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RESEARCH**

APPLICATION NUMBER:

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	October 9, 2014
From	Banu Karimi-Shah, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA# 22-535
Applicant	InterMune, Inc.
Date of Submission	May 23, 2014
PDUFA Goal Date	November 23, 2014
Proprietary Name / Established (USAN) names	Pirfenidone/ Esbriet
Dosage forms / Strength	Hard Gelatin Capsule/ 267 mg
Proposed Indication	Treatment of patients with idiopathic pulmonary fibrosis (IPF)
Recommended:	Approval

1 Introduction

On May 23, 2014, InterMune provided a resubmission to New Drug Application (NDA) #22-535 for pirfenidone for the treatment of patients with idiopathic pulmonary fibrosis (IPF). Pirfenidone is a new molecular entity, and has been granted orphan drug, fast track, and breakthrough designations. The proposed tradename is Esbriet; a 267 mg capsule is proposed for marketing. The proposed dosage is 3 capsules three times a day (TID) with food for a total daily dose of 2403 mg/day. Because of side effects (e.g. nausea, dyspepsia, dizziness), InterMune proposes a two week dose titration to reach maintenance dosing.

This 505(b)(1) application was originally submitted on November 4, 2009. The application was reviewed with a priority timeline and discussed at a Pulmonary Allergy Drugs Advisory Committee (PADAC) Meeting in March 2011. The application was not approved in the first review cycle due to failure of the clinical development program to demonstrate substantial evidence of efficacy. Pirfenidone failed to meet its primary efficacy endpoint (change in forced vital capacity) in one of two pivotal studies. The Applicant received a Complete Response Letter on May 4, 2010. In the resubmission, the Applicant has provided the results of a third placebo-controlled study with pirfenidone in patients with IPF. The newly submitted study (Study 016), taken together with the data from the two previously conducted studies (004 and 006), has resolved the deficiencies.

This memorandum provides an overview of the application, with a focus on the clinical efficacy and safety results. The PDUFA date for this application is November 23, 2014; however, based on the results of the application, and unmet medical need of patients who suffer from IPF, the Division has expedited the review and approval of this application.

2 Background

Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, fatal lung disease of unknown etiology, characterized by fibrotic interstitial infiltrates that are consistent with the histopathologic pattern of usual interstitial pneumonia (UIP).¹ It is the most common type of interstitial lung disease, estimated to affect 132,000 to 200,000 people in the United States. Approximately 50,000 new cases are diagnosed each year, and as many as 40,000 Americans die from IPF each year. IPF is typically seen in older adults (men more commonly than women), usually occurring between the ages of 50-70 years, and is characterized by progressive dyspnea, non-productive cough, and progressive pulmonary insufficiency. The natural course of IPF is variable. As the interstitial fibrosis and architectural distortion advance, the lungs become increasingly non-compliant, and work of breathing and dyspnea increase. Patients with IPF typically experience slowly progressive worsening of lung function over time, but some experience rapid declines and frequent hospitalizations in late stages of the disease.² While the course of the disease is variable, the prognosis is uniformly poor, with a median survival of about 3-5 years after diagnosis.

Inflammation and indices of immune activation have been identified in the lungs of patients with IPF, suggesting that immune response may play a role in the disease mechanism. Historically, treatment has been targeted toward blocking the inflammatory and/or fibrotic response in IPF, using agents such as corticosteroids and immunosuppressives. However, these therapies have been of little/no benefit to IPF patients. In fact, in 2011, the American Thoracic Society issued an official statement, citing evidence-based guidelines, which demonstrated that the quality of the evidence for clinical benefit of any drug therapy used in IPF was weak.³ Interestingly, recent trials of historical standard-of-care treatment regimens have shown increased mortality.⁴ No therapeutic agents have been approved in the United States for IPF. Historically, lung transplantation has been the only therapeutic option for patients with IPF.

¹ ATS/ERS. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). *Am J Respir Crit Care Med.* 2000;161:(2 Pt 1):646-64.

² Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med.* 2005;142 (12 Pt 1):963-7.

³ Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 2011;183:788-824.

⁴ Raghu G, Anstrom KJ, King TE Jr, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med.* 2012 May 24; 366(21):1968-77.

Choice of the most appropriate and clinically meaningful efficacy endpoints in IPF clinical development programs has been an ongoing topic of both internal and external discussion. Use of forced vital capacity (FVC) has been both supported and discouraged in the literature.⁵ Hesitation regarding the use of FVC stems from concerns that FVC has not been validated as a surrogate for disease progression or other clinically important endpoints (e.g. mortality). While it appears that monitoring for a change in a lung function parameter such as FVC would be logical, given that IPF causes progressive pulmonary function decline, there are several unknowns, most important of which is what constitutes a clinically important treatment difference. While we do not know with certainty the amount of change in FVC that is clinically important, some experts and literature have considered a 10% change to be a clinically important threshold.^{6,7}

While we agree that mortality benefit would be the most unequivocal and clinically important endpoint in this progressively fatal disease, we acknowledge the advice of experts and published literature that speaks to the impractical nature of designing trials designed to look at survival in IPF. Therefore, we have accepted the study designs for pirfenidone that proposed lung function decline as their primary efficacy variable. However, due to the residual uncertainties around FVC, we have emphasized that other clinically important secondary endpoints including survival should provide convincing supportive evidence that the disease has been affected through drug use.

Regulatory History

The development of pirfenidone was initiated in the US by Marnac, Inc. InterMune acquired the rights to pirfenidone in the US from Marnac in 2002 and opened an IND in the US in April 2003. Another sponsor, Shionogi, licensed the rights to pirfenidone in Japan. Pirfenidone was granted Orphan Drug Status in 2004 for the treatment of IPF. Fast Track Designation was granted in May 2008. The new drug application (NDA) was first submitted to the Agency on November 4, 2009. Prior to the submission, key milestone meetings were held with the Applicant, including an End-of-Phase 2 meeting and a Pre-NDA meeting, in December 2004, and September 2008, respectively.

During the first review cycle, the application was reviewed by the PADAC. While the committee was in favor of approval, and likely trying to respond to an unmet need, the Division issued a Complete Response (CR) letter, due to lack of demonstration of efficacy. Two studies were conducted with lung function (forced vital capacity, FVC) as the primary endpoint; only one of the studies met the primary endpoint. In order to resolve the deficiencies, the Applicant was instructed to conduct a placebo-controlled clinical trial that demonstrated a statistically significant benefit in all-cause mortality with pirfenidone, or alternatively, to conduct a third clinical trial with FVC as the primary endpoint, which replicated the efficacy of pirfenidone compared to placebo. The CR letter emphasized that

⁵ Raghu G, et al. IPF: Clinically Meaningful Primary Endpoints in Phase 3 Clinical Trials. *Am J Respir Crit Care Med* 2012; 185: 1044-1048.

⁶ King TE, Safrin S, Starko KM, et al. Analysis of Efficacy End Points in a Controlled Trial of Interferon- γ 1b for Idiopathic Pulmonary Fibrosis. *CHEST* 2005; 127: 171-177.

⁷ Collard HR, King TE, Bartelson BB, et al. Changes in Clinical and Physiologic Variables Predict Survival in Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 2003; 138: 538-542.

the findings must be robust and provide evidence of a clinically meaningful response, including a responder analysis that favored pirfenidone. Finally, the letter stated that all-cause mortality data from the to-be-conducted clinical trial pooled with the all-cause mortality data from the two previously conducted studies (004 and 006) should also provide supportive evidence of benefit.

Pertinent regulatory interactions between InterMune and the Agency with respect to this resubmission include an End-of-Review Meeting in August 2010 and a Type C Meeting in March 2011. During the March 2011 Type C meeting, the following pertinent issues were discussed:

- The design of Study 016 was discussed; importantly, it was noted that the proposed duration of the study was 52 weeks, whereas the previously conducted studies had been of 72 weeks duration. The Division expressed concern that the newly proposed study was shorter, citing the fact that the earlier failed study showed a statistically positive effect for pirfenidone at 48 weeks that did not persist at 72 weeks. The Division cautioned that shortening the treatment duration to 52 weeks may introduce risk into the clinical development program should a mortality benefit not be demonstrated at this time point, as mortality was being used to justify the use of FVC as the primary efficacy endpoint.
- Requirements for the establishment of pirfenidone's efficacy were also discussed. The Division stated the most straightforward path was to show that the new study achieved its primary endpoint (FVC), and that there was supportive evidence of a benefit in survival.

In May 2014, the Division reviewed and found safe to proceed an Expanded Access Treatment Protocol (Study 031). In addition, pirfenidone was granted designation as a Breakthrough Therapy on July 17, 2014.

Foreign Marketing

InterMune was granted marketing authorization for pirfenidone in the EMA through the centralized procedure in February 2011 and in Canada in October 2012. As of August 2013, pirfenidone was commercially available in Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Norway, Sweden, and the United Kingdom. Independent of InterMune, other sponsors have obtained marketing authorization for pirfenidone for the treatment of IPF in Japan (2008), India (2010), China (2011), Argentina (2012), South Korea (2012), and Mexico (2013).

3 Chemistry and Manufacturing

The CMC reviewer, Dr. Xiaobin Shen, recommended approval of pirfenidone.

Pirfenidone is a small, synthetic, non-peptide molecule and is a new molecular entity. It is a white to pale yellow powder that is slightly soluble in water and non-hygroscopic. The drug substance is a white to pale yellow powder that is manufactured at (b) (4)

(b) (4) Pirfenidone is prepared through (b) (4)

Specifications for the starting materials, reagents, and in-process control are

adequate. The structure of pirfenidone was confirmed by a combination of the spectroscopic and analytic techniques. Specifications for pirfenidone drug substance include appearance, identification, assay, related substances, water content, residue on ignition, heavy metals, loss on drying and particle size distribution. The support of drug substance is referenced to DMF (b) (4), which has been deemed adequate by the CMC review.

The drug product is manufactured as size 1 capsules, with each capsule containing 267 mg pirfenidone. The drug product is manufactured at (b) (4). There are two presentations. The white body and white cap capsules are to be marketed in the United States. The blue body and gold cap capsules are to be marketed in Europe and Canada. The two presentations (b) (4). The excipients used include croscarmellose sodium, microcrystalline cellulose, povidone, and magnesium stearate. The capsules are supplied in 250 cc HDPE bottles containing 270 capsules and in three blister card configurations. Up to 48 months real time stability data are provided to support a 48 month expiry. Additional supportive real time and accelerated stability data also support this claim.

All manufacturing and testing facilities associated with this application have acceptable inspection status.

4 Pharmacology/Toxicology

InterMune submitted pharmacology and toxicology study reports to support chronic administration of pirfenidone during the first review cycle. From a non-clinical pharmacology/toxicology standpoint, the application was recommended for approval during the first review cycle. The nonclinical studies included pharmacology, safety pharmacology, ADME, toxicology studies with durations up to 6 months in rats and 9 months in dogs, reproductive toxicity, genotoxicity, carcinogenicity in mice and rats, and photosafety. A high level summary of the findings is provided here.

A full battery of safety pharmacology studies were conducted with pirfenidone that included assessments of neurological, cardiovascular, respiratory, and gastrointestinal effects. Neurological effects of pirfenidone were assessed in mice that received pirfenidone as single oral doses up to 300 mg/kg. A number of clinical signs were observed in a dose-related manner that included sedation, ptosis, abnormal posture, decreased body temperature, disturbance of gait, and lower spontaneous motor activity. All symptoms disappeared by 1-2 hours post-dose. Effects of pirfenidone on the respiratory and cardiovascular systems were assessed in rats and dogs that received single oral or intravenous doses up to 300 mg/kg. Dose-related increases of heart rate were observed in both rats and dogs. Reflective of increased heart rate, dose dependent decreases of the RR interval were observed. Further, sinus tachycardia (heart rate >190 bpm) was evident in dogs that received higher oral or intravenous doses. For dogs that received single oral doses up to 100 mg/kg or an intravenous infusion of 9.2 mg/kg bolus followed by the 88 mg/kg/hour infusion, the QTc interval did not exhibit any evidence of prolongation. With respect to gastrointestinal effects, pirfenidone caused dose-dependent and significant

inhibition of the gastric emptying rate at oral doses ≥ 30 mg/kg and small intestinal transport at oral doses ≥ 100 mg/kg in rats.

In a 6-month oral toxicology study in rats, target organs of toxicity included the liver, thyroid gland, adrenal gland, and urinary bladder. Hepatocyte necrosis, centrilobular hypertrophy, and increased liver weights were noted. The increased liver weights appeared to be associated with hepatocellular hypertrophy and increases of cytochrome P450 levels and isozyme activities. Follicular cell hyperplasia of the thyroid gland was observed. Of note, findings in the liver and thyroid gland were more pronounced in the 2-year carcinogenicity study in terms of incidence and severity and appeared to correlate with neoplastic findings. An increased incidence of vacuolization of cells in the zona fasciculata of the adrenal gland was observed. Inflammatory cell infiltration in the lamina propria and transitional cell hyperplasia of the bladder and crystals in the urine were noted.

In a 9-month oral toxicology study in dogs, target organs of toxicity were the liver and submaxillary glands. Alkaline phosphatase (ALP) activities were increased and hepatocellular hypertrophy was observed. This finding appeared to be associated with induction of several cytochrome P450 isozymes. The relationship between this histopathological finding and elevation of ALP activity was unclear. Acinar hypertrophy of mucous glands in the submaxillary gland was observed. Findings in the submaxillary glands and liver might be judged to be monitorable in a clinical setting. Hepatocellular hypertrophy is generally regarded as an adaptive change and not necessarily adverse.

Pirfenidone was negative in a standard battery of genotoxicity tests.

Studies with guinea pigs and hairless mice identified several clinical signs of skin phototoxicity such as erythema, edema, and thickening of the skin after oral administration of pirfenidone with concomitant ultraviolet (UV) irradiation for up to one month. A photocarcinogenicity study was not deemed necessary given the severity of the patient population and labeling recommendations can inform patients of the risks and behavior modification (sunscreen, sun avoidance) that can minimize the risks.

Pirfenidone had no effects on fertility and reproductive performance in rats at oral doses up to 1000 mg/kg/day. In embryofetal development study with rats and rabbits that received oral doses up to 1000 and 300 mg/kg/day, respectively, there was no evidence of teratogenicity. In the presence of maternal toxicity for rats, acyclic/irregular cycles were seen in rats at oral doses ≥ 450 mg/kg. Further, prolongation of the gestation period, decreased numbers of live newborn, and reduced pup viability and body weights were seen in rats at an oral dose of 1000 mg/kg. Pirfenidone was found to distribute into the milk of lactating female rats at higher exposure levels than found in plasma. Based upon these findings, Dr. Luqi Pei recommends that the pregnancy category should be C.

Pirfenidone was tumorigenic in mice and rats. In a 2-year mouse carcinogenicity study, pirfenidone produced increased incidences of hepatocellular adenomas and carcinomas and hepatoblastomas. In a 2-year rat carcinogenicity study, pirfenidone produced increased

incidences of hepatocellular adenomas and carcinomas, and uterine adenocarcinomas. The relevance of tumor findings in mice and rats to humans is not clear.

5 Clinical Pharmacology

InterMune submitted a clinical pharmacology program to support administration of pirfenidone during the first review cycle. From a clinical pharmacology standpoint, the application was recommended for approval during the first review cycle. A very high level summary of the findings of both the original review and review of the re-submission is provided here.

Pirfenidone is recommended for administration with food, primarily because the frequency of AEs may be lower with food compared to fasting. Food decreases the C_{max} by ~49% and AUC by ~16% compared to fasting. The terminal elimination T_{1/2} of pirfenidone is about 3 hours. Following oral administration in the fed state, pirfenidone is slowly absorbed with a T_{max} of 3-4 hours following administration (0.5 hours in the unfed state). Pirfenidone is primarily metabolized by CYP1A2. 5-Carboxy-pirfenidone is the major metabolite formed by CYP1A2, and is inactive. Approximately 80% of a pirfenidone dose is eliminated in the urine. Pharmacokinetics are affected by co-administration of strong CYP1A2 inhibitors or inducers. Fluvoxamine (a strong CYP1A2 inhibitor) and ciprofloxacin (a moderate CYP1A2 inhibitor) increased pirfenidone AUC_{0-inf} by 400% and 81% and C_{max} by 70% and 23%, respectively. Dose modifications for pirfenidone in those patients who must be concomitantly treated with fluvoxamine or ciprofloxacin are included in the package insert.

AUC_{0-∞} and C_{max} was 46% and 68% of the exposure in non-smokers. Smoking is known to induce CYP1A2, which is the chief metabolizing enzyme of pirfenidone. Patients should be encouraged to stop smoking before treatment with pirfenidone. Otherwise, smoking should be avoided when using pirfenidone.

In patients with moderate hepatic impairment, the AUC and C_{max} of pirfenidone were increased by 1.6 to 1.4 fold, respectively. Similar increase was noted in patients with mild, moderate, and severe renal impairment. However, the AUC of the metabolite (5-carboxy-pirfenidone) was increased up to 5.6 fold in patients with severe renal impairment. Because the clinical program included patients with renal impairment and review of safety data did not suggest a safety signal, no dose adjustment is recommended in patients with mild to moderate renal impairment or hepatic impairment as the increased exposure to pirfenidone is similar. Because of the lack of data in patients with end stage renal disease or severe liver disease, use of pirfenidone in these patients is not recommended.

The Applicant conducted a thorough QT study that did not show an effect on the QT interval; however, the study had some issues that limit the conclusions. The study did not demonstrate the effect of the positive control, moxifloxacin, and the suprathreshold dose (1.6 x therapeutic dose) did not cover the maximum pirfenidone exposure (e.g. 4 fold increase with co-administration of fluvoxamine). However, the clinical program included ECG monitoring and evidence of QT prolongation was not noted. The limitations of the TQT study are noted in the package insert and do not preclude approval.

In an analysis of the treatment response across the three studies, Dr. Rekić (the clinical pharmacology reviewer), sought to analyze the variability in the placebo response, as the placebo arms behaved differently in each of the three studies. In his analysis, he found that three covariates were found to significantly correlate with the rate of decline in FVC: baseline % predicted FVC, baseline body weight, and use of oxygen at baseline. Details of this analysis can be found in his review.

6 Clinical Microbiology

The previous two microbiology reviews resulted in acceptable finding with the exception of an issue related to the sample size used for the microbial limits assay. In this review cycle, only the response to the microbiology deficiency was reviewed and found to be acceptable. There are no outstanding issues from a clinical microbiology standpoint.

7 Clinical/Statistical- Efficacy

An overview of the relevant clinical studies that form the basis of review and regulatory decision-making for this application are shown in Table 1. The design and conduct of these studies are described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8.

Of note, Studies 004 and 006 comprised the original NDA submission; Study 016 is the new study in the re-submission. An overview of the efficacy findings will be summarized in this review.

Table 1. Summary of Pirfenidone Clinical Program					
Study ID [sites] Study Period	Design	Duration	Treatment	N	Endpoints *
Original Submission					
004 [US, Canada, Mexico, UK, France, Italy, Poland, Australia] Jul 2006-Nov 2008	R, DB, PC	72 weeks	Pirfenidone 2403 mg/day [†] Pirfenidone 1197 mg/day [†] Placebo	174 87 174	- change in % predicted FVC from baseline - time to worsening IPF - progression free survival [‡]
006 [US, Australia, Belgium, Germany, Ireland, Spain, Switzerland] Apr 2006-Oct 2008	R, DB, PC	72 weeks	Pirfenidone 2403 mg/day [†] Placebo	171 173	- change in % predicted FVC from baseline - time to worsening IPF - progression free survival [‡]
Resubmission					
016 [US, Australia, Brazil, Croatia, Israel, Mexico, New Zealand, Peru, Singapore] Jun 2011 – Feb 2014	R, DB, PC	52 weeks	Pirfenidone 2403 mg/day [†] Placebo	278 277	- change in % predicted FVC from baseline - change from baseline in 6MWT - progression free survival [‡]
R= randomized, DB=double-blind, PC=placebo controlled, FVC=forced vital capacity, 6MWT=6 minute walk test * bold font indicates primary endpoint. Other endpoints listed are important secondary endpoints. [†] Total daily dose divided TID [3 x 267 mg] and [3 x 133 mg] [‡] Progression free survival in trial 016 was a composite of earliest time to death, ≥10% decline in % predicted FVC, or ≥50 m decline in 6MWT; Progression free survival in 004 and 006 was composite of earliest time to death, 10% decline in % predicted FVC, or 15% decline in % predicted DLco.					

Original Submission

- **Study Design – Studies 004 and 006**

Studies 004 and 006 were similarly designed (with the exception that Study 004 had an additional low dose treatment group), randomized, double-blind, placebo-controlled, clinical trials to assess the efficacy and safety of pirfenidone for the treatment of patients with IPF. The duration of the trials was 72 weeks, and patients received study treatment from randomization until approximately 72 weeks after the last patient had been randomized into the study.

Because of gastrointestinal adverse events (AEs) with pirfenidone, a two week titration period to the maintenance dose was specified as shown below. Because of the potential for photosensitivity, patients were advised to avoid sun exposure and use sunscreen daily. Dose modifications were allowed for symptoms of fatigue, gastrointestinal side effects, photosensitivity, and liver function test abnormalities.

Treatment days	Number of capsules TID with food	Total Daily Dose (mg/day)
1-7	1	801
8-14	2	1602
15+	3	2403

Concomitant therapies, including corticosteroids, cytotoxic, immunosuppressive, cytokine modulating, endothelin receptor antagonists, and any concomitant treatment for IPF were not allowed during the study. Patients who met predefined criteria for acute respiratory decompensation, acute IPF exacerbation, or progression of disease were permitted to receive certain IPF therapies.

Clinic visits were scheduled weeks 2, 4, 6, 12, and then every 12 weeks. Efficacy was assessed by pulmonary function tests (FVC, DLco), worsening of IPF, progression free survival, dyspnea as measured by the UCSD SOBQ (University of California, San Diego, Shortness of Breath Questionnaire), and the 6-minute walk test (6MWT) with Borg rating of breathlessness. Pulmonary function tests (PFTs) were performed according to ATS guidelines. Patients who discontinued were followed for vital status assessment until study completion (approximately 120 weeks).

- **Efficacy Variables – Studies 004 and 006**

The primary efficacy variable was the absolute change in percent predicted FVC from Baseline to Week 72 for the pirfenidone 2403 mg/day treatment group compared to placebo. The pre-specified primary analysis of the primary endpoint was a rank ANCOVA with the lowest rank imputation for missing data due to death. A strategy for handling missing data and death was specified and deemed acceptable.

Important secondary efficacy variables included:

- time to worsening of IPF - time to acute IPF exacerbation, IPF-related death, lung transplantation, or respiratory hospitalization, whichever came first
- progression free survival - time to first occurrence of either:

- 10% absolute decline in % predicted FVC **or**
- 15% absolute decline in % predicted DLco **or**
- death

Survival (time to death) was an exploratory efficacy variable.

- Efficacy Results: Studies 004 and 006

A total of 779 IPF patients were randomized; 435 and 344 patients were enrolled at 64 and 46 sites in North America, Europe, and Australia, in Study 004 and Study 006, respectively. Baseline characteristics were generally balanced across treatment groups. Baseline characteristics across the two studies were also generally similar, except for a larger proportion of patients in Study 006 on supplemental oxygen and residing in the US. The study population, based on pooled study results, had a mean age of 67 years; 61% were ≥ 65 years and 19% were ≥ 75 years. Most patients were male (72%), white (97%), and current or former smokers (67%). Approximately 90% of patients met criteria for definite IPF on HRCT and nearly half had definite UIP on surgical lung biopsy. Baseline mean percent predicted FVC and DLco were 75% and 47%, respectively. In both studies, over 80% of patients completed study treatment and over 90% completed the study, when deaths and lung transplant patients were classified as completers.

1. *Change from Baseline in Percent Predicted Forced Vital Capacity (FVC)*

The results in Table 2 show that patients receiving pirfenidone had a smaller mean decline from baseline in % predicted FVC compared to those receiving placebo at Week 72 ($p < 0.001$, rank ANCOVA) in Study 004. The effect size was an absolute difference in change from baseline percent predicted FVC of 4.4%. In contrast, there was no statistically significant reduction in the mean decline from baseline in % predicted FVC in pirfenidone treated patients in Study 006 at Week 72.

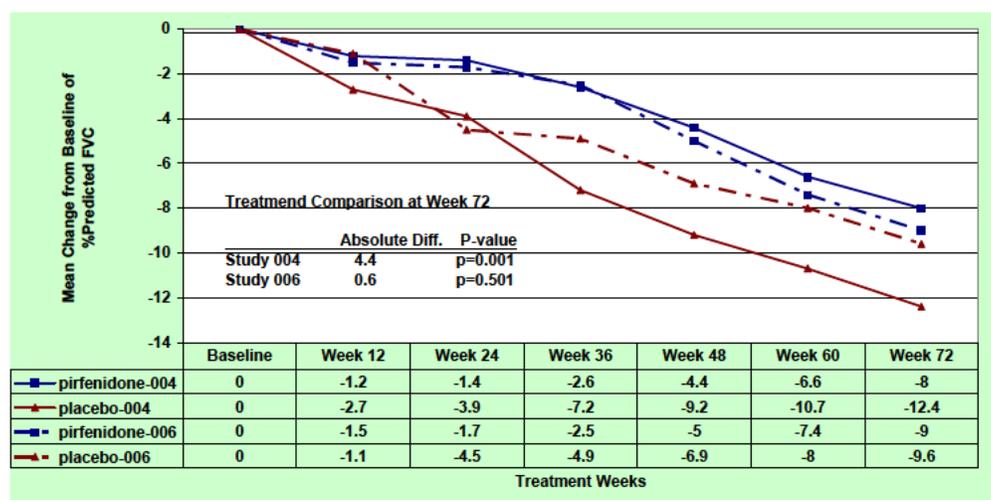
Table 3. Mean Change from Baseline in Percent Predicted FVC in All Randomized Patients (rank ANCOVA w/ imputation) – Studies 004 and 006 (Original Submission)				
	Pirfenidone 2403 mg/day	Placebo	Treatment Comparison (Pirfenidone vs. Placebo)	
	Mean Change in Percent Predicted FVC (SD)^{a,b}		Absolute Difference^c	p-value^d
Study 004				
	N=174	N=174		
Baseline ^e	74.5 (14.5)	76.2 (15.5)	--	--
Week 12	-1.2 (6.8)	-2.7 (9.5)	1.5	0.061
Week 24	-1.4 (7.5)	-3.9 (12.1)	2.5	0.014
Week 36	-2.6 (9.1)	-7.2 (15.6)	4.6	< 0.001
Week 48	-4.4 (12.1)	-9.2 (17.2)	4.8	<0.001
Week 60	-6.6 (15.5)	-10.7 (17.6)	4.1	<0.001
Week 72	-8.0 (16.5)	-12.4 (18.5)	4.4	0.001
Study 006				
	N = 171	N = 173		
Baseline ^e	74.9 (13.2)	73.1 (14.2)	--	--
Week 12	-1.5 (10.7)	-1.1 (4.5)	0.5	0.021
Week 24	-1.7 (11.2)	-4.5 (12.7)	2.8	<0.001
Week 36	-2.5 (13.4)	-4.9 (15.0)	2.4	0.011

Table 3. Mean Change from Baseline in Percent Predicted FVC in All Randomized Patients (rank ANCOVA w/ imputation) – Studies 004 and 006 (Original Submission)				
	Pirfenidone 2403 mg/day	Placebo	Treatment Comparison (Pirfenidone vs. Placebo)	
	Mean Change in Percent Predicted FVC (SD)^{a,b}		Absolute Difference^c	p-value^d
Week 48	-5.0 (15.6)	-6.9 (15.4)	1.9	0.005
Week 60	-7.4 (18.2)	-8.0 (17.2)	0.6	0.172
Week 72	-9.0 (19.6)	-9.6 (19.1)	0.6	0.501

a. Mean change from baseline is calculated as post minus baseline
b. For missing values if the patient was alive on the protocol-specified visit, the imputation was by the SSD method. If the patient died on or before the protocol-specified date, then 0 was imputed for the assessment. If the patient was not randomized early enough to have had a particular visit by the end of the study, no imputation was done
c. Absolute difference in mean change from baseline: pirfenidone – placebo; positive absolute difference favors pirfenidone; negative favors placebo
d. A rank ANCOVA, comparing pirfenidone 2403 mg/d vs. placebo, with standardized ranked change from Baseline as the outcome variable, treatment and geographic region (USA and ROW) as fixed effects, and standardized ranked Baseline as a covariate. Missing data due to a patient's death were ranked as worse than any non-death and according to time until death.
e. Baseline percent predicted FVC was defined as the mean of the maximum acceptable FVC measurements obtained during the Screening and Day 1 Visits.
Source: Table 11-7, p. 135, PIPF-004 CSR, and Table 11-7, p. 126, PIPF-006 CSR, Module 5, and Table 8, Biometrics Review, Dr. Feng Zhou.

Although the primary endpoint was at Week 72, an evaluation of the change from baseline percent predicted FVC over time is of interest and is shown in Figure 1 below. In Study 006, there was a separation of the treatment groups between weeks 24 up to week 60. After week 60, the results for treatment groups were similar, due primarily to a difference in the decline of the placebo group around week 24.

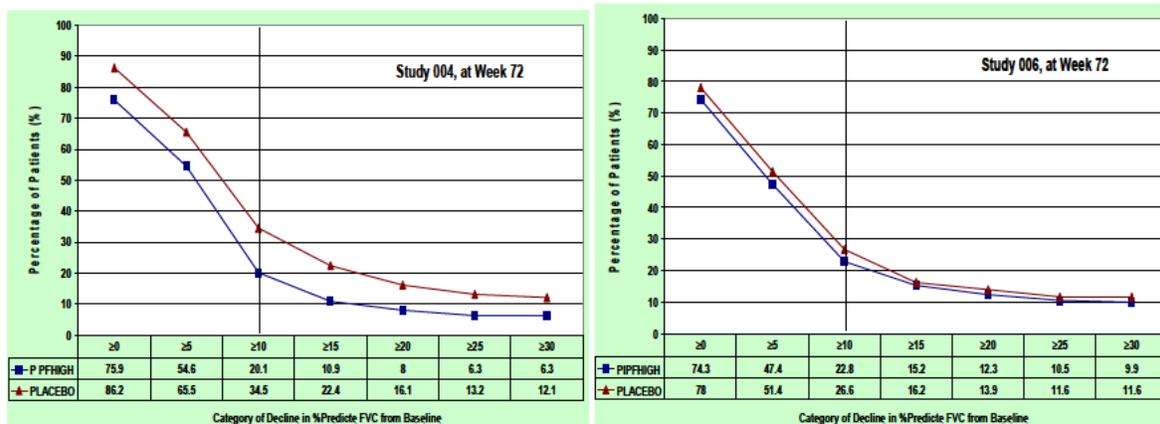
Figure 1. Mean Change in Percent Predicted FVC from Baseline*



* pre-specified imputation for missing data; Rank ANCOVA

A responder analysis was also performed using the primary efficacy variable, and the results are shown in the following cumulative distribution plots prepared by the Agency's statistical reviewer. Using an absolute decline in % predicted FVC of 10% to define a responder, there was no difference between pirfenidone and placebo groups in Study 006. In Study 004, 20% of patients treated with pirfenidone had a decline greater than 10% compared to 35% of patients in the placebo group (see Figure 2).

Figure 2. Cumulative % of Patients of Change from baseline in %Predicted FVC



Note: For missing values if the patient was alive on protocol specified visit the imputation was by the smallest sum of differences (SSD) method. If the patient died on or prior to the protocol specified date then the 0 was imputed for the assessment. If a patient was not randomized early enough to have had a particular visit by the end of the study no imputation was done.
 Percent change from baseline = 100*(post baseline-baseline)/baseline.

Key secondary endpoints included progression-free survival (PFS) and worsening of IPF. Death was also examined as an important endpoint. Results of both Studies 004 and 006 are presented, but it is important to note that because Study 006 did not meet its primary endpoint, results of secondary endpoints should be interpreted carefully.

2. Progression-Free Survival

In Studies 004 and 006, PFS was a composite endpoint defined as time to first occurrence of either a 10% absolute decline in % predicted FVC, a 15% absolute decline in % predicted DLco, or death. As shown in the table below, the results for PFS were statistically significant in Study 004 and numerically favorable in Study 006. The results were driven primarily by the disease progression criterion of 10% decline in percent predicted FVC.

Table 4. Progression-Free Survival -Studies 004 and 006 (Original Submission)			
	Pirfenidone 2403mg/day	Placebo	Hazard Ratio^c (95% CI) p-value^b
	N of Event^a (%)	N of Event^a (%)	
Study 004			
N of Randomized	174	174	
Death or disease progression ^d	45 (26.2)	62 (35.8)	0.64 (0.44, 0.95), 0.023
Decline %predicted FVC \geq 10%	28 (16.3)	39 (22.5)	--
Decline %predicted DL _{CO} \geq 15%	9 (5.2)	9 (5.2)	--
Death before disease progression ^e	8 (4.7)	14 (8.1)	--
Study 006			
N of Randomized	171	173	
Death or disease progression ^d	54 (31.8)	60 (34.9)	0.84 (0.58, 1.22), 0.355
Decline %predicted FVC \geq 10%	31 (18.2)	41 (23.8)	--
Decline %predicted DL _{CO} \geq 15%	10 (5.9)	9 (5.2)	--
Death before disease progression ^e	13 (7.6)	10 (5.8)	--
<p>[a] Patients with no post-Baseline FVC or DLCO values were excluded from the analysis (2 patients in the pirfenidone 2403 mg/d group and 1 patient in the placebo group were excluded).</p> <p>[b] p-value was based on the log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d with placebo.</p> <p>[c] Hazard ratio was based on the Cox proportional hazard model</p> <p>[d] Based on occurrence of event or censoring in the absence of the event. Time to event was the event date minus randomization date plus one. The censoring date was the last FVC or DLCO during the Treatment Period. Deaths after this visit were counted if they occurred within 24 weeks of the visit.</p> <p>[e] Excludes deaths that were not the reason for treatment discontinuation and occurred more than 28 days after the last study treatment, and deaths that were not the reason for study withdrawal and occurred more than 98 days after the last study visit for patients who did not complete the study.</p>			

3. Worsening of IPF

Worsening of IPF was a composite endpoint defined as time to acute IPF exacerbation, IPF-related death, lung transplantation, or respiratory hospitalization. Neither study demonstrated a statistically significant benefit on time to worsening of IPF.

Table 5. Worsening of IPF – Studies 004 and 006 (Original Submission)			
	Pirfenidone 2403mg/day	Placebo	Hazard Ratio^c (95% CI) p-value^d
	N of Event (%)	N of Event (%)	
Study 004			
N of Randomized	174	174	--
Worsening IPF ^a	26 (14.9)	30 (17.2)	0.84 (0.50, 1.42), 0.515
Acute IPF exacerbation	2 (1.1)	3 (1.7)	--
Lung transplantation	2 (1.1)	2 (1.1)	--
Respiratory hospitalization	21 (12.1)	24 (13.8)	--
IPF-related death ^b	1 (0.6)	1 (0.6)	--
Study 006			
N of Randomized	171	173	--
Worsening IPF ^a	24 (14.0)	32 (18.5)	0.73, (0.43, 12.4), 0.248
Acute IPF exacerbation	2 (1.2)	1 (0.6)	--
Lung transplantation	2 (1.2)	2 (1.2)	--
Respiratory hospitalization	17 (9.9)	23 (13.3)	--
IPF-related death ^b	3 (1.8)	6 (3.5)	--
<p>a Based on first occurrence of event, or censoring in the absence of the event. Time to event was the event date minus randomization date plus one. The censoring date was the last available contact or time of lung transplantation (if one occurred) or the end of the Treatment Period.</p> <p>b Excludes deaths that were not the reason for treatment discontinuation and occurred more than 28 days after the last study treatment, and deaths that were not the reason for study withdrawal and occurred more than 98 days after the last study visit for patients who did not complete the study.</p> <p>c p-value was based on the log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d with placebo.</p> <p>d Hazard ratio was based on the Cox proportional hazard model.</p>			

4. Death

Evaluation of death is the most clinically relevant endpoint in IPF studies. Deaths were defined in a number of ways in this application;

- On-treatment (treatment-emergent): deaths that occurred after the first dose and within 28 days after the last dose of study treatment
- Treatment period: deaths that occurred within the time period pre-specified by censoring rules in the protocols for Studies 004 and 006, which defined the date a patient was censored as the earliest of the last available contact dates, or time of lung transplantation if one occurred, or the end of the treatment period (before September 30 or 25, 2008 for trials 004 and 006, respectively).
- Vital Status at End of Study: all deaths that occurred at anytime during the study, regardless of whether patients continued on study treatment or study assessments (approximately 120 weeks).

In Studies 004 and 006, cause of death was not adjudicated. The Applicant presented an analysis of deaths that occurred by the end of the treatment period. The Agency performed survival analyses examining those deaths which occurred on-treatment and at vital status – end of study. On-treatment (or treatment emergent) deaths are generally considered important for evaluating the safety of a drug, while vital status follow-up is considered to be most informative of the efficacy of a drug with respect to survival.

The various analyses of all-cause mortality are shown in the table below.

Table 6. Survival Analysis: Studies 004 and 006			
	Number of Events (%)		
All cause death	Pirfenidone 2403mg/day	Placebo	Hazard Ratio[†] (95% CI), p value[‡]
Study 004	N=174	N=174	
On Treatment	11 (6.3)	15 (8.6)	0.68 (0.31, 1.49), p=0.336
Treatment Period	11 (6.3)	17 (9.8)	0.61 (0.28, 1.29), p=0.191
Vital Status – End of Study	14 (8.0)	20 (11.5)	0.68 (0.34, 1.34), p=0.268
Study 006	N=171	N=173	
On Treatment	10 (5.9)	15 (8.7)	0.66 (0.30, 1.48), p=0.314
Treatment Period	16 (9.4)	17 (9.8)	0.95 (0.48, 1.87), p=0.872
Vital Status – End of Study	18 (10.5)	17 (9.8)	1.06 (0.55, 2.07), p=0.856
Pooled Studies 004/006	N=345	N=347	
On Treatment	21 (6.1)	30 (8.7)	0.68 (0.39, 1.18), p=0.167
Treatment Period	27 (7.8)	34 (9.8)	0.78 (0.47, 1.29), p = 0.333
Vital Status – End of Study	32 (9.3)	37 (10.7)	0.85 (0.53, 1.37), p=0.509
[†] Hazard ratio was based on the Cox proportional hazard model, with geographic region (USA and ROW) as a factor. [‡] p-value based on log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d to placebo			

Neither trial demonstrated a survival benefit for pirfenidone, regardless of the analysis methodology used. On-treatment analyses of both studies individually and pooled were numerically in favor of pirfenidone. However, the confidence intervals were large, and statistical significance was not achieved. The vital status analysis was numerically favorable for pirfenidone in Study 004, but Study 006 did not show any difference between treatment groups. When the vital status analysis of mortality was assessed in the pooled population, the result again was numerically in favor of pirfenidone; however, statistical significance was not achieved.

During the original review cycle, the interpretation of the data provided by Studies 004 and 006 was challenging, given that the results were affected by a differential response in the placebo group in Study 006. While many theories were proposed for the variable manner in which the two placebo groups behaved in Studies 004 and 006, it remained unclear as to which study represented the true efficacy of pirfenidone. While Study 004 showed a statistically significant benefit of pirfenidone over placebo, the effect size was small and of unknown clinical significance. Multiple sensitivity analyses confirmed that only Study 004 demonstrated a statistically significant benefit of pirfenidone over placebo. Secondary endpoints, including survival, did not consistently support that pirfenidone was effective in IPF.

In accordance with our regulations, the Agency requires *substantial evidence* of effectiveness. Substantial evidence consists of adequate and well-controlled investigations on the basis of which it could be concluded that the drug will have the effect it is purported or labeled to have. The Agency usually requires more than one trial to provide independent substantiation of efficacy.⁸ Although IPF is an orphan disease, the requirements to establish effectiveness are not different, with the exception that the overall database may be smaller. As FVC as a primary efficacy endpoint was already subject to some uncertainty,

⁸ FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

consistency and reproducibility of results was required. The Agency determined that substantial evidence of efficacy had not been demonstrated, and pirfenidone was not approved in the first review cycle.

Resubmission

- Study Design – Study 016

Study 016 was similar in design to Studies 004 and 006. Important differences in design/conduct include the following:

- Study duration was 52 weeks (as opposed to 72 weeks in Studies 004 and 006)
- Inclusion of patients with a lower percent-predicted DLco, higher FEV1/FVC ratio, and longer time since IPF diagnosis

The primary efficacy variable remained the change in percent predicted FVC from baseline analyzed by rank ANCOVA with the lowest rank imputation for missing data due to death.

Key secondary endpoints were different (or with different definitions) in Study 016. These included:

- Progression free survival, which was defined as time to first occurrence of either:
 - 10% absolute decline in % predicted FVC **or**
 - Decline in 6MWT distance ≥ 40 m **or**
 - Death
- Change from baseline in 6MWT distance

Survival was important endpoint as well. In the statistical analysis, survival was pre-specified to be examined in a pooled fashion with Studies 004 and 006 at 52 weeks, as a means of supporting the primary endpoint (FVC).

- Efficacy Results: Study 016

A total of 555 IPF patients were randomized (n=278 in the pirfenidone 2403 mg/day group and n=277 in the placebo group) at 127 sites in the US, Australia, Brazil, Croatia, Israel, Mexico, New Zealand, and Peru. Baseline characteristics were generally balanced across treatment groups and similar to the population from Studies 004 and 006. The study population had a mean age of 68 years; ~50% were ≥ 65 years and 20% were ≥ 75 years. Most patients were male (77-80%), white (92%), and former smokers (63%).

Approximately 95% of patients met criteria for definite IPF on HRCT and ~30% had definite UIP on surgical lung biopsy. Baseline mean percent predicted FVC and DLco were 68% and 44%, respectively. In accordance with modifications to the inclusion criteria for Study 016, mean baseline percent predicted FVC and DLco were slightly lower than in Studies 004 and 006. Time since IPF diagnosis was 1.7 years in both treatment groups in Study 016 (slightly longer than then 1.3 and 1.1 years since IPF diagnosis in 004 and 006, respectively). In both studies, over 80% of patients completed study treatment, with approximately 88% completing the study, when deaths and lung transplant patients were classified as completers.

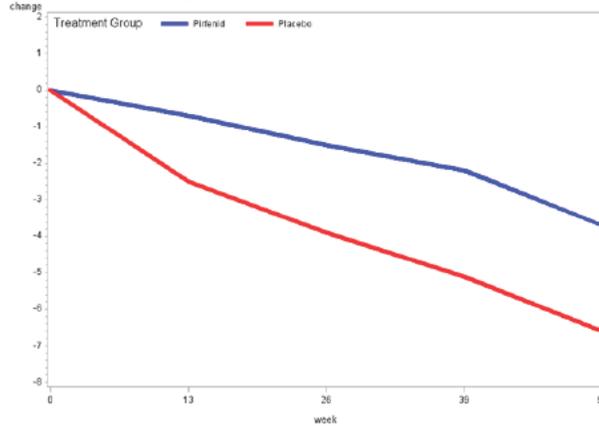
1. Change from Baseline in Percent Predicted Forced Vital Capacity

The results in Table 6 show that patients receiving pirfenidone had a smaller mean decline from baseline in % predicted FVC compared to those receiving placebo at Week 52 ($p < 0.001$, rank ANCOVA) in Study 016. The effect size was an absolute difference in change from baseline percent predicted FVC of 2.9%.

Table 6. Mean Change from Baseline in Percent Predicted FVC in All Randomized Patients (rank ANCOVA w/ imputation) – Studies 016 (Resubmission)				
	Pirfenidone 2403 mg/day	Placebo	Treatment Comparison (Pirfenidone vs. Placebo)	
	Mean Change in Percent Predicted FVC (SD)^{a,b}		Absolute Difference^c	p-value^d
Study 004				
	N=278	N=277		
Baseline ^e	67.8 (11.2)	68.6 (10.9)	-0.8	--
Week 13	-0.7 (4.0)	-2.5 (4.4)	1.8	<0.001
Week 26	-1.5 (4.5)	-3.9 (5.2)	2.4	<0.001
Week 39	-2.2 (5.1)	-5.1 (6.4)	2.9	<0.001
Week 52	-3.7 (6.7)	-6.6 (6.7)	2.9	<0.001
a. Mean change from baseline is calculated as post minus baseline b. For missing values if the patient was alive on the protocol-specified visit, the imputation was by the SSD method. If the patient died on or before the protocol-specified date, then 0 was imputed for the assessment. If the patient was not randomized early enough to have had a particular visit by the end of the study, no imputation was done c. Absolute difference in mean change from baseline: pirfenidone – placebo; positive absolute difference favors pirfenidone; negative favors placebo d. A rank ANCOVA, comparing pirfenidone 2403 mg/d vs. placebo, with standardized ranked change from Baseline as the outcome variable, treatment and geographic region (USA and ROW) as fixed effects, and standardized ranked Baseline as a covariate. Missing data due to a patient's death were ranked as worse than any non-death and according to time until death. e. Baseline percent predicted FVC was defined as the mean of the maximum acceptable FVC measurements obtained during the Screening and Day 1 Visits.				
Source: Biometrics Review, Dr. Yongman Kim.				

Although the primary endpoint was at Week 52, an evaluation of the change from baseline percent predicted FVC over time is of interest and is shown in Figure 3 below.

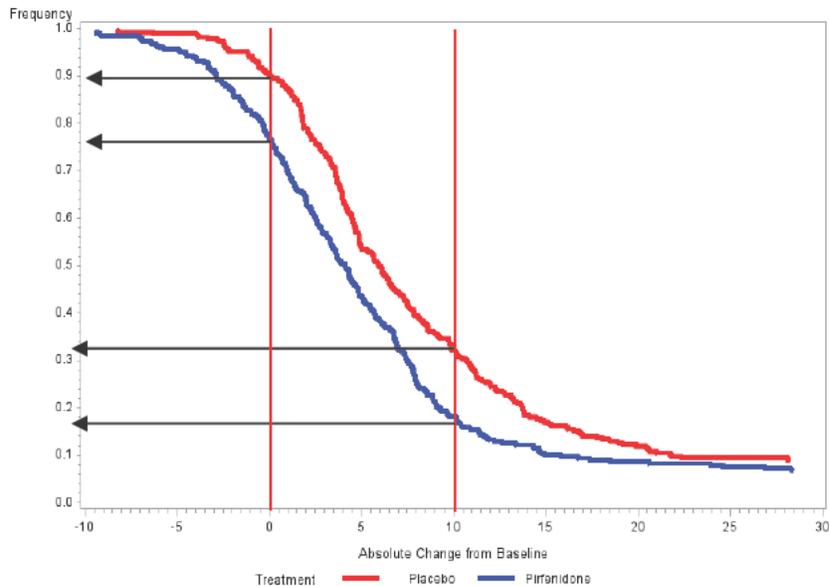
Figure 3. Mean Change from Baseline in Percent Predicted FVC*



*pre-specified imputation for missing data; Rank ANCOVA, Biometrics Review, Dr. Yongman Kim.

A continuous responder analysis was also performed using the primary efficacy variable, and the results are shown in the following cumulative distribution plots prepared by the Agency’s statistical reviewer. In this analysis, all patients who discontinued treatment due to death or lung transplantation were considered non-responders (i.e. highest decline in % predicted FVC). The positive treatment effect of pirfenidone was demonstrated by consistent separation of the curves across the different levels of response. Using an absolute decline in % predicted FVC of 10% to define a responder, 17% of patients treated with pirfenidone had a decline greater than 10% compared to 32% of patients in the placebo group. Using a threshold of $\geq 0\%$ decline (or no improvement), 90% of placebo patients experienced $\geq 0\%$ decline versus 77% of pirfenidone-treated patients (see Figure 4).

Figure 4. Cumulative Distribution of Patients by Change in Percent Predicted FVC from Baseline to Week 52 – Study 016. The red lines indicate a $\geq 10\%$ decline or $\geq 0\%$ decline.



For missing values if the patient was alive on protocol specified visit the imputation was by the smallest sum of differences (SSD) method. If the patient died on or prior to the protocol specified date then the 0 was imputed for the assessment. If a patient was not randomized early enough to have had a particular visit by the end of the study no imputation was done. Percent change from baseline = $100 \times (\text{post baseline} - \text{baseline}) / \text{baseline}$.

2. Progression Free Survival

In Study 016, PFS was a composite endpoint defined as time to first occurrence of either a 10% absolute decline in % predicted FVC, a 50 meter decline in 6MWT distance, or death. The 6MWT distance was a new addition to this composite endpoint, replacing DLco decline in Studies 004 and 006. While the results were statistically significant, as shown in Table 7 below, the results were driven primarily by criterion of 6MWT decline and decline in FVC. The clinically significant difference in 6MWT has not been adequately defined and FVC was measured as the primary endpoint.

Table 7. Progression-Free Survival – Study 016 (Resubmission)			
	Pirfenidone 2403mg/day	Placebo	Hazard Ratio^c (95% CI) p-value^b
	N of Event^a (%)	N of Event^a (%)	
N of Randomized	278	277	
Death or Disease Progression	74 (26.6)	117 (42.2)	0.57 (0.43, 0.77), <0.001
Decline % predicted FVC ≥ 10%	18 (6.5)	49 (17.7)	--
Decline in 6MWT ≥ 50m	46 (16.5)	54 (19.5)	--
Death	10 (3.6)	14 (5.1)	--

[a] Patients with no post-Baseline FVC or DLCO values were excluded from the analysis (2 patients in the pirfenidone 2403 mg/d group and 1 patient in the placebo group were excluded).
[b] p-value was based on the log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d with placebo.
[c] Hazard ratio was based on the Cox proportional hazard model
Source: Biometrics Review, Dr. Yongman Kim

3. Change from Baseline in 6-Minute Walk Test Distance

Change from baseline in 6MWT was analyzed using the same rank ANCOVA model as in the primary analysis. The mean decline in 6MWT distance in patients treated with pirfenidone was lower compared to patients treated with placebo (-33.6 vs. -60.2 meters, respectively; difference of 26.7 meters). While the Applicant's analysis demonstrated a statistically significant difference, these results were not robust, as sensitivity analyses conducted by the Agency's statistical reviewer using different imputation methods (placebo mean imputation) did not achieve statistically significant results. Further, it is uncertain what magnitude of difference constitutes a clinically meaningful change for a patient with IPF.

4. Death

In Study 016, patients who discontinued study treatment before Week 52 were followed for vital status through Week 52. Mortality data were collected regardless of treatment discontinuation to the end of the treatment period; patients who discontinued treatment early were followed for vital status to the end of the treatment period (52 weeks). On-treatment deaths were defined as those patients who died while on-treatment or within 28 days of the last dose of treatment. Study 016 did not demonstrate a statistically significant survival benefit for pirfenidone at vital status [HR 0.55, 95% CI: 0.26, 1.15] at 52 weeks or on-treatment [HR 0.57, 95% CI: 0.28, 1.16, p=0.114], although the results numerically favored pirfenidone.

As none of the studies was powered individually to evaluate mortality, pooled analyses of mortality were conducted as a means of supporting a novel primary endpoint (FVC).

The Applicant had pre-specified the pooling of the three studies (004, 006, and 016) at 52 weeks to examine mortality. For the pooled analyses of mortality, data from patients receiving pirfenidone or placebo in Studies 004 and 006 were censored at Day 365 (52 weeks) if an event had not occurred earlier, to provide an equal duration of follow-up as in Study 016. In addition, a post-hoc exploratory pooled analysis of mortality (time to death) was conducted to the primary endpoint assessment in each of the phase 3 studies (i.e. to 52 weeks in Study 016, and to 72 weeks in Studies 004 and 006).

Pooled analyses of on-treatment mortality, treatment period mortality (as defined earlier in this memo), and vital status mortality were also examined. The results of these analyses for each of the studies individually, and pooled, are summarized in Table 8 below.

Table 8: Survival Analysis of All-Cause Mortality: Summary Table			
	Number of Events (%)		
All-cause death	Pirfenidone 2403mg/day	Placebo	Hazard Ratio[†] (95% CI), p value[‡]
Study 004	N=174	N=174	
On-Treatment	11 (6.3)	15 (8.6)	0.68 (0.31, 1.49), p=0.336
Cut off at 52 Weeks	5 (2.9)	13 (7.5)	0.37 (0.13, 1.04), p=0.049
To Study Primary EP	8 (4.6)	15 (8.6)	0.51 (0.22, 1.20), p=0.116
Treatment Period	11 (6.3)	17 (9.8)	0.61 (0.28, 1.29), p=0.191
Vital Status –End of Study	14 (8.0)	20 (11.5)	0.65 (0.33, 1.29), p=0.217
Study 006	N=171	N=173	
On-Treatment	10 (5.9)	15 (8.7)	0.66 (0.30, 1.48), p=0.314
Cut off at 52 Weeks	6 (3.5)	9 (5.2)	0.66 (0.24, 1.87), p=0.435
To Study Primary EP	13 (7.6)	15 (8.7)	0.87 (0.41, 1.82), p=0.704
Treatment Period	16 (9.4)	17 (9.8)	0.95 (0.48, 1.87), p=0.872
Vital Status –End of Study	18 (10.5)	17 (9.8)	1.07 (0.55, 2.08), p=0.833
Study 016	N=278	N=277	
On-Treatment	7 (2.5)	14 (5.1)	0.51 (0.21, 1.27), p=0.143
Treatment Period (52 weeks)*	11 (4.0)	20 (7.2)	0.55 (0.26, 1.15), p=0.105
Vital Status –End of Study	12 (4.3)	21 (7.6)	0.57 (0.28, 1.16), p=0.11
Pooled Studies 004/006	N=345	N=347	
On-Treatment	21 (6.1)	30 (8.7)	0.68 (0.39, 1.18), p=0.167
Treatment Period	27 (7.8)	34 (9.8)	0.78 (0.47, 1.29), p = 0.333
Vital Status –End of Study	32 (9.3)	37 (10.7)	0.85 (0.53, 1.36), p=0.493
Pooled Studies 016/004/006	N=623	N=624	
On-Treatment	28 (4.5)	44 (7.1)	0.63 (0.39, 1.00), p=0.050
Cut off at 52 Weeks	22 (3.5)	42 (6.7)	0.52 (0.31, 0.87), p=0.011
To Study Primary EP	32 (5.1)	50 (8.0)	0.63 (0.41, 0.98), p=0.040
Treatment Period	38 (6.1)	54 (8.7)	0.69 (0.46, 1.05), p=0.079
Vital Status-End of Study	44 (7.1)	58 (9.3)	0.75 (0.50, 1.11) p=0.142

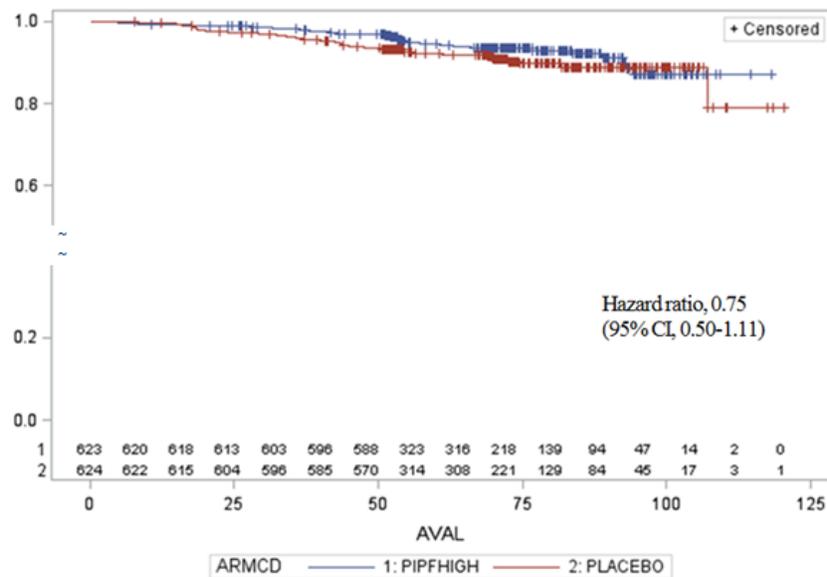
[†] Hazard ratio was based on the Cox proportional hazard model, with geographic region (USA and ROW) as a factor.
[‡] p-value based on log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d to placebo
 On-treatment: death occurred on study medication or within 28 days of the last dose of study medication
 Treatment period: deaths that occurred within the time period pre-specified by the censoring rules for each of the studies, for study 016, this was at 52 weeks, and to the study primary endpoint.
 Vital Status –End of Study: deaths that occurred at anytime during the study regardless of whether patients continued on study treatment or study assessments
 Cut off at 52 weeks: deaths in studies 004 and 006 were censored at day 365 to provide and equal duration of follow-up as in Study 016
 To Study Primary EP: Deaths occurring up to 52 weeks in Study 016 and up to 72 weeks in Studies 004 and 006

In general, the mortality analysis favored pirfenidone over placebo. As the table illustrates, the results drift towards being more numerically favorable when earlier time points are examined. Notably, the pooled analyses demonstrate that there is a statistically significant difference between the pirfenidone and placebo groups on all-cause mortality while on-treatment, when all data was examined at 52 weeks (cut off at 52 weeks), and when measured at 52 weeks for Study 016 and 72 weeks for 004/006 (to study primary endpoint).

The results of different analyses of mortality are displayed here to inform discussion, as mortality is a clinically important endpoint in IPF. However, there are certain aspects of each of these analyses which require cautious interpretation. For example, while the analysis at the cut-off of 52 weeks was pre-specified prior to the conduct of Study 016, the results of the Studies 004 and 006 were known prior to the planning of Study 016. It is notable that the same survival analysis of all-cause mortality at 72 weeks for studies 004 and 006 demonstrated HR 0.61 [95% CI: 0.28, 1.29] and HR 0.95 [95% CI: 0.48, 1.87], respectively (as shown in Table 6). When survival was evaluated at a cut-off of 52 weeks in Studies 004 and 006, the hazard ratio was numerically more favorable than it was at 72 weeks. Other analyses were done post-hoc and/or with prior knowledge of previous results of Studies 004 and 006. Therefore, the robustness of these results is uncertain.

Death can be defined and analyzed in a number of different ways, depending on the outcome of interest. In general, on-treatment mortality has been thought to inform the safety of a drug, while vital-status assessment has been thought to inform the efficacy of a drug with respect to disease modification/survival. When examining deaths at vital status-end of study, it is notable that pirfenidone is not statistically better than placebo; however, the result is numerically favorable [HR: 0.75, 95% CI: 0.50, 1.11] (See Figure 5).

Figure 5. Kaplan-Meier Curve for Time to Death Assessed at Vital Status: Studies 016, 004, and 006



Taking all these complexities into account, it is difficult to say with certainty which analysis represents “the truth” regarding the effect of pirfenidone on all-cause mortality.

The Agency has encouraged the investigation of mortality as an endpoint in IPF clinical trials. In this particular case, it was the Agency's intention that the mortality analysis support and provide credibility to an uncertain primary endpoint (FVC). For the reasons stated above, the Division does not agree that the pooled analyses of mortality provided by the Applicant (at 52 weeks and at the primary endpoint assessment for each study) are robust enough to support that pirfenidone reduces all-cause mortality as compared to placebo, given that the vital status-end of study evaluation does not demonstrate a statistically significant survival benefit. While statistical significance has not been demonstrated, in general there is evidence that survival numerically favors pirfenidone, which in turn provides support of the primary efficacy endpoint (FVC) to establish the efficacy of pirfenidone in IPF.

Efficacy Summary

With the submission of Study 016, the application now includes replicate, statistically significant results for the efficacy of pirfenidone compared to placebo with respect to change from baseline in lung function (forced vital capacity, FVC). While there is uncertainty around the use of FVC as a primary endpoint in IPF clinical trials, replication in two studies, as well as numerical support from important secondary endpoints, including survival, provide substantial evidence of efficacy and support the approval of pirfenidone for the treatment of IPF.

8 Safety

The safety database for pirfenidone comes primarily from Studies 004, 006, and 016. The safety data from Studies 004 and 006 were evaluated at the time of the original submission. Addition of data from Study 016 has not led to a change in the overall safety profile. Therefore, for the purposes of this review, and because the three studies together will inform labeling, the safety discussion in this review will focus on the pooled safety database of all three studies and on the dose proposed for marketing (2403 mg/day). When relevant, differences from the safety profile in the original submission may be noted. Safety assessments in the phase 3 clinical trials included adverse events (AEs), physical examinations, vital signs, electrocardiograms, and laboratories. Pirfenidone is approved for marketing outside of the U.S. A summary of the worldwide post-marketing experience will also be reviewed here.

Controlled Clinical Studies

- **Extent of Exposure**

In Studies 004, 006, and 016, 623 patients received 2403 mg/day of pirfenidone and 624 patient received placebo. The mean treatment duration was similar between treatment and placebo groups (14.2 months vs. 14.4 months, respectively). Because dose reductions were allowed per-protocol for management of adverse events, it is important to note that the majority of patients remained at or near the full dose (2403 mg/day) for the planned treatment period of 52 weeks in Study 016 and \geq 72 weeks in Studies 004 and 006, with approximately 65% of patients receiving average doses of 2200 mg/day or higher and approximately 80% receiving average doses of 1800 mg/day or higher. The demographic and baseline characteristics are similar to those described in Section 7.

- Adverse Events Leading to Discontinuation

More patients discontinued treatment early due to adverse events in the pirfenidone treatment group (14.6%) than in the placebo group (9.6%). Adverse events leading to discontinuation by ≥ 2 patients in the pirfenidone group and at a higher frequency than the placebo group included rash (1.3% vs. 0), nausea (1.1% vs. 0), weight decreased (0.8% vs. 0), photosensitivity reaction (0.6% vs. 0.2%), respiratory failure (0.5% vs. 0.2%), hepatic enzyme increased (0.5% vs. 0.2%), bladder cancer (0.5% vs. 0), vomiting (0.3% vs. 0.2%), GERD (0.3% vs. 0), malaise (0.3% vs. 0), and dysgeusia (0.3% vs. 0).

- Adverse Events Leading to Dose Reduction or Treatment Interruption

Overall, more patients in the pirfenidone group compared to the placebo group required a dose reduction (46% vs. 29%, respectively) or treatment interruption (41% vs. 25%, respectively). Expectedly, dose reduction or treatment interruptions for adverse events occurred more frequently in the pirfenidone group (43%) compared to the placebo group (16%). Adverse events leading to dose reduction or interruption were most commonly due to GI disorders (19% pirfenidone, 6% placebo) and skin disorders (18% pirfenidone vs. 2% placebo). Within GI disorders, the most common adverse events leading to dose reduction/treatment interruption included nausea (7.5% pirfenidone, 1.6% placebo), diarrhea (4.2% pirfenidone, 1.9% placebo), and vomiting (2.9% pirfenidone, 0.6% placebo). Within skin disorders, the most common adverse events leading to dose reduction/treatment interruption included rash (9.8% pirfenidone, 1.0% placebo), photosensitivity reaction (3.9% pirfenidone, 0.2% placebo), and pruritis (2.1% pirfenidone, 0.2% placebo). The above-listed adverse events include those that were identified in the dose-reduction guidelines for the phase 3 protocols.

- Deaths

Deaths were discussed in detail in the efficacy discussion. Generally, fewer patients in the pirfenidone group than in the placebo group died within 28 days of the last dose from any cause. In both groups, IPF was the most common cause of death [pirfenidone n=10 (1.6%) vs. placebo n=21 (3.4%)]. Other causes of death in more than 2 patients were respiratory failure (5 patients, 0.8% in both groups) and pneumonia (3 patients, 0.5% in both groups). All other causes occurred in 2 or fewer patients.

- Serious Adverse Events

The proportions of patients who experienced at least one serious adverse event (SAE) were similar in the pirfenidone and placebo groups (27% vs. 29%, respectively). The proportion of patients with an SAE is not surprising given the long duration of the trials and the older population with a severe disease and multiple co-morbidities. Overall, the incidence of individual SAEs was low, and the three most frequently reported SAEs (IPF, pneumonia, and respiratory failure) were reported in a smaller proportion of pirfenidone-treated patients compared with placebo-treated patients. SAEs that were reported more frequently in the pirfenidone 2403 mg/day group compared to placebo included the following: coronary artery disease [n=7 (1.1%) vs. n=3 (0.5%)] and angina pectoris [n= 6 (1.0%) and n=2 (0.3%)].

- Common Adverse Events

Overall 99% of patients treated with pirfenidone and 98% of patients treated with placebo reported AEs. The sponsor defined common adverse events as those occurring in $\geq 5\%$ of patients in any treatment group. When looking at common adverse events, 97% of pirfenidone- and 94% of placebo-treated patients experienced an AE. Table 9 shows those common adverse events that occurred in $\geq 5\%$ and more frequently in pirfenidone versus placebo-treated patient, presented in order of decreasing frequency. Nausea, rash, and abdominal pain were the most common adverse events reported in patients treated with pirfenidone 2403 mg/day.

Table 9. Common Adverse Events Occurring in $\geq 5\%$ of Pirfenidone-Treated Patients and More Commonly than Placebo		
Preferred Term	Number of Patients, n (%)	
	Pirfenidone 2403mg/day (N=623)	Placebo (N=624)
Nausea	225 (36.1)	97 (15.5)
Rash	189 (30.3)	64 (10.3)
Abdominal Pain [†]	180 (28.9)	102 (16.3)
Upper respiratory tract infection	167 (26.8)	158 (25.3)
Fatigue	162 (26.0)	119 (19.1)
Diarrhea	161 (25.8)	127 (20.4)
Headache	137 (22.0)	120 (19.2)
Dyspepsia	115 (18.5)	43 (6.9)
Dizziness	112 (18.0)	71 (11.4)
Vomiting	83 (13.3)	39 (6.3)
Anorexia	81 (13.0)	31 (5.0)
GERD	69 (11.1)	44 (7.1)
Sinusitis	68 (10.9)	64 (10.3)
Insomnia	65 (10.4)	41 (6.6)
Weight Decreased	63 (10.1)	34 (5.4)
Arthralgia	62 (10.0)	44 (7.1)
Photosensitivity Reaction	58 (9.3)	7 (1.1)
Decreased Appetite	50 (8.0)	20 (3.2)
Pruritis	49 (7.9)	33 (5.3)
Influenza	41 (6.6)	38 (6.1)
Asthenia	40 (6.4)	24 (3.8)
Pharyngolaryngeal pain	38 (6.1)	36 (5.8)
Dysgeusia	36 (5.8)	14 (2.2)
Non-cardiac chest pain	32 (5.1)	25 (4.0)

[†] includes preferred terms abdominal pain, abdominal pain upper, abdominal distension, and stomach discomfort

The majority of patients reported adverse events as mild or moderate (67%) in severity. Approximately one-third of patients (33%) experienced severe (Grade 3) or life-threatening (Grade 4) adverse events (Table 10).

Table 10. Adverse Events by Severity†		
	Number of Patients, n (%)	
	Pirfenidone 2403mg/day (N=623)	Placebo (N=624)
At least one AE	617 (99.0)	611 (97.9)
Maximum intensity grade		
Grade 1 (mild)	87 (14.0)	104 (16.7)
Grade 2 (moderate)	324 (52.0)	307 (49.2)
Grade 3 (severe)	175 (28.1)	155 (24.8)
Grade 4 (life-threatening)	31 (5.0)	45 (7.2)

†Severity classified by CTCAE criteria.

There were a slightly larger proportion of patients in the pirfenidone group compared to the placebo group with at least one Grade 2 (52% vs. 49%) or Grade 3 AE (28% vs. 25%). Among common adverse events (those AEs occurring in $\geq 5\%$ of patients), those of Grade 3 intensity that occurred in ≥ 3 patients in either treatment group and in a larger number of pirfenidone-treated patients were primarily gastrointestinal (nausea, diarrhea, GERD, vomiting) or dermatologic (rash, photosensitivity reaction). Similarly, among the common adverse events, the only events of Grade 4 intensity that occurred more commonly in pirfenidone-treated patients compared to placebo were pneumonia (3 vs. 2) and dyspnea (1 vs. 0); however, these two adverse events were not reported overall in more pirfenidone-treated patients compared to placebo-treated patients.

- Adverse Events of Special Interest

Prior to the original submission of Studies 004 and 006, a number of clinically important events were selected as adverse events of interest (AESIs). After unblinding of data from studies 004 and 006, these AESIs were reviewed, and the list was refined to include only those adverse events that occurred with an increased frequency in patients receiving pirfenidone. No new AESIs were identified with the addition of data from Study 016, and two previously identified events (fatigue and hyponatremia) were eliminated based on this review. In addition, reports from post-marketing experience (see below) identified two new events of interest: agranulocytosis and angioedema.

1. *Liver-Related Adverse Events*

Elevation of serum liver transaminases is a known safety signal with pirfenidone. The cumulative liver safety data which is comprised of studies 004, 006, and 016 is consistent with the liver safety profile observed in the original submission (studies 004 and 006).

- a) Hepatic Events

The Applicant conducted a Standard MedDRA Query (SMQ) of “Possible Drug-Related Hepatic Disorders – comprehensive search”. More pirfenidone patients reported an adverse event in this SMQ than placebo patients (9.5% vs. 4.3%).

Table 11. Hepatic Events[†] Occurring in ≥1% of Pirfenidone-Treated Patients and More Frequently than Placebo – Pooled Safety Database (Studies 004, 006, 016)		
	Number of Patients, n (%)	
	Pirfenidone 2403mg/day (N=623)	Placebo (N=624)
Any hepatic event	59 (9.5)	27 (4.3)
GGT increased	24 (3.9)	11 (1.8)
ALT increased	20 (3.2)	9 (1.4)
AST increased	17 (2.7)	9 (1.4)
Liver function abnormal	8 (1.3)	3 (0.5)

[†]Possible Drug-Related Hepatic Disorders – Comprehensive Search (SMQ) MedDRA Version 11.0.
Source: ISS, Table 28, p. 101

Hepatic events that were deemed SAEs were reported in 6 pirfenidone patients (1.0%) and 1 (0.2%) placebo patient. The SAEs in the pirfenidone patients were hepatitis (n=2, 0.3%), liver function test abnormal (n=2, 0.3%), ALT/AST increased (n=1, 0.2%), and hepatic neoplasm (n=1, 0.2%). None of the SAEs resulted in death.

In most of these cases, pirfenidone was permanently discontinued (even when confounding factors were noted), and liver enzyme abnormalities resolved. It is notable that in one patient with a reported SAE of moderate liver function test abnormality, treatment was interrupted, ALT and AST elevations resolved, treatment was restarted, and subsequent liver transaminases were within the normal range or mildly elevated throughout the remainder of study participation.

One patient with an SAE of severe hepatitis was reported by the Applicant as a potential Hy's law case. The patient was a 75 year-old male with IPF, diabetes, hypercholesterolemia who was concomitantly taking multiple medications including atorvastatin, naproxen, and metformin. The patient began pirfenidone with normal liver transaminases, but a slightly elevated total bilirubin (~1.5x ULN). During the course of treatment his liver transaminases and bilirubin increased (ALT to 5x ULN, AST to 4x ULN, total bilirubin 2.5x ULN), however his alkaline phosphatase was also noted to be elevated (3x ULN). Multiple confounding medications were discontinued, as well as pirfenidone. Mild scleral icterus was also noted. The patient underwent genetic testing that confirmed the diagnosis of Gilbert's disease and pirfenidone was not re-started. Liver enzyme abnormalities resolved, and the patient later expired due his underlying IPF.

b) Liver Enzyme Elevations

In all three studies, serial liver enzyme testing was required, with more frequent testing in the early months of treatment. In addition, dose modification guidelines based on liver enzyme abnormalities were also protocol-specified in all three studies. The primary analyses of liver chemistry data in the pooled safety database by multiples of the upper limit of normal are shown in the table below.

Table 12. Worst Elevations in Liver Chemistry Tests by Multiples of the Upper Limit of Normal– Pooled Safety Database (Studies 004, 006, 016)		
	Number of Patients, n (%)	
	Pirfenidone 2403mg/day (N=623)	Placebo (N=624)
AST increased		
3 to 4.99 x ULN	8 (1.3)	3 (0.5)
5 to 9.99 x ULN	4 (0.6)	0
10 to 19.99 x ULN	1 (0.2)	0
ALT increased		
3 to 4.99 x ULN	12 (1.9)	2 (0.3)
5 to 9.99 x ULN	6 (1.0)	1 (0.2)
10 to 19.99 x ULN	2 (0.3)	0
AST or ALT increased		
3 to 4.99 x ULN	15 (2.4)	3 (0.5)
5 to 9.99 x ULN	6 (1.0)	1 (0.2)
10 to 19.99 x ULN	2 (0.3)	0
Alkaline Phosphatase increased		
> 1.5 x ULN	8 (1.3)	3 (0.5)
Total Bilirubin increased		
>1 to 1.49 x ULN	15 (2.4)	28 (4.5)
> 1.5 to 1.99 x ULN	0	2 (0.3)
> 2 x ULN	1 (0.2)	0
ALT or AST + Total Bilirubin increased		
> 3 x ULN + > 2 x ULN	1 (0.2)	0

Source: ISS, Table 3.13-56N, p. 4857

In the pooled safety database, ALT and AST elevations were infrequent, but did occur in a larger proportion of pirfenidone patients than placebo patients. In the majority of cases, liver enzyme elevation first occurred in the initial 6 months of treatment. The two pirfenidone patients with ALT or AST elevations of 10 to 19.99 X ULN were the patient described above with undiagnosed Gilbert’s disease, and one additional patient who had an asymptomatic rise in her liver enzymes at day 169 after pirfenidone was started (ALT 449 U/L, AST 189 U/L, and GGT 199 U/L), with resolution after study drug discontinuation.

For ALT or AST elevations 3 to 5x ULN (in the absence of symptoms or bilirubin > 2 x ULN), the protocols allowed dose reduction or interruption if clinically appropriate, with subsequent re-titration to full dose, as tolerated. Fifteen (15) pirfenidone-treated patients had a maximum post-baseline ALT or AST elevation of 3 to 5x ULN (see Table 10). Of note, 12 of these patients remained on pirfenidone until study completion, with n=7 on a full dose, and n=5 on a reduced dose. Also of note, the 3 discontinued patients stopped treatment for reasons unrelated to the liver.

Two additional cases meeting Hy’s Law criteria were identified by the Applicant in the post-marketing database. Both occurred early in treatment (by Week 13), and showed reversal of the elevated liver enzymes on study drug discontinuation.

The Applicant proposes that regular liver enzyme monitoring and dose-modification guidelines are necessary, especially during the first 6 months of therapy, with new onset

symptoms prompting even more frequent testing. The Applicant proposes in labeling that ALT, AST, and bilirubin should be measured prior to initiation of therapy with pirfenidone in all patients, then monthly for the first 6 months and every 3 months thereafter. If a patient exhibits a greater than 3 but less than 5 X ULN ALT and/or AST elevation without hyperbilirubinemia after starting pirfenidone therapy, confounding medications should be discontinued and the patient monitored closely, including with repeat liver chemistry tests. The daily dose may be maintained at full dose, if clinically appropriate, or reduced or interrupted (e.g. until liver chemistry tests return to normal), with subsequent upward titration to full dose as tolerated. If a patient exhibits the same enzyme abnormalities as listed above with symptoms or hyperbilirubinemia, or greater than 5 x ULN ALT and/or AST, pirfenidone should be permanently discontinued and the patient should not be re-challenged.

The Division obtained consultation from the OSE regarding the liver safety signal, in order to better inform the labeling of pirfenidone, as it was unclear if routine monitoring should be included in the labeling. After consultation with our OSE colleagues, the Division has decided that the monitoring and dosage modification guidelines as proposed by the Applicant are reasonable, as they are based on what was done during the clinical development program.

2. Photosensitivity and Rash

Rash was reported for 30% of pirfenidone patients and 10% of placebo patients. In the pirfenidone treatment group, 4 patients (0.6%) had a severe (Grade 3) rash, one patient had an SAE, and 8 patients (1.3%) discontinued secondary to rash. Photosensitivity reaction was reported for 9% of pirfenidone patients versus 1% of placebo patients. In the pirfenidone group, 5 patients (0.8%) had a severe (Grade 3 rash), 1 patient had an SAE, and 4 patients (0.6%) discontinued treatment. The majority of patients who reported rash or photosensitivity reaction did so within the initial 6 months of treatment. There were no rash or photosensitivity events that were considered life-threatening, led to hospitalization, or resulted in death. Specifically, there were no cases of Stevens-Johnson syndrome, erythema multiforme, pemphigus, or toxic epidermal necrolysis (TEN) reported.

3. Gastrointestinal Adverse Events

The most common GI adverse events reported more frequently in pirfenidone patients when compared with placebo include nausea (36% vs. 16%), diarrhea (26% vs. 20%), dyspepsia (19% vs. 7%), vomiting (13% vs. 6.3%), and GERD (11% vs. 7%). Overall, the GI events tended to be mild to moderate in severity, with few discontinuations ($\leq 1\%$) and few hospitalizations (n=5) overall.

4. Dizziness and Falls

Dizziness was reported for more patients in the pirfenidone group as compared with placebo patients (18% vs. 11%, respectively). An analysis of the relationship between falls and dizziness revealed that 5.4% (6/112) pirfenidone patients who reported dizziness fell at some time after the dizziness was reported.

Post-marketing Safety

As of August 2013, pirfenidone was commercially available in 13 countries (Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Luxembourg, Norway, Sweden, and the United Kingdom). Approximately 15,000 patients have been exposed to pirfenidone as of February 2014. The safety profile in the post-marketing setting is consistent with that in the controlled clinical trials with two exceptions. Two new adverse events of agranulocytosis (3 patients) and angioedema (14 patients) cases were identified in the post-marketing setting.

Safety Summary

The three phase 3 trials are adequate to assess the safety of pirfenidone for this patient population. Overall, there were numerically fewer deaths in the pirfenidone treatment groups compared to placebo. More patients discontinued study treatment due to AEs in the pirfenidone groups compared to placebo. Overall, the incidence of SAEs was balanced across treatment groups, and the three most frequently reported SAEs (IPF, pneumonia, and respiratory failure). Adverse events (most commonly GI-related or skin-related) also led to dose reduction and/or treatment interruption more frequently in the pirfenidone treated patients. The clinical program suggests that pirfenidone has some significant safety signals, the most notable of which is the signal for liver injury. Given the devastating nature of IPF, we consider this risk to be manageable via careful labeling, which will include a description of the risk, recommendations for monitoring, dose modification, and/or treatment interruption.

9 Advisory Committee Meeting

During the first review cycle, a Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was held on March 9, 2010. The committee was asked questions regarding the efficacy and safety data and a question regarding approval. The committee was split regarding whether there was substantial evidence of efficacy (7 yes, 5 no). Safety was not a major concern as the committee voted that the safety data was adequate for patients with IPF (9 yes, 3 no). Regarding the approval question, the results were in favor of approval (9 yes, 3 no). Notably, two committee members who voted that there was not sufficient efficacy data subsequently voted in favor of approving pirfenidone. After the advisory committee meeting, the Agency received communications from academic physicians, patients, and patient advocacy groups that voiced concern as to whether efficacy had been established for pirfenidone. Subsequently, the original submission was also discussed at a Center Regulatory Briefing on April 6, 2010. The general consensus of the panel was that efficacy had not been demonstrated. While the advisory committee was in favor of approval, and likely trying to respond to an unmet need, the Division assessed the totality of the data and expert input, and issued a Complete Response, due to lack of demonstration of efficacy.

A PADAC was not convened for the resubmission. With the resubmission, the Applicant has provided replicate evidence of efficacy with respect to a lung function endpoint, and an integrated analysis of all three studies which suggests a survival benefit. The safety profile remains consistent with what was reviewed and presented to the committee in 2011. As a result, an additional PADAC meeting was not required as there were no outstanding issues to be discussed or uncertainty around approvability.

10 Pediatrics

Idiopathic pulmonary fibrosis is a disease of older adults. Pediatric studies were waived for pirfenidone as IPF does not occur in the pediatric patient population. In addition, as a drug with orphan designation, a pediatric development plan is not required.

11 Other Relevant Regulatory Issues

Final report of the DSI inspections revealed adherence to Good Clinical Practices. Minor deficiencies were noted, but these were isolated and deemed unlikely to impact data integrity and patient safety. During review of the submission no irregularities were found that would raise concerns regarding data integrity. All studies were performed in accordance with acceptable ethical standards. The Applicant provided the required financial disclosure information for investigators. The financial disclosure information (review attached at the end of this memo) did not suggest a conflict with the investigators.

12 Labeling

The Applicant submitted a product label in the new PLR format. The main areas of revision include changes to Section 14 Clinical Studies, to present the data by efficacy endpoint, [REDACTED] ^{(b) (4)}. The Division has also asked that the Applicant include a cumulative responder distribution for FVC. Reporting of the survival analysis was a topic of extensive internal discussion within the Agency. As a result of the discussion, the decision was made to include the mortality analysis at vital status assessment, with inclusion of a Kaplan-Meier curve. Major changes to the labeling have been agreed upon at the time of this review; however minor changes to labeling are still under discussion.

From a safety standpoint, consultation with the OSE liver safety team helped to inform revisions to dosage modification and the warnings/precautions section regarding elevated liver enzymes. Various labeling consultants also provided input on the PI and PPI, and their revisions were incorporated.

13 Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The recommended regulatory action is **Approval**. From a clinical standpoint, the Applicant has demonstrated substantial evidence of efficacy for pirfenidone. In the submitted program, Studies 016 and 004 demonstrated a statistically significant improvement in the change from baseline in percent predicted FVC, which was supported by important secondary endpoints including mortality.

- Risk-Benefit Assessment

The efficacy of pirfenidone has been adequately established for the reasons outlined above; replicate evidence showing benefit in FVC decline is supported by a numerical trend in favor of pirfenidone. The two phase 3 studies (004 and 006) submitted in 2011 were considered adequate to assess the safety of pirfenidone. The new submission provides the

safety data from a third study (016). The safety profile remains relatively unchanged from the original review cycle. The clinical program suggests that elevated liver enzymes, gastrointestinal adverse events, photosensitivity, and rash are pirfenidone-related safety signals. For the most part, these appear to be patient tolerability issues which can be managed by dosage modification. Liver injury, though a concerning safety signal, can be managed through labeling. Demonstration of efficacy for a disease such as IPF, which is uniformly progressive and fatal, and for which there are currently no approved or effective therapies, firmly establishes a risk-benefit assessment in favor of approval of pirfenidone.

- Recommendation for Postmarketing Risk Management Activities

Beyond routine pharmacovigilance, no post-marketing risk management activities are recommended nor required.

- Recommendation for other Postmarketing Study Commitments

There are no post-marketing study commitments or requirements at this time.

- Recommended Comments to Applicant

None

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA 22-535

Submission Date(s): May 23, 2014

Applicant: InterMune, Inc.

Product: Pirfenidone capsules

Reviewer: Banu Karimi-Shah

Date of Review: October 6, 2014

Covered Clinical Study (Name and/or Number): PIPF-016

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: 168 investigators; 1104 sub-investigators		
Number of investigators who are sponsor employees (including both full-time and part-time employees): None		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>None</u>		
<p>If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):</p> <p>Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____</p> <p>Significant payments of other sorts: _____</p> <p>Proprietary interest in the product tested held by investigator: _____</p> <p>Significant equity interest held by investigator in sponsor of covered study: _____</p>		
Is an attachment provided with details of the disclosable financial interests/arrangements:	N/A	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	N/A	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) None.		
Is an attachment provided with the reason:	Yes <input type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

Discuss whether the applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*.⁹ Also discuss whether these interests/arrangements, investigators who are sponsor employees, or lack of disclosure despite due diligence raise questions about the integrity of the data:

- If not, why not (e.g., study design (randomized, blinded, objective endpoints), clinical investigator provided minimal contribution to study data)
- If yes, what steps were taken to address the financial interests/arrangements (e.g., statistical analysis excluding data from clinical investigators with such interests/arrangements)

Briefly summarize whether the disclosed financial interests/arrangements, the inclusion of investigators who are sponsor employees, or lack of disclosure despite due diligence affect the approvability of the application.

The applicant submitted FDA Form 3454 certifying investigators and their spouses/dependents were in compliance with 21 CFR Part 54. No potentially conflicting financial interests were identified.

⁹ See [web address].

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

BANU A KARIMI SHAH
10/09/2014