—a term used in progression-free survival—is defined as a $\geq 10\%$ decrease in VC, some subjects showed a temporary $\geq 10\%$ decrease in VC followed by recovery despite the previous assumption that once the VC level declines, it would never recover. **c.** Outliers were observed in temporal SpO₂ data. The case

review committee discussed these concerns and concluded that a third-party organization (Data and Safety Monitoring Board) should review in a blinded manner the data for 208 subjects, who were already scheduled to be included in the population for analysis, to evaluate the appropriateness of the analysis methodology (handling of missing data, definition of progression-free survival, and correlativity of changes in the lowest SpO₂ and those in VC).

- The Data and Safety Monitoring Board conducted a blinded review and recommended that the primary endpoint should be changed to VC and the secondary endpoints should be changed to the lowest SpO₂ during exercise and progression-free survival.
- After in-house discussion on the recommendations made by the committee, the applicant concluded that, based on the considerations listed below, it was appropriate to accept the recommendation to alter the primary endpoint from the lowest SpO₂ during exercise to VC:
 - a.** Since the validation study of the lowest SpO₂ during exercise in the treadmill walk test was not yet completed, its appropriateness as an endpoint was not fully verified.
 - b.** Clinical studies of idiopathic pulmonary fibrosis conducted outside of Japan reported that changes in forced vital capacity (FVC) over 6 or 12 months predicted prognosis (Latsi PI, et al. *Am J Respir Crit Care Med.* 2003;168:531-7, Collard HR, et al. *Am J Respir Crit Care Med.* 2003; 168:538-42, Flaherty KR, et al. *Am J Respir Crit Care Med.* 2003;168:543-8), and that a decrease in FVC by $\geq 10\%$ was an effective index for evaluating exacerbation of the condition (King TE, et al., *Chest.* 2005;127:171-7). Also, VC or FVC is increasingly being used as the primary endpoint in clinical studies because they are easy-to-measure parameters with good reproducibility (Ranghu G, et al. *N Engl J Med.* 2004;350:125-33, Demedts M, et al. *N Eng J Med.* 2005;353:2229-42).
 - c.** ■■■ Inc. employed %FVC as the primary endpoint in the Phase III study of Pirfenidone in Europe and the U.S. that was initiated in 20■■ and the primary endpoint was accepted by relevant regulatory authorities.
 - d.** In the Japanese Phase III study, VC was being measured every 4 weeks and thus the efficacy assessment seemed less likely to be affected by study discontinuation cases, compared to the lowest SpO₂ during exercise, which was measured only every 12 weeks.
 - e.** The unexpectedly large fluctuations between each time point in the lowest SpO₂ values observed in the Japanese Phase III study might compromise the reliability of the measurement results, and changes in the lowest SpO₂ were unlikely to be assessed correctly in 49 of 252 subjects who failed to complete a 6-minute walk test because SpO₂ reached the cut-off value (82%).

Recognizing the recent trend that %FVC has been becoming the mainstream as the primary endpoint in clinical studies of idiopathic pulmonary fibrosis conducted outside of Japan, PMDA asked the applicant to explain the appropriateness of selecting VC as the primary endpoint in view of relationships between the characteristics of idiopathic pulmonary fibrosis and changes in VC.

The applicant responded that it was reasonably appropriate to select VC as the primary endpoint because decreased pulmonary capacity is characteristic of idiopathic pulmonary fibrosis after consideration of the following points: Fibrosing of pulmonary interstitial tissues, characteristic of idiopathic pulmonary fibrosis, is thought to increase the elastic contractility of the lungs thereby decreasing the lung volume, pulmonary capacity, and pulmonary compliance and increasing the forced expiratory volume in 1 second percent (FEV₁%) (Mishima M. *Japanese Journal of Thoracic Diseases.* 2003;62:S55-60); and in the American Thoracic Society and the European Respiratory Society (ATS/ERS) International Consensus Statement, abnormal pulmonary functions such as restrictive ventilator defect (decreased VC often accompanied by an increase in the FEV₁/FVC ratio) and pulmonary gas exchange impairment (increased AaDO₂ or decreased DLco) were described as major diagnostic criteria for idiopathic pulmonary fibrosis (American Thoracic Society. *Am. J. Respir. Crit. Care Med.* 2000;161:646-64). The

applicant further presented the following reasons for changing the primary endpoint from the lowest SpO₂ during exercise to actual values of VC, which had originally been selected as a secondary endpoint, and newly adding a %VC-related parameter to correspond to %FVC, the primary endpoint used in clinical studies of Pirfenidone conducted outside of Japan: FVC was not selected as an endpoint in the Japanese Phase III study; and VC and FVC, both of which serve as indices of pulmonary capacity, are considered to have an equivalent clinical relevance in diseases associated with restrictive ventilation disorders such as idiopathic pulmonary fibrosis although, in the presence of obstructive ventilator defect, the two parameters produce largely different results from each other due to the occurrence of air trapping (Kanai I. *Kanai's Manual of Clinical Laboratory Medicine*. 1983;29:972-1045).

Understanding that the applicant could not help but select a rather explorative parameter as the primary endpoint in the circumstances in which no established parameters existed for the assessment of idiopathic pulmonary fibrosis at initiation of the Japanese Phase III study, PMDA finds it acceptable to alter the primary endpoint pertaining to Pirfenidone, considering the current global trend in drug efficacy studies of this disease and the fact that VC had originally been selected as a key secondary endpoint in parallel to SpO₂. PMDA also checked the blindness of the study data reviewed by the Data and Safety Monitoring Board and the independence of the committee by reviewing the written procedures and minutes provided by the applicant and concluded that there was no particular concern.

4.(ii).B.(2) Efficacy

Based on the observation in the Phase III study that the numerical difference in VC changes was only 70 mL between the high dose and placebo groups and that the VC changes and progression-free survival (a parameter related to VC) were the only parameters that suggested efficacy, and that no other parameters showed significant changes in synchrony with the VC changes, PMDA asked the applicant to give their view on how they could claim clinical relevance based on those results.

With respect to the discussion of the clinical relevance of Pirfenidone, the applicant presented the following findings reported in aforementioned papers: “the risk of death in subjects in whom FVC declined by ≥10% at 6 and 12 months was 2.06 times and 1.70 times, respectively, higher than that in

subjects with unchanged FVC” (Flaherty, et al.), “the risk of death in subjects in whom FVC declined by ≥10% during follow-up subsequently rose to be 2.4 times higher than that in subjects in whom FVC remained unchanged or increased” (King, et al.), and “changes in FVC at 6 and 12 months serve as prognostic factors” (Collard, et al.). Collard et al. also proposed a formula²³ for determining a hazard ratio from an observed percentage change, created by fitting a Cox proportional hazard model. The applicant further stated: When the formula proposed

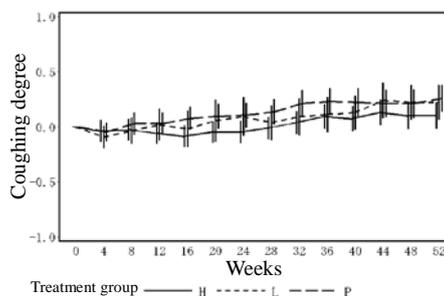


Figure. Changes in coughing over time

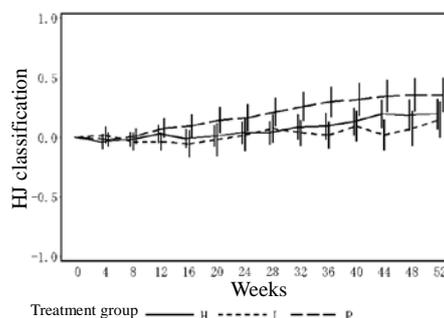


Figure. Changes in Hugh-Jones classification over time

²³ Hazard ratio for change (x) = $e^{[(x) \cdot \ln(\text{hazard ratio for unit change})]}$; where, x is a percentage change; hazard ratio for unit change is a hazard ratio per 6-month unit percentage change (1%) of 0.934 (hazard ratio at a percentage change of -10% is 1.979).

by Collard et al. was employed in determining hazard ratios from VC changes (-3.75% for the high dose group, -6.67% for the placebo group) at 12 months in the Phase III study, the hazard ratios for the two treatment groups were 1.292 and 1.577, respectively. The 5-year survival rates corresponding to those hazard ratios were 34.1% and 26.9%, respectively, showing a difference of 7.2% between the groups. Likewise, VC changes (-2.08% for the high dose group, -4.17% for the placebo group) at 6 months produced a difference of 5.3% in the 5-year survival rate between the high dose and placebo groups.

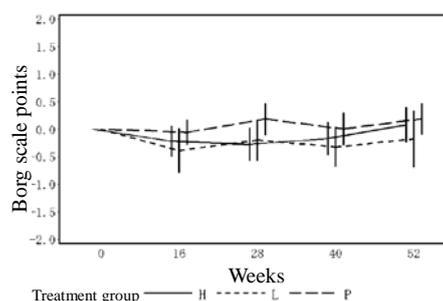


Figure. Changes in Borg scale values over time

In addition, when the applicant ex post compared changes in parameters of clinical symptoms – “degree of coughing,” “Hugh-Jones classification,” and “modified Borg scale” – at 52 weeks from baseline (Hugh-Jones classification and modified Borg scale are indices for assessment of breathlessness), no significant difference was detected in any parameter between the high dose and placebo groups. However, when changes over time in individual parameters were analyzed, as shown in the previous figure, changes observed in the Pirfenidone group were almost consistently larger than those in the placebo group, though an intergroup difference for each symptom was small. The applicant claimed that those findings also suggested the clinical relevance of Pirfenidone.

Taking into the account the fact that a temporary decrease in VC by $\geq 10\%$ followed by recovery was detected in some subjects during assessment of progression-free survival, PMDA requested that the applicant explain the reliability of VC measurements in clinical studies of Pirfenidone and also to examine whether an efficacy could be explained based on the progression-free survival even when those subjects were excluded from analysis and progression was defined as death or two consecutive decreases in VC by $\geq 10\%$.

The applicant claimed that VC-related findings obtained from the clinical studies of Pirfenidone were worth consideration for the following reasons: **a.** Analysis of the presence or absence of influencing factors at each time point of change in subjects showing large intraindividual VC changes revealed a possibility of respiratory adverse events being involved in such changes in some subjects but no other obvious influencing factors were identified. **b.** Analysis by study site showed no tendency of a disproportionate distribution of subjects with large intraindividual changes among study sites, indicating that no particular problem existed in VC measurement in the clinical studies of Pirfenidone. **c.** Although very few studies at present report VC changes over time in subjects with idiopathic pulmonary fibrosis, in particular, VC changes measured every month as in the clinical studies of Pirfenidone, the changes in %FVC observed every 3 months in placebo-treated subjects in a clinical study of INF- γ indicated that some subjects showed improvement in the face of an worsening trend observed in the overall population (Martinez FJ, et al. *Ann Intern Med.* 2005;142:963-7). The applicant also claimed that the results of the analysis of progression-free survival in this study was reliable for the following reasons: When, 39 subjects (11 receiving high doses, 8 receiving low doses, and 20 receiving placebo) in whom VC temporarily declined by $\geq 10\%$ and then increased or recovered to a decrease of $< 10\%$ at the final assessment or the discontinuation of the study were excluded from the analysis of the 119 subjects showing exacerbation (40 receiving high doses, 21 receiving low doses, and 58 receiving placebo) in the Phase III study, a log rank test comparing the distribution of progression-free survival between the placebo and high dose groups and between the placebo and low dose groups produced *P* values of 0.086 and 0.087, respectively. This led to

the conclusion that, as seen in the analysis results ($P = 0.028$ and $P = 0.066$, respectively) based on the definition of progression, Pirfenidone significantly prolonged progression-free survival compared to placebo. Additional analysis using death or two consecutive decreases in VC by $\geq 10\%$ as the definition of progression demonstrated that progression-free survival in the high dose group was significantly longer than that in the placebo group ($P = 0.059$), although there was no significant difference between the low dose and placebo groups ($P = 0.103$).

The Phase II study produced results for the lowest SpO₂ during exercise suggesting the efficacy of Pirfenidone, whereas the results for the lowest SpO₂ during exercise in the Phase III study were not indicative of the efficacy of Pirfenidone and furthermore a trend to exacerbation was observed in subjects receiving high doses of Pirfenidone compared to those receiving placebo. PMDA asked the applicant to give their view on why the results of these two studies were inconsistent with each other.

The applicant gave PMDA the following information:

In the Phase II study, “PaO₂ at rest ≥ 70 tor and SpO₂ during exercise $\leq 90\%$ (within 1 month prior to enrollment)” was used as an inclusion criterion related to severity. In the Phase III study, however, this criterion was replaced by “SpO₂ during exercise in a 6-minute treadmill walk test conducted at baseline meets both of the following two criteria: **a.** a difference between SpO₂ at rest and the lowest SpO₂ during exercise $\geq 5\%$ and **b.** the lowest SpO₂ during exercise $\geq 85\%$.” In addition, for the purpose of securing a sufficient number of patients completing the walk test, the walking pace on the treadmill was also changed from 40 to 80 m/min (which was used in the Phase II study) to 30 to 80 m/min for the Phase III study. These changes caused differences in the distribution of the walking pace and the lowest baseline SpO₂ between studies. Regression analysis was therefore performed on data derived from each study to evaluate the effects of the walking pace and lowest baseline SpO₂ on changes in the lowest SpO₂. The results suggested that the lowest baseline SpO₂ affected changes in the lowest SpO₂ in both studies and the walking pace affected changes in the lowest SpO₂ only in the Phase III study, demonstrating a different trend between the studies. The concurrent distribution of the walking pace and lowest baseline SpO₂ in the Phase III study is presented in the table below. Contrary to the expectation that the two parameters would correlate with each other, some subjects had a lowest baseline SpO₂ of $\geq 91\%$ despite slow walking, whereas others had a lowest baseline SpO₂ of $< 87\%$ despite fast walking. In addition, analysis of the relationships between the lowest baseline SpO₂ and changes in the lowest SpO₂ in the Phase III study produced seemingly conflicting results such as a larger decrease in the lowest SpO₂ in subjects with a lowest baseline SpO₂ of $\geq 91\%$ and a smaller decrease in the lowest SpO₂ in subjects with a lowest baseline SpO₂ of $< 87\%$. These findings suggested the following: Since the walking pace was adjusted to be faster for patients with a difference of $< 5\%$ between the SpO₂ at rest and lowest SpO₂ and to be slower for those with a lowest SpO₂ of $< 85\%$ in order to meet the relevant inclusion criteria of the Phase III study, patients with a severe condition may have been regarded, based on the lowest SpO₂ level, as having a mild condition, and patients with a mild condition may have been regarded as having a severe condition. In particular, more patients with an apparently mild condition may have been assigned to high doses of Pirfenidone rather than to placebo and those patients showed a large decrease in the lowest SpO₂, resulting in a failure to demonstrate the efficacy of Pirfenidone based on the changes in the lowest SpO₂.

Table. Concurrent distributions of the walking pace and lowest baseline SpO₂ in the Phase III study

	High dose					Placebo				
	Lowest baseline SpO ₂					Lowest baseline SpO ₂				
Walking pace	<87%	≥87% <89%	≥89% <91%	≥91%	Total	<87%	≥87% <89%	≥89% <91%	≥91%	Total
30 m/min	7	8	8	5	28	5	5	5	1	16
40 m/min	5	5	4	2	16	1	8	4	5	18
50 m/min	2	5	5	5	17	1	6	7	2	16
60 m/min	3	5	4	1	13	2	6	7	4	19
70 m/min	0	2	7	6	15	2	2	6	6	16
80 m/min	0	2	5	11	18	2	2	7	8	19
Total	17	27	33	30	107	13	29	36	26	104

The applicant provided PMDA with the following additional information:

The applicant performed a simple regression analysis using the lowest SpO₂ as a response variable and background factors and baseline factors as explanatory variables, thereby extracting as influencing factors a history of smoking, the presence or absence of previous treatments (corticosteroids), walking pace, lowest SpO₂, VC, TLC, and %VC. Among those factors, they selected %VC, lowest SpO₂, walking pace, and the presence or absence of previous treatments (corticosteroids) as variables and subsequently performed analysis of covariance using as covariates all six influencing factors and the four factors selected as variables, respectively. In either analysis of covariance, the inversion phenomenon observed between the high dose and placebo groups in terms of changes in the lowest SpO₂ was dissolved (-1.56 for the high dose group and -1.71 for the placebo group; -1.57 for the high dose groups and -1.65 for the placebo group, respectively).

In consideration of the fact that the numerical difference in the VC changes was marginal between the Pirfenidone and placebo groups in the Phase III study, and because the applicant's interpretation of the difference in relationship to clinical relevance appears nothing but speculation, PMDA does not think that those study results clearly indicate the clinical relevance of Pirfenidone. However, idiopathic pulmonary fibrosis is an intractable disease with poor prognosis associated with irreversible fibrosing of the lungs and there are no standard therapies for this disease that have been proved to be effective in improving patient survival and quality of life. In addition, the Japanese guidelines for the treatment of idiopathic pulmonary fibrosis (Committee for Preparing Guidelines for the Diagnosis and Treatment of Diffuse Pulmonary Diseases, the Japanese Respiratory Society, *The Manual for the Diagnosis and Treatment of Idiopathic Pulmonary Fibrosis*, 2004) define an achievable treatment target as "inhibiting exacerbation of the condition even if improvement is not attained." Under those circumstances, and considering that the Phase II and III studies produced reproducible results showing an inhibitory effect of Pirfenidone on VC exacerbation, which is characteristic of this disease, together with the fact that clinical symptoms also showed a similar trend, PMDA concludes that the efficacy of Pirfenidone has a acceptable level of clinical relevance. However, since only a limited number of patients were analyzed in the Japanese clinical studies, the efficacy of Pirfenidone should be further investigated in post-marketing surveillance as well as in ongoing clinical studies conducted outside of Japan.

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

4.(ii).B.(3).1 Rationale for dosage and administration

Since the proposed dosage and administration of Pirfenidone are not based on a dose-finding study, PMDA asked the applicant to provide the rationale for the proposed dosage and administration.

The applicant responded as follows:

Since idiopathic pulmonary fibrosis is an orphan disease, it would not be feasible to conduct a dose-finding study using multiple treatment groups with different dose levels. In this situation, the applicant selected a daily dose of 1800 mg—a figure obtained by multiplying 30 mg/kg/day by 60 kg (the assumed average body weight)—as a dosage to be verified in clinical studies based on the following considerations: **a.** In a US Phase I multiple-dose study of Pirfenidone (300 to 2400 mg/day; ascending 3-day multiple dosing at each dose level), the doses ≥ 1200 mg/day were associated with higher frequencies of adverse events and the doses ≥ 1800 mg/day were not tolerated by some subjects. **b.** In a US open-label clinical study of Pirfenidone in which a daily dose of 40 mg/kg was employed, 87% (47 of 54) of treated subjects experienced adverse drug reactions. **c.** In a Japanese clinical study (5.3.5-07), dose reduction from the planned 40 mg/kg/day to 30 mg/kg/day was necessary in some subjects. In addition, because a daily dose of 1800 mg caused adverse events requiring dose reduction in some subjects in the Japanese Phase II study, the applicant introduced an additional 1200 mg/day group to confirm the efficacy and safety of Pirfenidone at a reduced dose in the Japanese Phase III study.

With respect to the proposed dosage and administration of Pirfenidone, it is planned that Pirfenidone will be administered in a dose titration manner over 4 weeks, starting at a dose of 600 mg/day, then at 1200 mg/day, ultimately increasing to 1800 mg/day, to reduce the incidence of gastrointestinal disorders in the early dosing period. PMDA asked the applicant to give the rationale for the appropriateness of this regimen including the dose titration period.

The applicant responded as follows:

In the Phase II study in which the dose titration period was 7 days, it was not possible to increase the dose to 1800 mg/day in 10 of 73 subjects due to adverse events, mainly gastrointestinal disorders. A review of the cumulative frequencies of gastrointestinal disorders revealed that these AEs primarily developed early in the dosing period. This finding made the applicant aware of the need to extend the dose titration period and it was decided to use a 4-week dose titration period in the Phase III study. The proportion of gastrointestinal disorders occurring in the dose titration period versus the total incidence of gastrointestinal disorders decreased from 41.0% (64 of 156) in the Phase II study to 19.6% (30 of 153) in the Phase III study, and the proportion of subjects who discontinued the study drug due to gastrointestinal disorders also decreased from 7.1% (7 of 99) in the Phase II study to 1.8% (2 of 109) in the Phase III study. These findings indicated that 4 weeks was appropriate as the dose titration period.

Although not agreeing that the dosage and administration of Pirfenidone was fully studied, PMDA understands that it is difficult to give in-depth consideration to the dosage and administration based on clinical study results in idiopathic pulmonary fibrosis which is an orphan disease, and considers that the proposed dosage and administration poses no particular problems on the basis of the clinical study results obtained. However, in light of the fact that the tolerability of Pirfenidone has rarely been evaluated at a dose of ≥ 1800 mg/day in Japan and that the ongoing clinical study conducted outside of Japan is verifying the suitability of a high dose of 2403 mg/day, a higher dose might be more appropriate as the clinical dose of Pirfenidone. PMDA therefore thinks that the future results of the clinical study conducted outside of Japan should be thoroughly analyzed and the appropriateness of the dosage and administration of Pirfenidone should be further verified.

4.(ii).B.(3).2 Dose reduction

PMDA asked the applicant to provide information as to whether subjects who experienced AEs recovered or improved after dose reduction in the Phase II and III studies.

The applicant responded as follows:

Thirty-three AEs resulted in Pirfenidone dose reduction in the Phase II study, and 22 and 6 AEs resulted in the dose reduction in the 1800 mg/day and 1200 mg/day groups, respectively, in the Phase III study. Aside from 1 death, the outcome of which could therefore not be determined all other AEs recovered or improved. Furthermore, of the 119 AEs necessitating dose interruption (60 AEs in the Pirfenidone group of the Phase II study and 50 AEs in the 1800 mg/day group and 9 AEs in the 1200 mg/day group in the Phase III study) all recovered or the condition improved except for 2 AEs that remained unchanged. Most of the AEs resulting in dose reduction or interruption were photosensitivity and decreased appetite + anorexia.

A maintenance dose of 1200 mg/day (target dose after the recovery of AEs) is planned for subjects requiring dose reduction or interruption due to AEs. In view of the absence of a difference in the frequencies of any AEs such as photosensitivity, gastrointestinal disorder, and liver function test abnormal between the 1200 mg/day and 1800 mg/day groups in the Phase III study, PMDA asked the applicant to explain the appropriateness of 1200 mg/day as a maintenance dose for subjects requiring dose reduction or interruption due to AEs from the perspective of safety.

The applicant responded as follows:

Although no major difference was found in the frequencies of AEs and ADRs between the 1200 mg/day and 1800 mg/day groups, when the frequencies of significant AEs (defined as events necessitating dose reduction, interruption, or study discontinuation) were compared, subjects given 1200 mg/day had fewer significant AEs (23.6%, 13 of 55 subjects) than those given 1800 mg/day (44.0%, 48 of 109 subjects). These findings suggested that doses of 1200 mg/day were more likely to make continuation of dosing possible, even in patients requiring dose reduction or interruption due to AEs. In addition, with respect to photosensitivity, a Pirfenidone-related AE requiring special attention, subjects given 1200 mg/day tended to have milder events than those given 1800 mg/day (in the 1200 mg/day group, mild, 80.0% [32 of 40], moderate, 20.0% [8 of 40]; in the 1800 mg/day group, mild, 71.4% [50 of 70], moderate, 28.6% [20 of 70]). Furthermore, of 39 subjects who reduced the dose or interrupted the drug in the 1800 mg/day group of the Phase III study, 12 subjects (including one subject who developed 2 relevant AEs) recovered or improved after the dose was reduced to 1200 mg/day. These subjects included 8 subjects with photosensitivity, 1 with nausea, 2 with decreased appetite + anorexia, 1 with abdominal distension, and 1 with dizziness. These findings suggested the relevance of employing a maintenance dose of 1200 mg/day, particularly in subjects requiring dose reduction or interruption due to the occurrence of photosensitivity.

Considering that the expected therapeutic effect of Pirfenidone is to inhibit disease progression, the maintenance of an effective dose level throughout the treatment period is essential. From this perspective, PMDA understands the relevance of proposing as a guide a certain dose level that reduces AEs and also guarantees the efficacy of Pirfenidone in patients who experience AEs necessitating dose reduction or interruption. However, a dose of 1200 mg/day might not reduce AEs to a satisfactory level. PMDA therefore thinks that the safety and efficacy of the dose level of 1200 mg/day should be further evaluated and the appropriateness of using this dose level as a maintenance dose in patients requiring dose reduction or interruption should be investigated in post-marketing surveillance.

4.(ii).B.(4) Safety

In order to prevent photosensitivity, an adverse drug reaction characteristic of Pirfenidone administration, subjects participating in the Phase III study were instructed to avoid exposure to intense ultraviolet rays as much as possible by wearing long-sleeved clothes, a hat/cap and a

sunscreen when they were outdoors. It is also planned that a cautionary statement to this effect will be included in the package insert of Pirfenidone and other precautions will be taken in a post-marketing setting. PMDA asked the applicant to provide information on patient compliance with this instruction in the Phase III study and their view on whether this precaution is sufficient to prevent photosensitivity.

The applicant responded as follows:

Since the occurrence of photosensitivity and its severity largely depends on how long individual subjects are outdoors, it was difficult to collect survey data on the subjects' living environments. In the Phase III study, the applicant not only provided subjects with *Anterior XL* (a commercial sunscreen) but also allowed them to use other sunscreens. For this reason, an in-depth survey of patient compliance with the instruction was not conducted in the Phase III study. However, from a calculation based on the amount of the sunscreen distributed to the study sites, each subject appeared to have used approximately 4.4 tubes of the sunscreen (subjects were to receive a new tube of sunscreen in exchange for a used tube returned to the investigator), suggesting that subjects generally complied with the instruction on the use of the provided sunscreens. When the frequency of photosensitivity was compared between the Phase II study, in which sufficient precautions were not taken against photosensitivity, and the Phase III study, the frequency of photosensitivity in subjects given 1800 mg of Pirfenidone was similar between the two studies (49.3% [36 of 73 subjects] and 51.4% [56 of 109], respectively), whereas that in subjects given placebo was higher in the Phase III study (Phase II; 0% [0 of 36], Phase III; 22.4% [24 of 107]). This finding suggested that in response to the warnings against photosensitivity in the Phase III study, investigators and patients may have been more aware of photosensitivity, thus resulting in a higher reported frequency. This contention is supported by the increased frequency of mild photosensitivity in the Phase III study. The frequency of photosensitivity by severity in the studies was as follows: mild, 48.0% (24 of 50 events) and moderate, 52.0% (26 of 50) in the Phase II study; mild, 71.4% (50 of 70) and moderate, 28.6% (20 of 70) in the Phase III study. Among subjects experiencing photosensitivity in the Phase II and III studies, 10.9% (8 of 73) and 2.8% (3 of 109), respectively, discontinued the study drug. These findings indicated that the Phase III study had fewer moderate events of photosensitivity and also fewer subjects who discontinued the study drug. On the basis of these findings, although not completely preventing photosensitivity, the current measures to avoid exposure to ultraviolet rays can reduce it to the level observed in the Phase III study.

PMDA considers it extremely important that patients be well aware of the risks and benefits of Pirfenidone and keep taking appropriate precautions against exposure to ultraviolet rays for the following reasons: **a.** In view of the facts that photosensitivity developed frequently in subjects receiving Pirfenidone and that a nonclinical study showed that the phototoxicity-inducing concentration of Pirfenidone was close to the photogenotoxicity-inducing concentration, there is a possibility that exposure to sunlight will cause skin cancer. **b.** Dose reduction or interruption due to the occurrence of photosensitivity may affect the therapeutic effect of Pirfenidone. PMDA therefore considers it necessary to distribute easy-to-follow information materials describing risks of photosensitivity associated with use of Pirfenidone and specific precautions against exposure to ultraviolet rays as well as to include a cautionary statement in the package insert so that all patients receiving Pirfenidone will without fail take necessary precautions. In addition, since the results of the Phase III study suggested a possibility that the current precautions against exposure to ultraviolet rays will not have a sufficient preventive effect, the post-marketing surveillance should include a detailed survey of the occurrence of photosensitivity, a consideration of the necessity of taking stricter precautions, and the evaluation of the risk of skin cancer in long-term use in relation to the occurrence of photosensitivity, its severity, and the time of onset.

4.(ii).B.(5) The clinical positioning of Pirfenidone

Corticosteroids, immunosuppressants, and other drugs are currently used in the treatment of idiopathic pulmonary fibrosis. PMDA asked the applicant to give their view on how Pirfenidone is positioned in clinical use in comparison with these drugs.

The applicant responded as follows:

The ATS/ERS International Consensus Statement tentatively recommended a combination of a corticosteroid and an immunosuppressant as the drug therapy for idiopathic pulmonary fibrosis. This recommended therapy is basically regarded as the standard treatment in Japan as well. However, considering the possibilities of these drugs inducing adverse drug reactions, a cautious stance is taken in using them in patients with this disease and, in reality, a non-treatment approach (with follow-up) is taken as an option for some patients. Since the study population in the Phase III study consisted mainly of patients with relatively mild severity, and who were under follow-up without any particular treatment before enrollment, the applicant believes, based on the results of the study, that Pirfenidone should first be used mainly in treatment-naïve patients. The applicant also predicts that if the use of Pirfenidone aggravates the patient's condition, Pirfenidone will be replaced by corticosteroids or immunosuppressants or these drugs will be added to the treatment regimen.

Table. Disposition of the patients receiving corticosteroids or other drugs concurrently in the Phase III study

Pretreatment	Category	High dose	Low dose	Placebo
No. of subjects evaluated		108	55	104
Corticosteroids	No	99 (91.7)	49 (89.1)	98 (94.2)
	Yes	9 (8.3)	6 (10.9)	6 (5.8)
Drugs other than corticosteroids*	No	86 (79.6)	42 (76.4)	83 (79.8)
	Yes	22 (20.4)	13 (23.6)	21 (20.2)

No. of subjects (%), *carbocysteine, clarithromycin, etc.

Although combination therapies using Pirfenidone and corticosteroids and/or immunosuppressants have not been studied in a clinical setting, the applicant considers that Pirfenidone can be concurrently used with these drugs for the following reasons: **a.** Nonclinical studies demonstrated that Pirfenidone has a weak immunosuppressive effect. **b.** Pirfenidone has only a weak capacity to induce/inhibit hepatic drug metabolizing enzymes and the metabolism of Pirfenidone involves multiple drug metabolizing enzymes. This suggests that Pirfenidone is unlikely to cause pharmacokinetic interactions with other drugs. **c.** The results of the Phase III study in terms of adverse events suggested that Pirfenidone is unlikely to increase the risk for immunocompromised conditions. **d.** The occurrence of photosensitivity associated with corticosteroids or immunosuppressants has not been reported to date. The use of these drugs with Pirfenidone is therefore unlikely to exacerbate photosensitivity, an AE specific to Pirfenidone.

PMDA thinks that the position of Pirfenidone in the pharmaceutical treatment of idiopathic pulmonary fibrosis should be further elucidated in relation to changes in VC levels and prognosis. The clinical studies of Pirfenidone were all conducted mainly in treatment-naïve patients with relatively mild severity. However, given the present situation in which there is no established standard therapy for idiopathic pulmonary fibrosis, Pirfenidone is likely to be used in a wider range of patients including those with severe conditions once it becomes commercially available. For this reason, the effects of various factors such as severity, age, complications, and concomitant drugs on the efficacy and safety of Pirfenidone should also be evaluated in post-marketing surveillance.

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

1. PMDA's conclusion on the results of document compliance review

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

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

The GCP on-site inspection conducted in accordance with the provisions of the Pharmaceutical Affairs Law for the documents appended to a new drug application (5.3.3-05, 5.3.5-02, and 5.3.5-03) revealed the following problems at some study sites: inappropriate management of the institutional review board (IRB) such as a failure to consult the IRB on whether the study should be continued or not in relation to reports notified by the sponsor on unexpected serious adverse drug reactions etc.; deviations from the protocol (e.g., a failure to conduct a patient examination upon study discontinuation); and a failure to keep source documents (some consent forms). However, PMDA found no major concerns and concluded that there should be no problem with conducting the regulatory review based on the application dossier submitted.

IV. Overall Conclusion

PMDA has concluded that the data and information submitted demonstrate a certain degree of efficacy of Pirfenidone for use in the treatment of idiopathic pulmonary fibrosis.

With respect to safety, photosensitivity frequently occurred, which suggests that Pirfenidone has a photocarcinogenic potential. However, in light of the present situation for the treatment of idiopathic pulmonary fibrosis, PMDA has concluded that Pirfenidone may be approved, provided that no particular problems are identified, taking into consideration expert advisors' opinions, after the applicant takes such measures as **a.** having patients fully understand the risks and benefits of Pirfenidone before starting the treatment, **b.** closely investigating the incidence of skin cancer in the post-marketing surveillance, and **c.** carefully following up patients treated with Pirfenidone and further investigating the safety in clinical use after the product launch because adverse drug reactions including gastrointestinal disorders and liver function test abnormal were observed.

Review Report (2)

August 20, 2008

Based on the Expert Discussion, the Pharmaceuticals and Medical Devices Agency (PMDA) additionally reviewed the following points and took the necessary measures. The expert advisors attending the Expert Discussion have stated that, with respect to the relationship with the product submitted for registration, none of them falls under the category stipulated in Section 1 or 2 (1) of “Regarding immediate measures against the problem of conflict of interests involving an outside expert for PMDA” (dated May 8, 2007).

1. Ensuring the appropriate use of Pirfenidone

Based on the matters discussed in the Expert Discussion, PMDA recommended that, to ensure that Pirfenidone will be used appropriately, the applicant prepare guidelines for the appropriate use of Pirfenidone describing how to diagnose idiopathic pulmonary fibrosis, cautions against photosensitivity and other adverse drug reactions, how to prevent and treat these reactions, and the necessity of obtaining informed consent. PMDA also asked the applicant to provide physicians with information on the diagnostic criteria employed in the Phase III study until the guidelines are completed. The applicant responded that they would prepare the guidelines as soon as possible in cooperation with the academic societies concerned, and would include the diagnostic criteria employed in the Phase III study in the section on clinical studies in the package insert.

PMDA further recommended that the applicant include in the WARNING section in the package insert a statement to the effect that Pirfenidone should be used under the supervision of a physician who is well versed in the treatment of idiopathic pulmonary fibrosis, because the differential diagnosis of idiopathic pulmonary fibrosis from idiopathic interstitial pneumonia or other similar diseases is essential for Pirfenidone to be used appropriately. In addition, since Pirfenidone tested positive for photogenotoxicity, PMDA recommended that the applicant include in the WARNING section of a statement to the effect that the possibility of light exposure causing skin cancer should be adequately explained to, and fully understood by, the patient before starting the treatment, and also include in the Other Precautions section a statement to the effect that Pirfenidone’s phototoxic (photosensitivity) concentration in plasma and the photogenotoxic concentration are close to each other. The applicant accepted these recommendations.

2. Repeated-dose phototoxicity study

The applicant conducted an additional repeated-dose phototoxicity study in hairless mice to evaluate the systemic effect of phototoxicity and the outcomes for the skin symptoms. The study results submitted are summarized as follows:

Pirfenidone was administered to hairless mice by gavage at a dose of 0 or 500 mg/kg/day for 1 month. Immediately after each gavage, the animals were irradiated with UV (5 J/cm²). Treatment with Pirfenidone followed by UV irradiation induced skin phototoxicity. However, treatment for 1 month did not exacerbate the skin response (erythema) observed. Histopathology of the skin showed some histological changes, including epithelial hyperplasia in the shoulder skin and auricles and single-cell necrosis, but these findings recovered to a satisfactory level in the 1-month recovery period. No abnormalities were found in blood chemistry or the histopathology of the internal organs and tissues, demonstrating that the skin phototoxicity had no systemic effect under the conditions of this study.

Based on the study results that repeated doses of Pirfenidone and repeated UV irradiations were not associated with the exacerbation of the skin lesions or any systemic effect, PMDA found no particular concerns about the effect of the repeated onset of phototoxicity on the skin or the adverse systemic effect of the phototoxicity-inducing substance.

3. Comparison with the results of clinical studies conducted outside of Japan

Since only a limited number of patients were evaluated in the Japanese clinical studies, PMDA requested that, when the results of the clinical study being conducted by [REDACTED], which is undertaking the clinical development of Pirfenidone outside of Japan, become available, the applicant compare the results with those obtained from Japanese studies, further evaluate the efficacy and safety of Pirfenidone and the appropriateness of the dosage in detail, and report the results of their review to PMDA as soon as possible.

The applicant responded that they would obtain the results of clinical studies conducted outside of Japan with the consent of [REDACTED], which is undertaking the clinical development of Pirfenidone outside of Japan, and report the detailed results of a comparative review of the study results from Japan and those from outside of Japan.

4. Post-marketing surveillance, etc.

Because the sample sizes employed in the clinical studies were small, photosensitivity occurred frequently, and light exposure may cause skin cancer, PMDA requested the applicant to plan such post-marketing surveillance as necessary to allow further evaluation of the safety and efficacy of Pirfenidone including safety and efficacy after long-term use.

The applicant responded that the post-marketing surveillance is scheduled to cover all patients treated with Pirfenidone. They further provided additional information on the surveillance as follows: **a.** The target number of patients will be approximately 1000. **b.** Whether appropriate patients have been selected or not will be checked based on the fourth revision of the clinical diagnostic criteria for idiopathic pulmonary fibrosis prepared by the MHLW research group for diffuse lung diseases. **c.** Patients will be followed up for 1 year, except those receiving continued doses of Pirfenidone who will be followed up for a further year, to investigate the incidences of adverse events (e.g., photosensitivity, gastrointestinal disorder, and liver function test abnormal) in clinical use. **d.** For patients developing skin cancer, the relationships between the presence or absence of photosensitivity, the severity of photosensitivity, and the time of onset will be evaluated. **e.** Appropriate efficacy parameters will also be selected for the surveillance.

PMDA considers that the applicant should conduct the surveillance as soon as possible and provide the clinical communities with newly obtained information without delay.

With respect to the dosage and administration, since patient age was not sufficiently evaluated in the clinical studies, the reference to age has been deleted from the description of appropriate dose increase/reduction.

On the basis of the above review, PMDA has concluded that Pirfenidone may be approved for marketing, provided that the dosage and administration is described as shown below. PMDA has also concluded that the re-examination period is 10 years, the drug substance and the drug product are designated as powerful drugs, and the drug product is not classified as a biological product or specified biological product.

[Dosage and administration]

The usual initial dosage for an adult is an oral dose of 200 mg of Pirfenidone administered three times daily (600 mg/day) after a meal, which is increased in increments of 200 mg up to 600 mg (1800 mg/day) while observing the patient's condition. The dose may be increased or decreased according to the symptoms observed.

(Appendix)

The summary of the submitted data and the outline of the review by PMDA regarding the drug master file (DMF) for Glaspia 200 mg Tablet (DMF No. 220MF10130)

[Brand name]	Pirfenidone
[Non-proprietary name]	Pirfenidone
[Name of submitter]	Signa S.A. de. C.V.
[DMF No.]	220MF10130

Summary of the submitted data pertaining to the drug substance

The manufacturing process for the drug substance consists of Step 1 ([REDACTED]), Step 2 ([REDACTED]), and Step 3 ([REDACTED]), and [REDACTED] and [REDACTED] are used as the starting materials. Step 1 is regarded as the critical process step, for which control items and control values are set for [REDACTED].

Outline of the review by PMDA

With regard to the manufacturing process for the drug substance and the fact that only Step 1 [REDACTED] is going to be registered as the reaction step, PMDA asked the DMF holder to explain whether or not it can be ensured that the quality of the drug substance is controlled adequately.

The DMF holder explained its view that the quality of the drug substance can be controlled on the grounds that (1) the starting material, [REDACTED], is [REDACTED], and [REDACTED], and that the starting materials for the production of Pirfenidone are manufactured in-house by Signa S.A. de. C.V. or by [REDACTED], and (2) that the following acceptance testing specifications are set to ensure the quality control of the drug substance: physical description, identification, purity ([REDACTED], [REDACTED]%; [REDACTED], [REDACTED]%), loss on drying, and assay.

PMDA asked the DMF holder to set the specifications for the reference materials used in the manufacture of the drug substance. The DMF holder complied with PMDA's request.

PMDA accepted these responses, and concluded that the quality control for the drug substance manufacturing process is adequate.

PMDA notes with concern that during the review process there were often times when the manufacturer on the DMF holder's side, the overseas registration representative, and the local administrative agent ("in-country caretaker") were not operating in close cooperation. In relation to this matter, some improvements, including replacement of the local administrative agent were made; however, because the lack of cooperation can result in potentially serious consequences in the case of problems, for example, quality control-related issues on the drug substance manufacturer's side, PMDA urged the local administrative agent to have a better understanding of the importance of creating a cooperative working relationship.