

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

Hepatology Consultation

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 22 September 2014
FROM: John R. Senior, M.D.
Associate Director for Science (Hepatology)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)

TO: Badrul Chowdhury, M.D., Director, Division of Pulmonary, Allergy, and
Rheumatology Products (DPARP)
Mary H. Parks, M.D, Deputy Director, DRARP
Banu A. Karimi-Shah, M.D., Clinical Team Leader, DPARP

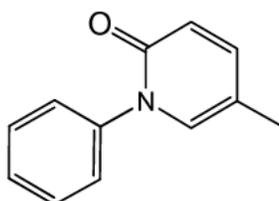
VIA: Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic effects of pirfenidone (ESBRIET[®], InterMune, Inc.), NDA 022535 submitted
4 November 2009 for treatment of idiopathic pulmonary fibrosis (IPF)

Documents reviewed:

- 1) Consultation request from DPARP dated 11 August 2014 asking for review of findings related to liver toxicity, desired response date 20 August 2014;
- 2) Previous review of original NDA dated 1 April 2010, by Dr. Banu Karimi Shah advising complete response; updated review of resubmission 29 August 2014
- 3) Submitted data on additional 555 subjects in the ASCEND study;
- 4) Request 21 August to sponsor for data reviewed by (b) (4)
- 5) Slide set 5 September by Dr. Karimi-Shah on pirfenidone and nintedanib
- 6) Selected pertinent medical literature articles

Pirfenidone (b) (4) was discovered about 1995 to be orally active against chemical-induced lung fibrosis in animals. It was anti-inflammatory and anti-fibrotic, was found to inhibit synthesis of transforming growth factor-beta (TGF- β) and tumor necrosis factor-alpha (TNF- α). Its chemical structure is 5-methyl-1-phenyl-2(1H)-pyridinone:



pirfenidone

As produced, it is a pale yellow powder, insoluble in water, soluble in many organic solvents. After many other treatments and combinations had failed, pirfenidone was the first drug that had showed real promise. It was first studied in patients with idiopathic pulmonary fibrosis (IPF) by Raghu et al. and reported in 1999. The sponsor of the drug was a Texas firm, Marnac, Inc. that later licensed the rights to develop it to the Japanese firm Shionogi that obtained October 2008 approval to market it in Japan, South Korea, and Taiwan as PIRESPA®. Marnac also licensed pifenidone to InterMune, in March 2002, who then submitted IND 067284 on 21 April 2003. InterMune carried out two pivotal clinical trials, PIPF-004 and -006, in North America, Europe, and Australia, referred to as the CAPACITY studies (Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes), reported by Noble et al. in 2011, well after submission of the NDA on 4 November 2009 and its Complete Response decision on 4 May 2010. That decision was reached after careful reviews, despite an Advisory Committee vote of 9-3 for approval, because study PIPF- 006 failed to support the favorable findings of the almost simultaneous study PIPF-004, as detailed in the reviews by Dr. Banu Karimi-Shah, who had been the primary clinical reviewer since November 2009 when the NDA was submitted, but her opinion was concurred with by Drs. Sally Seymour, Badrul Chowdhury, and Curtis Rosebraugh. No good explanation was found for the discrepancy in efficacy between the two studies, despite some retrospective speculations by the sponsor. The main issue was the dependence on reduced rate of decline of forced vital capacity (FVC) as a surrogate for efficacy, in face of no reduction in mortality and unclear definitions of how much reduction in FVC, how soon, and for how long would be needed.

Meanwhile, pirfenidone was approved for treating IPF in India as PIRFENEX in October 2010, in Europe as ESBRIET in 2011, in China as ETUARY in 2013, and in Mexico as KITOSCELL LP in 2014 for both IPF and liver fibrosis..

In consequence of the 2010 complete response (non-approval), the sponsor InterMune, initiated another study dubbed as ASCEND, results of which were recently published (King et al. 2014). The study was conducted under a new protocol from 13 June 2011 to 6 February 2014 at 127 sites (87 in the United States, 11 in Australia, 8 in Peru, 6 in Brazil, 5 in Israel, 5 in Mexico, 2 in Croatia, 2 in New Zealand, and 1 in Singapore). The clinical review by Dr. Karimi Shah is now available, and the published paper reports that 278 patients with IPF randomized to 2403 mg/day pirfenidone for 52 weeks showed >10% decline of FVC in 16.5%, compared to 31.8% in the 277 randomized to placebo, and 22.7% who showed no decline, compared to 9.7% in those on placebo.. The pirfenidone-treated group also showed reduced decrease in 6-minute walking distance, and 3 deaths from IPF after 52 weeks, compared to 7 in those on placebo. The study population included very few patients from Europe, where pirfenidone had been approved and placebo treatment was unethical.

The major adverse effect was gastrointestinal intolerance of the drug, with dyspepsia, anorexia, nausea, vomiting, only partially ameliorated by taking medication with meals. It was initially administered as one capsule containing 267 mg pirfenidone t.i.d. with meals in the first week, two capsules t.i.d. the second week, and three capsules t.i.d. thereafter. It was deemed important for patients to reach and tolerate the full dose of 9 capsules/day (2403 mg) because a lower dose of 9 capsules of 133 mg pirfenidone each (1197 mg/day) was not effective, as found in study PFIF 004. Increases in serum activities of ALT, AST, and GGT were found more often in

patients taking pirfenidone than placebo, but the elevations were frequently reversible, not progressive to serious liver injury and dysfunction. This had been noted with the previous NDA review in 2009, and was confirmed by the additional data from study PFIF 016 currently under review. Because of the very short turn-around requested for this consultation, and the informal decision of DPARP that the drug is now approvable, I was asked to focus on labeling to be recommended for this drug and another new drug (nintedanib, NDA 205832) also currently under review, which will be commented upon separately. However, I shall be interested in InterMune's reply to the DPARP 21 August request for details concerning their consultant's (b) (4) opinion on four cases and the data given to him.

Comment: Effects in slowing progression of IPF by both drugs suggest that possibly they may be used together as well as separately. With approval of both agents, it will no longer be ethical to conduct placebo-controlled studies. It was announced in August 2014 that Roche has acquired InterMune for \$8.3 billion (Rockoff and Plumridge, today), which may result in a competitive marketing battle between two large sponsoring companies to extend sales of the drugs. This is an exciting time, but the enthusiastic celebrations should be tempered by humility because only 1,270 patients with PDF have been treated with effective doses of the two agents, compared to another 1057 randomized to placebo. Neither drug cures or completely stops the relentless progression of IPF, at least so far. Both drugs are very likely to be promoted aggressively to tens or hundreds of thousands of IPF patients worldwide. But much remains to be learned about how to use these drugs, singly or in combination, how to optimize beneficial effects and minimize the very uncomfortable gastrointestinal adverse effects. How labeling may be used to encourage prescribers to continue to study and report adequately to the sponsors the results in patients is problematical; recommendations can be made but not enforced. There is a reasonable aim to harmonize the labeling for both drugs so that neither company can derive marketing advantage. At present there is not much to claim about a marketing advantage for the efficacy of either agent, and there are as yet almost no data on head-head comparisons, or use of combinations.

The situation with respect to possible liver injury and dysfunction is that both pirfenidone and nintedanib have been found apparently to cause at least transient elevations of aminotransferase activities indicating probable hepatocellular injury, with a few also showing some functional disturbance as indicated by rising serum bilirubin concentration, but no cases of liver failure have yet been attributed to the drug. It is a little reassuring that despite marketing of pirfenidone in Japan, South Korea, and Taiwan since 2008, in India since 2010, in Europe since 2011, and in China since 2013, that no cases have been published in which liver failure was probably caused by the drug. (There is no post-marketing experience with nintedanib in IPF patients, but perhaps some in patients with cancers treated with it, a different population.)

It may be considered useful to recall the experience with another drug important for prevention of another serious disease, tuberculosis. Isoniazid was found to cause frequent elevations of AST activities in about 15% of patients started on it, and could cause liver failure and death if used for too long in certain patients (Black et al., 1975; Kopanoff et al., 1978). A key observation leading to understanding was made by Mitchell et al. (1975) who showed that even drug-induced AST elevations >10xULN with bilirubin >2.5xULN was reversible despite continuing administration, presumably by liver adaptation to the drug. It is well known that the human liver can regenerate after 2/3 of it is resected or damaged, but it became understood the hepatocytes can also change

and adapt to chemicals even with less injury than resection or total necrosis. Four decades later we appreciate that of the 10-20% of patients who show serum transaminase elevations after starting isoniazid, almost all of them can adapt to the drug if given time, and only 1 or 2 per thousand (0.1-0.2%) cannot do so, and must have the isoniazid permanently stopped. After much concern and controversy, it was finally realized (Nolan et al., 1999) that the drug could be used safely if patients on isoniazid preventative treatment were carefully monitored for signs or symptoms of hepatotoxicity (anorexia, nausea, vomiting, jaundice, progressive rise of serum AST >5xULN, and resolution of findings after interrupting treatment with isoniazid). Because pirfenidone and nintedanib frequently cause anorexia, nausea, vomiting, the symptoms cannot be counted upon to indicate hepatotoxicity, so reliance must be placed on laboratory measures and very early detection of whole liver dysfunction. Rising bilirubin or prothrombin time (or INR) must be used to indicate early dysfunction. It may also be possible to recognize the adaptation phenomenon whereby the liver can change and become tolerant of a drug that initially causes hepatocellular injury and mild dysfunction, when using a drug important for suppressing a bad disease such as IPF or cancer.

Both sponsors have recognized that at least mild liver injury may be caused by these new drugs for treating IPF, and have proposed labeling to detect it, with action taken to prevent continuing the drug in the rare patient who is liver-intolerant of the drug or whose liver is unable to adapt. A draft suggestion for labeling is provided on the following page, to be discussed when clinical reviews have been completed and sufficient information has been gathered and analyzed.

Comment: It goes beyond the question of possible hepatotoxicity (how to detect it, how to prevent it from becoming serious, and how to avoid it) to say that it is clear that much is yet to be learned about these drugs and how best to use them. It has been recommended (Ryerson et al., 2014) that a worldwide registry of patients with IPF be established, including centers for treatment where special expertise exists, and I strongly agree with that idea. In some ways it may be unfortunate that Roche has paid a large amount to acquire the rights to pirfenidone because it will naturally lead to their seeking to expand the market, increase sales, and recoup their large investment. It is a time when cooperation is needed, and competition may be its enemy. These two drugs act by different mechanisms but at similar sites in the cycle of the progressive cycle of fibrosing lung injury and dysfunction as summarized very recently by Ahluwalia et al. (2014) in their appended diagram, referred to at the end of this document.

The problem with pirfenidone of gastrointestinal intolerance is especially troublesome, and the schedule of weekly increases in dosing from one to two to three capsules t.i.d. appears to be too rapid for some patients. Because the drug is then to be taken for the rest of their lives, perhaps it is reasonable to accept that some patients may need more time to adjust to the full daily regimen of 2403 mg. No clear instructions on how to take pirfenidone with respect to meals, but this is an opportunity to investigate alternatives.

Comment: Pirfenidone is water insoluble, so perhaps it should be given with or after lipid dietary constituents such as vegetable oils or other fatty items without increasing the overall fat content, avoiding trans-fatty acids and excess cholesterol. Dietary fats are partitioned in the intestinal epithelial cells into water soluble products that go directly to the liver via the portal vein, and fatty materials that bypass the liver as chylomicrons via the thoracic duct.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

JOHN R SENIOR
09/23/2014

Summary Basis for Regulatory Action

Date	May 4, 2010
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	22-535
Applicant Name	InterMune
Proprietary / Established (USAN) Names	Esbriet Pirfenidone
Dosage Forms / Strength	Capsule 267 mg
Proposed Indication(s)	treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function
Action:	<i>Complete Response</i>

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding pirfenidone and I refer the reader to the reviews in the action package for a more detailed discussion. Pirfenidone is a new molecular entity developed to treat the orphan indication IPF. The mechanism of action of pirfenidone is unknown but is asserted by InterMune to be based on anti-inflammatory and antifibrotic effects. The proposed dose is to titrate up to three of the 267 mg capsules three times a day (total daily dose 2403 mg). Pirfenidone was approved for the treatment of IPF in Japan in October 2008.

As discussed in the other reviews, IPF is a chronic, progressive, diffuse parenchymal lung disease characterized by interstitial fibrosis and progressive pulmonary insufficiency expressed clinically as symptoms of nonproductive cough and progressive dyspnea that uniformly leads to death. The prevalence of IPF ranges from 14 to 43 per 100,000 persons and has a median survival of 3 to 5 years but progression can vary widely between individuals. There presently are not any proven effective non-surgical treatments (lung transplant is the only option), and due to the relentless progression and lethality of IPF, there is understandably a great deal of desperation by clinicians and patients to find effective medical therapy.

As I will discuss further below, the reviewable efficacy data for this application consisted of two clinical efficacy trials (PIPF-004, PIPF-006). The primary endpoint for both trials was absolute change from baseline to Week 72 in percent predicted Forced Vital Capacity (FVC), which has many issues the main one being that change in FVC is not an established surrogate of benefit in this disease and will be discussed later in this review. While trial 004 met its pre-specified primary endpoint, trial 006 did not. When looking at the totality of the data, there also were not reassuring trends in secondary clinically important measures (including mortality) upon which to rely. As such, the application fails to meet the standard of substantial evidence of efficacy and will receive a CR action.

Efficacy

This has been thoroughly covered in Drs. Karimi-Shah, Seymour, Chowdhury and Ms. Zhou's reviews. Efficacy for this application was evaluated in two trials, 004 and 006. Each was a randomized, double-blind trial of 72 weeks duration with subjects randomized to pirfenidone 2403 mg/day or placebo (study 004 also had a pirfenidone 1197 mg/day arm). Below is a summary table of the two trials from Dr. Seymour's review (page 6).

Table 1 Summary of Clinical Program						
Study No.	Description	Subjects	Design	Dose	Duration	Endpoints
PIPF-004 US, Canada, Mexico, UK, France, Italy, Poland, Australia Jul 2006- Nov 2008	Phase 3 efficacy and safety trial	435 patients with IPF	R, DB, PC	Pirfenidone 2403 mg total daily dose [3x267mg TID] (n=174) Pirfenidone 1197mg total daily dose [3x133mg TID] (n=87) Placebo TID (n=174)	72 weeks	-change in % predicted FVC from baseline - time to worsening IPF - progression free survival
PIPF-006 US, Australia, Belgium, Germany, Ireland, Spain, Switzerland Apr 2006- Oct 2008	Phase 3 efficacy and safety trial	344 patients with IPF	R, DB, PC	Pirfenidone 2403 mg total daily dose [3x267mg TID] (n=171) Placebo TID (n=173)	72 weeks	-change in % predicted FVC from baseline - time to worsening IPF - progression free survival

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. If both trials demonstrated efficacy for this endpoint, due to the similarities between the trials, the protocol specified that the secondary outcome variables were to be analyzed using pooled data from both trials. Important secondary endpoints that Dr. Seymour highlighted in her review (page 9) included:

- time to worsening of IPF - time to acute IPF exacerbation, IPF-related death, lung transplantation, or respiratory hospitalization, whichever comes 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

As the other reviewers have expressed, we are concerned with the primary endpoint as FVC has not been an established surrogate for use to monitor disease progression. While it would seem intuitive that monitoring a lung parameter such as FVC would be appropriate given that IPF causes progressive respiratory decline, there are some issues that could make analysis challenging as pointed out by Dr. Karimi-Shah. Because FVC is not validated, there is not any guidance regarding what rate of decline is clinically important for IPF, or what type of comparison should be made, i.e. mean declines, responder analysis, slope of decline.

As such, a ‘hard’ endpoint such as mortality would be ideal. However, many experts (including one of two SGE’s we have consulted) are concerned about the practicalities of using this endpoint in a study. They have cautioned that the desperation of the patient causes them to ‘shop’ clinical trials, making long-term clinical trials very difficult to perform, particularly in a limited population. As such, and due to lack of suitable alternatives and not wanting to stall develop programs, we are willing to consider change in FVC, but due to the uncertainties surrounding its use, we need convincing evidence that there was been a substantial and clinically important change in modulating respiratory decline through drug use (including support from other secondary endpoints). While we do not have a recognized amount of change in FVC that we consider clinically important, some experts and literature (as discussed by Dr. Seymour and others) considered a 10% change to be clinically important. This amount of change is useful in putting the trial results in context.

Below from Dr. Seymour’s review (Page 9-10) are the definitions of different definitions applied to the dataset used for the efficacy analysis.

- Treatment Period – data for all patients up to the September 2008 cutoff used by InterMune; some patients would have > 72 weeks treatment; this dataset was used for some efficacy analysis
- On-Treatment - data for all patients while on study medication and 28 days after the last dose of study medication; primary dataset for safety endpoints
- Vital Status at End of Study – data including the Treatment Period (Sept 2008 cut-off) and subsequent follow up; used for vital status only

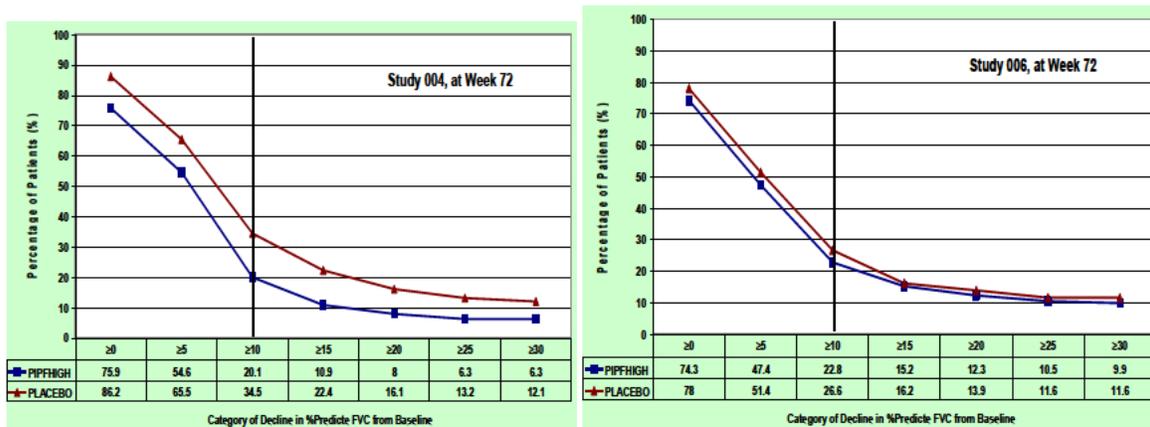
Below is a summary table of the efficacy results (Dr. Seymour’s review page 10).

Table 2 Primary Efficacy Endpoint				
Mean Change in Percent Predicted FVC from Baseline to Week 72*				
	Pirfenidone 1197mg/day	Pirfenidone 2403mg/day	Placebo	Difference from Placebo (p value)[†]
PIPF-004	-9.9 (n=87)	-8.0 (n=174)	-12.4 (n=174)	4.4 (p < 0.001)
PIPF-006		-9.0 (n=171)	-9.6 (n=173)	0.6 (p=0.501)
* Missing data imputed: if patient died, then 0 imputed; if patient alive imputation by the sum of squared differences method (SSD)				
[†] comparison for pirfenidone 2403mg/day group; rank ANCOVA with imputation of missing data				

As demonstrated above, trial 004 did demonstrate a statistically different change comparing pirfenidone to placebo with a difference in absolute change from baseline percent predicted FVC of 4.4%, while trial 006 was not statistically significant.

While we have not defined a necessary difference in FVC change between active drug and placebo in IPF needed to demonstrate clinical significance, Dr. Seymour’s review included a responder analysis figure (page 11) demonstrating that there is a difference between pirfenidone and placebo groups in change from baseline percent predicted FVC when using a 10% cut point for Trial 004 but not for Trial 006.

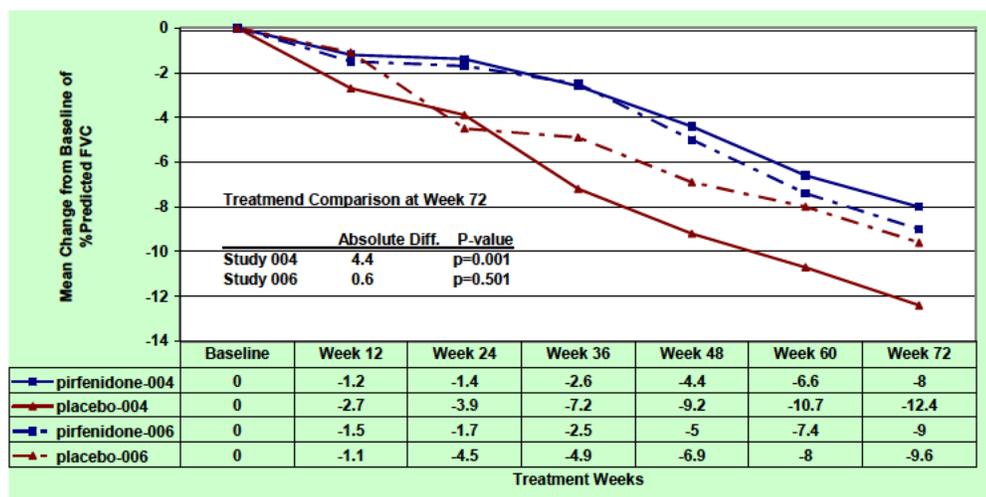
Figure 1 Cumulative % of Patients of Change from baseline in %Predicted FVC



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.

The primary endpoint compared the landmark change of FVC at 72 weeks. Below is a Figure from Dr. Seymour’s review (page 11) that demonstrates the FVC evaluations over time.

Figure 2 Mean Change in Percent Predicted FVC from Baseline*



* pre-specified imputation for missing data; Rank ANCOVA

This figure demonstrates that the decline in FVC for the pirfenidone groups in trial 004 and 006 was very similar over the course of 72 weeks, but there was a difference in the placebo groups decline with separation around week 24. While this could be a demonstration of the variable nature of the decline in lung function (waxing and waning) that occurs in IPF, it is perplexing and does not help in illumination of which of these studies is demonstrating what the ‘truth’ is regarding the effect pirfenidone has in the treatment of IPF. While one could come up with many theories (like the sponsor has) on why there were difference between the two trial’s placebo groups (and why trial 004 is the ‘truth’), they are theories and none give

satisfying arguments that the evidence is substantial that pirfenidone has the effect purported. Also, while trial 004 does have a highly significant p-value for the primary endpoint and we will sometimes consider a single trial, 004 does not fulfill the criteria for single trial consideration in that the total effect size on FVC was very small, there is uncertainty regarding using FVC as an endpoint, it did not use a primary ‘hard’ endpoint such as mortality, and because of all the uncertainty surrounding the results, a reasonable person would not consider it unethical to conduct another trial.

The sponsor evaluated numerous secondary endpoints, and Dr. Seymour has a nice summary of the most relevant ones she had identified. I agree with her assessment. For the most part, there was not consistent evidence using the secondary endpoints that would support a conclusion that pirfenidone was effective in IPF. Regarding mortality, below is an edited table taken from Dr. Seymour’s review (page 14).

Table 3 Survival Analysis on Death				
All cause death	Number of Events (%)			Hazard Ratio [†] (95% CI), p value [‡]
	Pirfenidone 1197mg/day	Pirfenidone 2403mg/day	Placebo	
PIPF-004	N=87	N=174	N=174	
On Treatment	8 (9.2)	10 (5.8)	14 (8.0)	0.71 (0.32, 1.60), p=0.413
Vital Status – End of Study	10 (11.5)	14 (8.0)	20 (11.5)	0.68 (0.34, 1.34), p=0.268
PIPF-006		N=171	N=173	
On Treatment		9 (5.3)	15 (8.7)	0.59 (0.26, 1.36), p=0.217
Vital Status – End of Study		18 (10.5)	17 (9.8)	1.06 (0.55, 2.07), p=0.856
Pooled PIPF-004 and 006		N=345	N=347	
On Treatment		19 (5.5)	29 (8.4)	0.65 (0.37, 1.16), p=0.146
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

While the numerical trends tend to favor pirfenidone treatment, neither individual trial nor the pooled data give convincing evidence of a mortality benefit.

Regarding progression-free survival, as discussed by the other reviewers, Trial 004 was statistically significant favoring pirfenidone treatment while Trial 006 was not. Regarding the compilation endpoint of worsening of IPF, although there were some numerical trends favoring pirfenidone treatment, neither trial demonstrated statistical significance.

I conclude that there is not substantial evidence of effectiveness to conclude that the drug will have the effect it purports in the label indication. The sponsor does not have replicate trials demonstrating efficacy of the primary endpoint, and the important secondary endpoints do not consistently provide support. As we are evaluating an endpoint (FVC) that is already tenuous,

we need consistency and reproducibility of results to have confidence that pirfenidone is actually doing something good for patients with IPF.

Safety

Dr. Seymour has a nice summary on the safety of pirfenidone that I will not repeat here. The main AEs were gastrointestinal, rash, and photosensitivity reactions. There were more study medication discontinuations due to AEs in the pirfenidone group compared to placebo (13% vs. 8%). Serious AEs were balanced between groups. Safety considerations will have to be considered in any risk-benefit analysis in future actions for pirfenidone, but due to the lack of effective therapies for this devastating disease, if the sponsor is able to provide convincing evidence of effectiveness in the future, thoughtful labeling that may include a REMS would probably mitigate most concerns.

I will briefly discuss the hepatic findings and possible Hy’s law cases referred to in Drs. Karimi-Shah, Seymour and Chowdhury’s review. Below is a table that Dr. Karimi-Shah constructed for me that has elevated ALT abnormalities.

Table 4: Most Out-of Range Post-Baseline Abnormalities in ALT (trials 004 and 006)			
Laboratory Test Result	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 345)	Placebo (N = 347)
ALT			
> ULN to > 2.5 x ULN	13 (14.9%)	49 (14.3%)	59 (17.1%)
> 2.5 x to 5 x ULN	0	12 (3.5%)	0
> 5 x to 20 x ULN	0	3 (0.9%)	1 (0.3%)
> 20 x ULN	0	0	1 (0.3%)
Missing Values	0	2	2

Source: Table 5-65 and Table 5-66, p. 275-6, Integrated Summary of Safety, Module 5.
 ALT: alanine aminotransferase; ULN: upper limit of normal

This table demonstrates an imbalance of ALT elevations between pirfenidone and placebo in the 2.5x to 5x grouping. While it is important to note imbalances of ALT < 5x, this by itself may not be problematic as many medications that do not cause overt liver failure have a similar effect on the liver. When evaluating drugs that may cause liver failure, we pay particular attention to ALT elevation imbalances that are > 5-fold. The table above has very few incidences so it is difficult to draw any conclusions, however there does not seem to be a clear imbalance of extreme ALT elevations.

Of the two cases in Dr. Karimi-Shah’s review that are under consideration to fulfill Hy’s Law criteria, the first is confounded by a cholestatic picture (greatly elevated alkaline phosphatase 10x ULN) as well as exposure to another drug (amoxicillin-clavulanate) that may have been responsible. I do not think that this case would be considered a Hy’s Law case as to make this assertion requires eliminating other potential causes such as infection or drug, and because it also requires that profound cholestasis is absent.

The second case that comes from a Japanese database for which the sponsor (and we), do not have access, would seem to fulfill Hy's Law criteria. At the very least, we should consider it a Hy's law case until such time that the sponsor can disprove this assumption. I agree with Dr. Karimi-Shah's assessment that the potential for significant hepatocellular injury with pirfenidone cannot be ruled out and should this drug be approved in the future, this issue will need to be addressed in labeling and a consideration for REMS for risk mitigation. However, considering the devastation of IPF and the present lack of established medical therapies, we would probably be willing to tolerate this type of risk if we are convinced that a therapy has a beneficial effect.

Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was held March 9, 2010. There were individual voting questions asking if efficacy (7 yes, 5 no) and safety (9 yes, 3 no) had been demonstrated as well as a question regarding if pirfenidone should be approved (9 yes and 3 no). Many comments were made from the panel members questioning whether the regulatory standard for efficacy had actually been met but panelists mentioned that they had weighted the severity of the disease, desperation of clinicians and patients including very moving testimonials made during the open public, and ultimately felt that the drug had some activity.

2. Conclusions and Recommendations

IPF is a devastating disease that presently does not have a recognized effective non-surgical therapy. Because of the limited amount of organs available for lung transplantation, as well as the morbidity associated with organ transplantation, patients and physicians are desperate for a non-surgical therapy that may have clinical benefits. We at the Agency also feel this desperation, however we must always be vigilant that we do not allow desperation to be substituted for evidence of efficacy. Approving a drug that does not have the purported effect could have devastating consequences for patients. Giving patients an ineffective drug puts them at risk for adverse effects (e.g. liver failure) without any benefit. As well, recognizing an ineffective drug therapy as effective could dampen urgency in developing therapies and delay further research efforts. There also are costs to society associated with providing a medical therapy such that we need to be sure that limited resources are used wisely for therapy that are actually effective.

Pirfenidone has one trial (004) that has statistical evidence of efficacy, and one that does not (006), on a surrogate endpoint (absolute change in mean change from baseline in FVC) that has not been correlated to improved clinical outcomes. The mean amount of change in FVC that was seen in the one trial that demonstrated that pirfenidone had an effect (4.4%) was less than what some might consider clinically important (>10%). While the pirfenidone arm in both studies had the same slope of decline in FVC, the placebo arms did not calling into questioning the true effect of the drug. Some secondary endpoints for 004 tended to trend in a positive direction, but not consistently and for 006 most did not.

It would seem to me, that since we are already relying on a surrogate marker, and are unclear on the minimal amount of change for that surrogate marker that is necessary to be considered clinically important, at the very least to fulfill our regulatory standard of substantial evidence of efficacy we would require replication of 004. Based on this, I recommend a CR action for lack of demonstration of efficacy.

Regarding what the sponsor would need to do to remediate this, at the very least they should have to replicate study 004 findings. I also think that other clinically important outcomes need to consistently trend favorable for pirfenidone use. We may also revisit the issue of whether an outcome study based on mortality can be completed.

There were also some chemistry, manufacturing and control issues as noted in Dr. Chowdhury's review that needed further attentions, but they did not seem to be substantial and should be easily remediated.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

CURTIS J ROSEBRAUGH
05/04/2010

SUMMARY REVIEW OF REGULATORY ACTION

Date: May 4, 2010

From: Badrul A. Chowdhury, MD, PhD
Director, Division of Pulmonary, Allergy and Rheumatology
Products, CDER, FDA

Subject: Division Director Summary Review

NDA Number: 22-535

Applicant Name: InterMune, Inc.

Date of Submission: November 4, 2009

PDUFA Goal Date: May 4, 2010

Proprietary Name: Esbriet

Established Name: Pirfenidone

Dosage form: Capsules

Strength: 267 mg capsules

Proposed Indications: Treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function

Action: Complete Response

1. Introduction

InterMune submitted this 505(b)(1) application for use of pirfenidone 267 mg capsules for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. The proposed dose is three capsules (267 mg each) three times a day for a total daily dose of 2403 mg, following a 2 week dose escalation schedule starting with one capsule three times a day for the first week and two capsules three times a day for the second week. The application is based on clinical efficacy and safety studies. This summary review provides an overview of the application, with a focus on the clinical efficacy and safety studies. The major issue with this application is lack of replicate demonstration of efficacy.

2. Background

IPF is a diffuse progressive parenchymal lung disease of unknown etiology, characterized by interstitial fibrosis of the lungs, nonproductive cough, and progressive dyspnea. In the United States, the prevalence of IPF is estimated to be 14 to 43 per 100,000 persons¹. Median survival in patients with IPF is estimated to be from 3 to 5 years². There are no medications approved for the treatment of IPF in the United States. IPF patients are often treated with corticosteroids and immunosuppressive agents, such as azathioprine and

¹ Raghu G, Weycker D, Edelsberg J, et al., Incidence and Prevalence of Idiopathic Pulmonary Fibrosis. *Am J Respir Crit Care Med* 2006; 174: 810-816.

² American Thoracic Society Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. *Am J Respir Crit Care Med* 2000; 161: 646-664.

cyclophosphamide. No clinical trials have demonstrated a clear clinical benefit for these therapeutic agents and the use of these agents is not FDA-approved.

Pirfenidone has been studied for various diseases including IPF for a long time. 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. Another company called Shionogi, licensed the rights to pirfenidone in Japan. Shionogi received marketing approval for pirfenidone for the treatment of IPF in Japan in October 2008, under the tradename Pirespa as a 200 mg tablet.

Pirfenidone was granted Orphan Drug Status in 2004 for the treatment of IPF. Pertinent regulatory interactions between InterMune and the Agency include an End of Phase 2 (EOP2) Meeting in December 2004, and a Pre-NDA meeting in September 2008. At these meetings the Division acknowledged that dose-ranging data were limited and advised inclusion of more than one dose in pivotal efficacy and safety studies. The Division mentioned that a single pivotal study would be unlikely to support approval unless the results were highly persuasive. The Division also raised concerns with the primary endpoint of change in forced vital capacity (FVC). The Division noted that mortality is the ideal primary endpoint for IPF clinical trials and FVC is not an established surrogate for mortality. Further, it is unclear what would constitute a clinically meaningful effect size for FVC. The Division noted that efficacy would be assessed by the totality of the data, including secondary endpoints.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product, Esbriet (pirfenidone) capsules, contains 267 mg pirfenidone and standard compendial excipients. The drug product is proposed to be packaged in bulk bottles of 270 capsules and in blister trays for a 14 day titration period or a 4 week maintenance period. The active pharmaceutical ingredient will be manufactured at (b) (4). The drug product will be manufactured at (b) (4). The packaging will be performed at (b) (4). All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate. An expiry of (b) (4) is proposed and supported by submitted data.

There are two outstanding CMC issues. First, the presence of a (b) (4) impurity needs to be addressed. Given the severity of IPF, presence of this impurity would not have impacted approval and could have been qualified post-approval. Qualification of this impurity will be listed as a deficiency in the action letter. Second, microbial limits testing method validation has not been finalized. This also will be listed as a deficiency in the action letter, if not resolved before the action.

4. Nonclinical Pharmacology and Toxicology

InterMune submitted a complete toxicology program that included general toxicology studies of 6 months duration in rats and 9 months duration in dogs, phototoxicity studies in guinea pigs and hairless mice, embryofetal development studies in rats and rabbits, and a 2 year carcinogenicity studies in mice and rats. In the general toxicology studies, the target organs of toxicity were liver, thyroid gland, adrenal gland, urinary bladder, and submaxillary glands. The proposed human dose has adequate safety margins for the animal toxicity findings. The phototoxicity studies showed clinical signs of skin phototoxicity with UV radiation. The embryofetal studies showed decreased number of live births and reduced pup viability and body weight. These findings support pregnancy category C classification for pirfenidone. The mouse carcinogenicity study showed increased incidence of hepatocellular adenomas, carcinomas, and hepatoblastomas. The rat carcinogenicity study also showed increased incidences of hepatocellular adenomas and carcinomas as well as uterine adenocarcinomas and adenomas. These findings will not impact the approval decision given the serious nature of human IPF disease.

5. Clinical Pharmacology and Biopharmaceutics

InterMune submitted a complete and adequate clinical pharmacology program for pirfenidone. Pirfenidone is recommended for administration with food, primarily because the frequency of adverse events (AEs) may be lower with food, compared to fasting. Food decreases the C_{max} by ~48% and AUC by ~16% compared to fasting. Pirfenidone is primarily metabolized by CYP1A2. The major metabolite is 5-carboxy-pirfenidone that is cleared in the urine. There is no significant accumulation of pirfenidone and 5-carboxy-pirfenidone at the proposed dosing regimen. The pharmacokinetics of pirfenidone are affected by co-administration of strong CYP1A2 inhibitors or inducers. Co-administration with fluvoxamine resulted in 4.0-fold increase in AUC in nonsmokers. (b) (4)

Smoking reduces the systemic exposure (AUC) of pirfenidone by ~54%. Smoking should be avoided when using pirfenidone.

InterMune conducted a thorough QT (TQT) study that did not show an effect on the QT interval; however 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 do not preclude approval.

6. Clinical Microbiology

Not applicable.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

There was also another study conducted by Shionogi in Japan (Study SP3) for submission to the Japanese regulatory authority. No patient level data were submitted with this application for our review. There were also some differences between studies 004/006 and study SP3 that make study SP3 less relevant. Therefore, this review will focus on the two InterMune studies 004 and 006 and will not mention study SP3 any further.

Table 1. Relevant clinical studies for the Pirfenidone program

ID	Study type	Study duration	Patient Age, yr	Treatment groups*	N † (ITT)	Study Year#	Countries
004	Efficacy and safety	72 week	40-80	Pir 2403 mg/day, given TID Pif 1197 mg/day, given TID Placebo	174 87 174	2008	US, Canada, Mexico, EU, Australia
006	Efficacy and safety	72 week	40-80	Pir 2403 mg/day, given TID Placebo	171 173	2008	US, EU, Australia
* Pir = pirfenidone 267 mg capsule # Year study subject enrollment ended							

b. Design and conduct of the studies

Studies 004, and 006, were similar in design and conduct except for the treatment arms as noted in Table 1. Both were randomized, double-blind, placebo-controlled, parallel group in design, conducted in patients with a diagnosis of IPF, using acceptable diagnostic criteria. Concomitant treatments, such as corticosteroids, cytotoxic drugs, immunosuppressive and immunomodulating agents, and endothelin receptor antagonists were not allowed. Patients who met predefined criteria for acute respiratory decompensation, acute IPF exacerbation, or progression of disease were permitted to receive certain therapies. The primary efficacy variable was the absolute change in percent predicted FVC from Baseline to Week 72 for the pirfenidone 2403mg/day treatment group compared to placebo. The pre-specified primary analysis of the primary endpoint was a rank ANCOVA. If the primary efficacy analyses from PIPF-004 and PIPF-006 each showed efficacy, then the secondary outcome variables were to be analyzed using pooled data from both studies in addition to the individual study analyses. The pooled secondary efficacy analyses were to be considered primary. Secondary efficacy variables included: time to worsening of IPF (defined as time to acute IPF exacerbation, IPF-related death, lung transplantation, or respiratory hospitalization, whichever comes first), and progression free survival (defined as time to first occurrence of either: 10% absolute decline in % predicted FVC or 15% absolute decline in %

predicted DLco or death). Safety assessments included recording of adverse events, vital signs, physical examination, clinical laboratory evaluation, and 12-lead ECG.

c. Efficacy findings and conclusions

The submitted clinical program does not support the efficacy of pirfenidone to reduce decline in lung function in IPF, or for any other aspect of IPF.

Results of the primary efficacy variable from the two studies are shown in Table 2. The results are statistically significant for one of the two studies. The effect size for the positive study was an absolute difference in change from baseline percent predicted FVC of 4.4%. An evaluation of the change from baseline percent predicted FVC over time is shown in Figure 1. In study 006, there was a separation of the treatment groups between weeks 24 to week 60, but after week 60, the results for treatment groups were similar. The absolute effect size for FVC that can be considered clinically meaningful and correlate with mortality or other patient-centered outcomes is not known. According to scientific literature and the ATS Consensus Statement², a $\geq 10\%$ increase in FVC over 3 to 6 months can be viewed as a favorable positive response. A continuous responder plot prepared by the Agency's statistical reviewer is shown in Figure 2. The x-axis shows the decline in % predicted FVC from baseline (or worsening) at week 72, and the y-axis show the corresponding percentage of patients achieving the level of % predicted FVC decline or greater. Using an absolute decline in % predicted FVC of 10% or greater to define a responder, the results between pirfenidone and placebo groups were similar in study 006. In study 004, 20% of patients treated with pirfenidone had at least 10% decline compared to 35% of patients in the placebo group.

The secondary efficacy variables did not provide meaningful support to the primary efficacy variable data in either of the studies.

Table 2. Mean change from baseline in percent predicted FVC from baseline to week 72 in all randomized patients (rank ANCOVA with imputation*)

	Pirfenidone 2403 mg/day	Pirfenidone 1197 mg/day	Placebo	Difference from Placebo	
				Absolute	p-value
Trial 004	-8.0	-9.9	-12.4	4.4	0.001
Trial 006	-9.0		-9.6	0.6	0.501

*Missing data imputation: 0 if patient died; sum of squared mean difference method if patient alive

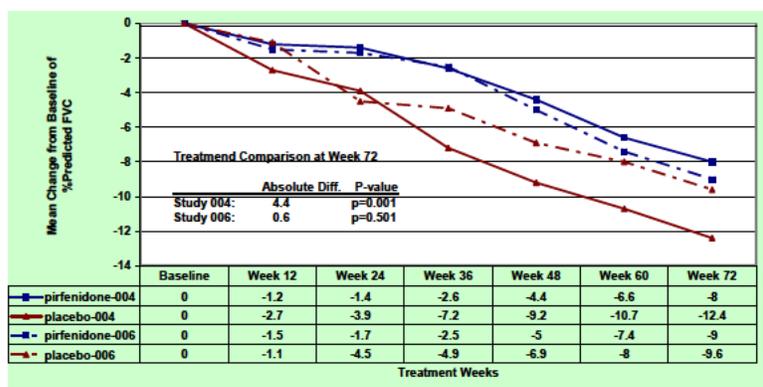


Figure 1. Mean change in percent predicted FVC from baseline, with pre-specified imputation for missing data. Rank ANCOVA.

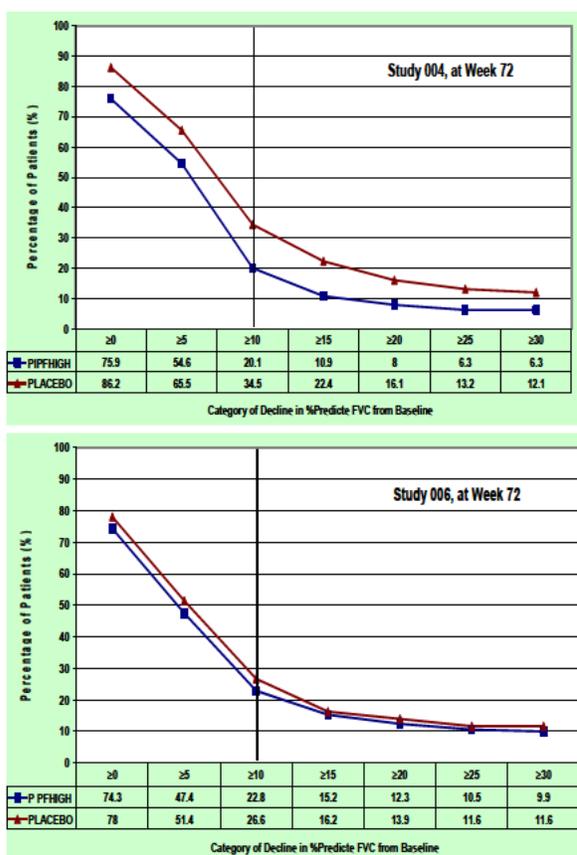


Figure 2. Cumulative % of patients of change from baseline in % predicted FVC.

Mortality is the most relevant endpoint for IPF studies and is the ideal endpoint for assessing efficacy of IPF therapy. Mortality data were analyzed in various ways by InterMune and by the Agency. Results of some relevant analyses are shown in Table 3. An issue with the mortality data was that in the studies, deaths were not adjudicated in the clinical trials. Investigators were asked to indicate via a checkbox on the mortality

case report form (CRF) whether the deaths were IPF-related. Nevertheless, the data provide useful information. The most relevant and convincing analysis is all-cause mortality measured at vital status assessment at the end of the study. In that analysis mortality benefit was not demonstrated for the two studies individually or pooled. The numerical trend generally favored pirfenidone, but the confidence intervals were large. Statistically significant benefit was seen in the pooled analysis of IPF-related on treatment mortality. This single benefit does not rise to the level of substantial evidence of efficacy due to the post-hoc nature of this analysis, limitations of lack of adjudication, and analysis of case narratives which raises questions regarding the consistency of the determination of the cause of death.

Table 3. Mortality analysis

	Number of events (%)			Hazard Ratio (95% CI), p-value*
	Pirfenidone 2403 mg/day	Pirfenidone 1197 mg/day	Placebo	
All cause death, vital status at end of study				
Trial 004	14 (8.0)	10 (11.5)	20 (11.5)	0.68 (0.34, 1.34), p=0.268
Trial 006	18 (10.5)		17 (9.8)	1.06 (0.55, 2.07), p=0.856
Trials 004+006	32 (9.3)		37 (10.7)	0.85 (0.53, 1.37), p=0.509
All cause death, on treatment				
Trial 004	10 (5.8)	8 (9.2)	14 (8.0)	0.71 (0.32, 1.60), p=0.413
Trial 006	9 (5.3)		15 (8.7)	0.59 (0.26, 1.36), p=0.217
Trials 004+006	19 (5.5)		29 (8.4)	0.65 (0.37, 1.16), p=0.146
IPF related death[†], vital status at end of study				
Trial 004	8 (4.6)	7 (8.0)	15 (8.6)	0.51 (0.22, 1.21), p=0.127
Trial 006	14 (8.2)		15 (8.7)	0.94 (0.45, 1.95), p=0.863
Trials 004+006	22 (6.4)		30 (8.6)	0.72 (0.42, 1.25), p=0.246
IPF related death[†], on treatment				
Trial 004	5 (2.9)	6 (6.9)	11 (6.3)	0.45 (0.16, 1.31), p=0.143
Trial 006	7 (4.1)		14 (8.1)	0.49 (0.20, 1.23), p=0.129
Trials 004+006	12 (3.5)		25 (7.2)	0.48 (0.24, 0.95), p=0.035
*Hazard ratio based on the Cox proportional hazard model with geographic region (US and ROW) as a factor. P-value based on long-rank test stratified by geographic region (US and ROW)				
[†] Post-hoc, unadjudicated				

8. Safety

a. Safety database

The safety assessment of pirfenidone was primarily based on studies shown in Table 1. The total number of patients exposed to pirfenidone is reasonable to assess safety.

b. Safety findings and conclusion

The two 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. The clinical program suggests that pirfenidone has some safety signals, including gastrointestinal AEs, liver laboratory

abnormalities, photosensitivity, and rash. There was one patient who appeared to meet Hy's Law criteria of liver injury. There were also 5 liver-related SAEs, and abnormalities in liver function tests were more common in the pirfenidone 2403mg/day treatment group compared to placebo. The animal carcinogenicity study was positive for pirfenidone. The number of cancers in the study was balanced across treatment groups, but the studies were too small to exclude a cancer risk. These safety findings would not preclude approval given the serious nature of IPF.

c. REMS/RiskMAP

Not relevant because this application will not be approved in this review cycle.

9. Advisory Committee Meeting

A Pulmonary-Allergy Drugs Advisory Committee meeting was held on March 9, 2010. Questions were asked about the efficacy, safety, and approvability of pirfenidone. 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 were adequate for patients with IPF (9 yes, 3 no). Regarding the approval question, the results were in favor of approval (9 yes, 3 no). Two committee members who voted that there was not sufficient efficacy data voted for approval of pirfenidone. The open public session of the meeting had many patients making emotionally moving statements on lack of availability of treatment options. After the Advisory Committee meeting, the Agency received many letters and statements from academic physicians with expertise in IPF treatment stating that in their view efficacy was not demonstrated with one of the two studies showing benefit in FVC only with a small effect size. There were also some letters from patients and patient advocacy groups raising the same concern.

The NDA was discussed at a Center Regulatory Briefing on April 16, 2010. The general consensus at the meeting was that efficacy was not demonstrated.

10. Pediatric

Specific pediatric studies are not necessary because IPF is a disease of adults and does not occur in the pediatric population. Furthermore, as an orphan drug program, pediatric studies are not required.

11. Other Relevant Regulatory Issues

a. DSI Audits

A DSI audit was requested for 3 clinical sites based upon high enrollment and favorable outcome for pirfenidone. 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. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There are no issues with financial disclosures in the studies.

c. Others

There are no outstanding issues with consults received from DDMAC, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There are no issues with the proposed proprietary name Esbriet. The proposed proprietary name was accepted by the DMEPA.

b. Physician Labeling

The applicant submitted a label in the Physician's Labeling Rule format. The labeling was not reviewed in detail during review of this application because the application cannot be approved based on the submitted data.

c. Carton and Immediate Container Labels

The carton and immediate container labels were not reviewed in detail because the application will not be approved in this review cycle.

d. Patient Labeling and Medication Guide

Not relevant because this application will not be approved in this review cycle.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The applicant has not submitted adequate efficacy data to support approval of pirfenidone to reduce decline in lung function in IPF, or for any other aspect of IPF. Therefore, the recommended action on this application is a Complete Response.

The comments below are for the Complete Response action letter.

1. The submitted data do not provide substantial evidence of efficacy of pirfenidone for the treatment of patients with IPF to reduce the decline in lung function. The positive finding of FVC in trial PIPF-004 was not replicated in trial PIPF-006. The clinical program also does not provide substantial replicate evidence of efficacy on other clinically meaningful efficacy measures. Mortality is the ideal primary endpoint in clinical trials in patients with IPF. The submitted data do not demonstrate a statistically significant benefit in all-cause mortality.

To support approval of pirfenidone for patients with IPF, conduct a placebo-controlled clinical trial that demonstrates a statistically significant benefit in all-cause

mortality with pirfenidone. Alternatively, to support approval of pirfenidone for patients with IPF to reduce decline in lung function, conduct a clinical trial with FVC as the primary endpoint which replicates the efficacy of pirfenidone compared to placebo. The findings must be robust and provide evidence of a clinically meaningful response, including a responder analysis that favors pirfenidone. All-cause mortality data from the to-be-conducted clinical trial pooled with the all cause mortality data from trials PIPF-004 and PIPF-006 should also provide supportive evidence of benefit.

b. Risk Benefit Assessment

A full risk-benefit assessment cannot be made because the efficacy of pirfenidone has not been adequately established for the reasons stated above. The clinical program is adequate to assess the safety of pirfenidone for this patient population. The clinical program suggests that pirfenidone has some safety signals, including gastrointestinal adverse reactions, potential for liver injury, photosensitivity, and rash. Without assurance of efficacy, the benefits of pirfenidone are not established and a risk-to-benefit assessment is not favorable.

c. Post-marketing Risk Management Activities

Not relevant because this application will not be approved in this review cycle.

d. Post-marketing Study Commitments

Not relevant because this application will not be approved in this review cycle.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

BADRUL A CHOWDHURY
05/04/2010

Cross-Discipline Team Leader Review

Date	April 23, 2010
From	Sally Seymour, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA# 22-535
Applicant	InterMune
Date of Submission	November 4, 2009
PDUFA Goal Date	May 4, 2010
Proprietary Name / Established (USAN) names	Pirfenidone Esbriet
Dosage forms / Strength	Capsule, 267mg
Proposed Indication(s)	treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function
Recommended:	Complete Response

1 Introduction

On November 4, 2009, InterMune submitted New Drug Application #22-535 for pirfenidone for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function. The proposed trade name is Esbriet. Pirfenidone is a new molecular entity and has orphan drug designation for the proposed indication. This NDA is a 505(b)(1) application.

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive, diffuse parenchymal lung disease of unknown etiology. It is characterized by interstitial fibrosis of the lungs, nonproductive cough and progressive dyspnea. In the United States, the prevalence of IPF is estimated to range from 14 to 43 per 100,000 persons¹. Median survival in patients with IPF is estimated to be from 3 to 5 years². Respiratory failure is the most frequent cause of death. Currently, no medications are approved for the treatment of IPF in the United States.

The exact mechanism of action of pirfenidone is unknown, but InterMune asserts that pirfenidone has anti-inflammatory and antifibrotic activity. A 267mg immediate release capsule is proposed for marketing. The proposed dosage is 3 capsules three times a day (TID) with food for a total daily dose of 2403mg. Because of side effects (e.g. nausea, dyspepsia, dizziness) InterMune proposes a two week dose titration to reach maintenance dosing.

This memorandum provides an overview of the application with a focus on issues that warrant further discussion, including the evidence of efficacy and safety. The PDUFA date for this application is May 4, 2010.

¹ Raghu G, Weycker D, Edelsberg J, et al., Incidence and Prevalence of Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2006; 174: 810-816.

² American Thoracic Society Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. Am J Respir Crit Care Med 2000; 161: 646-664.

2 Background

Idiopathic Pulmonary Fibrosis

IPF is a chronic, progressive, diffuse parenchymal lung disease of unknown etiology. The pathogenesis is poorly understood. The characteristic finding on lung biopsy is a pattern of usual interstitial pneumonia (UIP). The disease is typically diagnosed after the age of 40-50 years, and is characterized by progressive dyspnea, nonproductive cough, fibrosis of the lung interstitium, and progressive pulmonary insufficiency. IPF is more common in men than women.

While many therapies are used to treat IPF, no medications are approved in the US for the treatment of IPF. IPF patients are often treated with a variety of therapies that include corticosteroids and immunosuppressive agents, such as azathioprine and cyclophosphamide. No clinical trials have demonstrated a clear clinical benefit for these therapeutic agents and the use of these agents is not FDA approved. To date, lung transplantation is the only intervention that can improve survival in IPF patients.

Few large, placebo-controlled clinical trials have been conducted in patients with IPF. Therapeutic development in IPF has faced challenges, including diagnostic criteria, trial design, dose selection, and endpoint selection. Early studies enrolled a heterogeneous population of patients with interstitial lung disease (ILD). In 2000, the American Thoracic Society (ATS) outlined criteria to distinguish IPF from other ILDs², which provided some consistency in the diagnosis of IPF. Ongoing interest from the academic community continues to refine the approach to diagnosis of IPF³. In the past, clinical studies in IPF patients have tended to be small in size, often open-label design without a placebo group. Since no therapies are approved for the treatment of IPF, clinical trials should include a placebo group to provide robust efficacy data². As IPF is a chronic progressive disease with survival estimated to be from 3 to 5 years following diagnosis, mortality is the ideal primary efficacy variable in IPF clinical trials. Established surrogates for IPF survival and other potential clinically meaningful endpoints (e.g. IPF exacerbations) are a matter of ongoing discussion in the literature³. Results of long term, prospective, placebo controlled clinical trials provide insight into the natural progression of IPF and may help establish surrogate endpoints. The difficulty with endpoint selection and need for long term clinical trials also presents a challenge for conducting formal dose ranging studies in IPF patients.

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 2003. Another sponsor, Shionogi, licensed the rights to pirfenidone in Japan. Pirfenidone was granted Orphan Drug Status in 2004 for the treatment of IPF. Pertinent regulatory interactions between InterMune and the Agency include an End of Phase 2 (EOP2) Meeting in December 2004 and a Pre-NDA meeting in September 2008. During the 2004 EOP2 meeting the following pertinent clinical issues were raised:

- limited phase 2 program and support for dose selection and dosing interval; consider inclusion of a second dose in the phase 3 program;

³ Noth I and Martinez FJ. Recent Advances in Idiopathic Pulmonary Fibrosis. CHEST 2007; 132: 637-650.

- single phase 3 study unlikely to be sufficient to support approval unless the results were highly clinically and statistically persuasive;
- concerns with primary endpoint (time to death or disease progression with 10% change FVC); mortality is ideal primary endpoint and surrogates not well-established; endpoints should be clinically meaningful; if disease progression endpoint, consider American Thoracic Society criteria for “failure to respond to therapy”², e.g. two or more of the following: $\geq 10\%$ \downarrow TLC or VC (or ≥ 200 mL change), $\geq 15\%$ \downarrow DLCO, worsening oxygen saturation ($\geq 4\%$ decrease)

During the September 2008, Pre-NDA meeting, the results of the phase 3 trials were not available. The main clinical concern raised by the Agency was regarding the primary efficacy variable, FVC. Mortality is the ideal primary endpoint and FVC is not an established surrogate for mortality and it is unclear what would constitute a clinically meaningful outcome based on FVC. The Agency noted that efficacy would be assessed by the totality of the data, including secondary endpoints.

Foreign Marketing

Shionogi received marketing approval for pirfenidone for the treatment of IPF in Japan in October 2008, under the tradename Pirespa in a 200mg tablet.

3 Chemistry and Manufacturing

Pirfenidone is a small, synthetic, non-peptide molecule and is a new molecular entity. The proposed commercial drug product for pirfenidone is a 267mg immediate release capsule. The active pharmaceutical ingredient is a white to pale yellow powder that is manufactured at (b) (4). The drug product includes the excipients sodium croscarmellose, microcrystalline cellulose, povidone, and magnesium stearate in a hard gelatin capsule. The drug product is manufactured at (b) (4). The product will be packaged in bulk bottles of 270 capsules and in blister trays for a 14 day titration period or a 4 week maintenance period. The packaging is performed at (b) (4). An expiry of (b) (4) is proposed and supported by submitted data. All inspections have been completed and are acceptable.

There are a few outstanding CMC issues. One is related to packaging of the blister trays and concern that the trays are not adequately (b) (4). This issue was conveyed to the Applicant on March 29, 2010. The second issue is regarding an impurity (b) (4) that needs to be qualified. InterMune has committed to conduct a bacterial mutagenicity assay to qualify the impurity. However, the draft report is not available until April 15, 2010, and the final report is stated to be available in about another two weeks. Given the severity of IPF, the qualification of this impurity is not an approvability issue as determined by the pharmtox and clinical review teams. Depending upon the action, the qualification of this impurity can be a deficiency (if CR action) or a post-marketing requirement (if AP action). Finally, a microbiology consult was obtained for microbial limits testing method validation. Additional information has been requested from the Applicant regarding microbial testing. The microbiology reviewer recommends approvable

action pending resolution of the microbiology issues. The CMC reviewer recommends approval action pending resolution of the above issues.

4 Pharmacology/Toxicology

InterMune submitted pharmacology and toxicology study reports to support chronic administration of pirfenidone. A very high level summary of the findings is provided here.

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.

Reproductive toxicity studies in rats showed that pirfenidone decreased numbers of live newborn and reduced pup viability and body weights. Based upon these findings, Dr. Grace Lee recommended 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.

One outstanding issue is regarding qualification of impurity [REDACTED] (b) (4) that is described in Section 4 above. Given the severity of IPF, the qualification of this impurity is not an approvability issue. The pharmacology/toxicology reviewer, Dr. Tim Robison, recommends approval.

5 Clinical Pharmacology

InterMune submitted a clinical pharmacology program to support administration of pirfenidone. A very high level summary of the findings 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 ~48% 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. The protein binding of pirfenidone is about 58% at concentration of 10 mg/L. Formal mass balance studies have not been performed.

Pirfenidone is primarily metabolized by CYP1A2. 5-Carboxy-pirfenidone is the major metabolite and it is cleared in the urine. 5-Carboxy-pirfenidone has shown no pharmacological activity against IPF. There is no significant accumulation of pirfenidone and 5-carboxy-pirfenidone at the proposed dosing regimen of 801 mg TID (2403mg/day).

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.

Pharmacokinetics are affected by co-administration of strong CYP1A2 inhibitors or inducers. Co-administration with fluvoxamine resulted in 4.0-fold increase in AUC in nonsmokers. Because of this, the concomitant administration of pirfenidone and fluvoxamine is not recommended. Smoking reduces the systemic exposure (AUC) to pirfenidone by approximately 54%. Patients should be encouraged to stop smoking before treatment with pirfenidone. Otherwise, smoking should be avoided when using pirfenidone.

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, but do not preclude approval.

The clinical pharmacology reviewer, Dr. Elizabeth Shang, finds the application acceptable pending agreed upon labeling.

6 Clinical Microbiology

This section is not applicable as pirfenidone is not an antimicrobial.

7 Clinical/Statistical- Efficacy

To support the safety and efficacy of pirfenidone for the proposed indication, InterMune submitted the results of two phase 3 clinical trials in patients with IPF: PIPF-004 and PIPF-006. InterMune also submitted a study report for a study conducted by Shionogi in Japan, SP3. However, the Agency cannot rely on the results of SP3 because InterMune did not submit the data for SP3 and thus the results cannot be verified by the Agency. In addition, there are some differences between the clinical trials conducted by InterMune and the Shionogi study. Therefore, this memo will focus on the InterMune clinical trials, which are outlined in the table below.

Table 1 Summary of Clinical Program						
Study No.	Description	Subjects	Design	Dose	Duration	Endpoints
PIPF-004 US, Canada, Mexico, UK, France, Italy, Poland, Australia Jul 2006- Nov 2008	Phase 3 efficacy and safety trial	435 patients with IPF	R, DB, PC	Pirfenidone 2403 mg total daily dose [3x267mg TID] (n=174) Pirfenidone 1197mg total daily dose [3x133mg TID] (n=87) Placebo TID (n=174)	72 weeks	-change in % predicted FVC from baseline - time to worsening IPF - progression free survival
PIPF-006 US, Australia, Belgium, Germany, Ireland, Spain, Switzerland Apr 2006- Oct 2008	Phase 3 efficacy and safety trial	344 patients with IPF	R, DB, PC	Pirfenidone 2403 mg total daily dose [3x267mg TID] (n=171) Placebo TID (n=173)	72 weeks	-change in % predicted FVC from baseline - time to worsening IPF - progression free survival

Dose Selection

There were no formal dose ranging trials in the clinical program. Dose ranging in IPF patients for the proposed indication can be challenging due to the need for long-term clinical trials to evaluate a treatment effect as there are no established pharmacodynamic surrogate endpoints. InterMune stated that the dose of pirfenidone in the phase 3 trials was derived from the 1800mg/day dose in the Shionogi study weight-normalized to the expected body weights in PIPF-004 and PIPF-006. A lower dose of study medication (1197mg/day) was included in PIPF-004 to provide additional safety information.

Phase 3 Trial Design

PIPF-004 and PIPF-006 were randomized, double-blind, placebo-controlled, clinical trials to assess the efficacy and safety of pirfenidone for the treatment of patients with IPF to reduce the decline in lung function. 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. PIPF-004 and PIPF-006 were similar in design

with a few key differences. One difference between the trials was that PIPF-004 included two active treatment groups: 2403 mg/day and 1197 mg/day and randomization was 2:2:1 for the 2403mg/day: placebo: 1197mg/day groups, respectively. In PIPF-006 randomization was 1:1 to 2403 mg/day or placebo.

Population – Diagnostic Criteria

For clinical trials in IPF patients, appropriate diagnostic criteria are important. The following were the pertinent inclusion criteria regarding diagnosis of IPF:

- age 40-80 years of age;
- clinical symptoms of IPF (dyspnea on exertion) for ≥ 3 months duration;
- diagnosis of IPF within 48 months of randomization;
- HRCT showing confident radiographic diagnosis of usual interstitial pneumonia (UIP), if surgical lung biopsy showing definite or probable UIP, HRCT criteria of probable UIP was sufficient;
- if < 50 years of age, open or video assisted thoracoscopic surgical (VATS) lung biopsy showing definite or probable UIP within 48 months of randomization and no features of alternative diagnosis on transbronchial biopsy or BAL (if performed);
- f) if ≥ 50 years of age, at least one of the following and absence of features that supported alternative diagnosis within 48 months of randomization:
 - 1) open or VATS lung biopsy that showed definite or probable UIP;
 - 2) transbronchial biopsy showing no alternative diagnosis;
 - 3) BAL showing no alternative diagnosis

The above diagnostic criteria are summarized in the table below. If the surgical lung biopsy or HRCT scans were ambiguous, the slides or HRCT images were evaluated by an adjudicator for a second opinion.

Table 2 Diagnostic Criteria for IPF				
	Patient Age ≥ 50 years		Patient Age < 50 Years	
HRCT findings	Definitive IPF	Probable IPF	Definitive IPF	Probable IPF
Pathologic findings	Nondiagnostic transbronchial biopsy or BAL, or surgical lung biopsy with UIP	Surgical lung biopsy with UIP	Surgical lung biopsy with UIP	Surgical lung biopsy with UIP

The diagnostic criteria for IPF utilized in PIPF-004 and PIPF-006 are acceptable and are consistent with the ATS consensus criteria². With regards to severity, the following were specified at study entry:

- FVC $\geq 50\%$
- DLco (Hgb-corrected) $\geq 35\%$
- FVC or DLco (Hgb-corrected) $\leq 90\%$
- no evidence of improvement in IPF over the previous year
- distance $\geq 150\text{m}$ (492 feet) with O₂ saturation $\geq 83\%$ on $\leq 6\text{L/min}$ of O₂ during 6MWT

Population – Pertinent Exclusion Criteria

Patients with the following were to be excluded: FEV1/FVC < 0.7 after bronchodilator administration, bronchodilator response, RV >120%, h/o significant environmental exposure known to cause pulmonary fibrosis, and diagnosis of connective tissue disease or other known explanation of ILD. There are numerous other entry criteria, which Dr. Karimi-Shah has outlined in the clinical review. In addition, use of cytotoxic, immunosuppressive, cytokine modulating, endothelin receptor antagonists or any medications being used for the treatment of IPF were not allowed within 28 days of screening.

Study Medication

Two doses of pirfenidone (2403 mg/d and 1197 mg/d) were included in the phase 3 clinical trials, but the pirfenidone 2403mg/day treatment group is the primary treatment group of interest. Study medication was administered with meals in divided doses on a TID schedule. 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.

Table 3 Dose Escalation for Pirfenidone		
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 generally 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 6MWT with Borg rating of breathlessness. PFTs were performed according to ATS guidelines. Patients who discontinued were followed for vital status assessment until study completion.

Efficacy Variables

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

If the primary efficacy analyses from PIPF-004 and PIPF-006 each showed efficacy, then the secondary outcome variables were to be analyzed using pooled data from both studies in addition to the individual study analyses. The pooled secondary efficacy analyses were to be considered primary. Secondary efficacy variables included:

- time to worsening of IPF - time to acute IPF exacerbation, IPF-related death, lung transplantation, or respiratory hospitalization, whichever comes 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

There were numerous other secondary endpoints, which are outlined in the clinical review. Survival was an exploratory efficacy variable.

A Data Monitoring Committee (DMC) met at regular intervals to review unblinded safety data. In addition to monitoring safety, the DMC requested a stopping rule regarding efficacy. If survival time using pooled data from PIPF-004 and PIPF-006 for the 2403mg treatment group versus placebo was highly statistically significant ($p=0.0001$), the DMC could recommend stopping the studies. The survival review was conducted at the 2nd and 3rd DMC meetings. The significance level for the primary analysis (absolute change % predicted FVC) for each study was 0.0498 to adjust for the two DMC mortality analyses.

There were two protocol amendments. The first protocol amendment in March 2007 extended the treatment period from 60 weeks to 72 weeks and increased the sample size based upon analysis of the Shionogi trial in Japan. The second protocol amendment in December 2007, provided for stopping rules for the DMC, clarified individual and pooled analyses, and other minor revisions.

Phase 3 Results

Demographics

A total of 779 patients were enrolled in the phase 3 clinical trials: 435 in PIPF-004 and 344 in PIPF-006. The majority of patients (66% in PIPF004 and 87% in PIPF-006) were enrolled in the US. In general, patients enrolled in the treatment groups in PIPF-004 and PIPF-006 were primarily white males with a mean age of 66-68 years. The demographic profile was fairly balanced among the treatment groups. In terms of IPF baseline characteristics, the mean baseline FVC was 73-76% predicted and the DLco was 46-48% predicted. Patients walked a mean of 378 to 418m during the 6MWT with mean worst SpO₂ of 88.4 to 89.2% during the 6MWT. A definite diagnosis of IPF by HRCT was noted in 88-95% of patients and 37-55% of patients had surgical lung biopsy. Fifty-eight to 66% of patients were previous smokers, but ≤ 5% were current smokers. Supplemental oxygen use differed in the two trials: 14-17% of patients in PIPF-004 vs. 28% in PIPF-006. There was an imbalance in the median time from IPF diagnosis to randomization, in that it was slightly shorter in PIPF-006 than in PIPF-004 (0.7 years vs. 1 year, respectively).

Datasets

Because many patients were treated beyond 72 weeks and patients were encouraged to stay in the study after discontinuing study medication, there are many ways to evaluate the data collected in the phase 3 trials. Before discussion of the results, it is important to discuss the

different datasets used for analysis of the efficacy and safety data in this review as the results may vary based upon the dataset.

- Treatment Period – data for all patients up to the September 2008 cutoff used by InterMune; some patients would have > 72 weeks treatment; this dataset was used for some efficacy analysis
- On-Treatment - data for all patients while on study medication and 28 days after the last dose of study medication; primary dataset for safety endpoints
- Vital Status at End of Study – data including the Treatment Period (Sept 2008 cut-off) and subsequent follow up; used for vital status only

Disposition, Compliance, Exposure

Patients who discontinued study medication were encouraged to stay in the trials. More patients discontinued study medication in the pirfenidone treatment groups (20-22%) than in the placebo groups (18%). The primary reason for discontinuation of study medication was adverse events, which were more common in the pirfenidone groups. In terms of study completion, around 81-84% of patients completed the study. Compliance was reasonable in that approximately 87-94% of patients were more than 80% compliant with treatment. Because patients received study treatment from randomization until approximately 72 weeks after the last patient had been randomized into the study, the duration of treatment was up to 118 weeks. The mean treatment duration was 71 weeks in PIPF-004 and 75 weeks in PIPF-006.

Efficacy Results - Primary Efficacy Variable

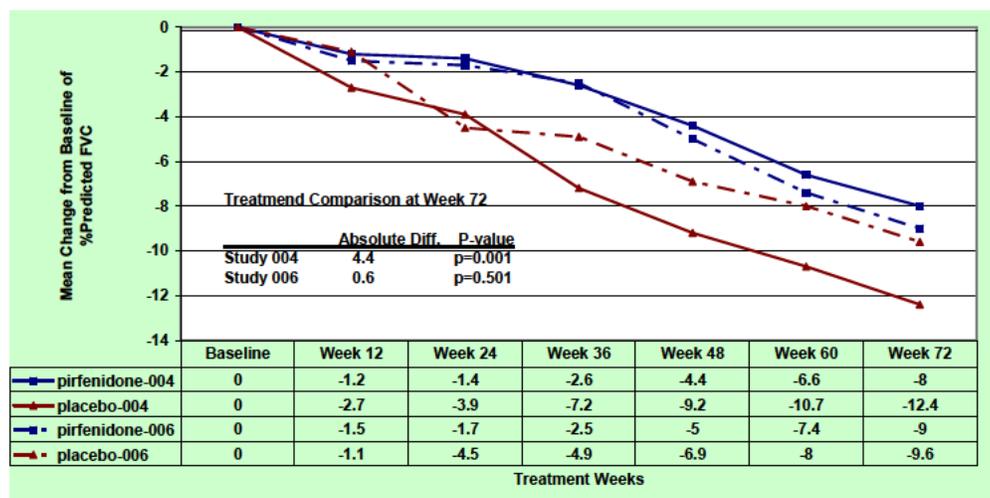
For the efficacy results, the emphasis is on the results from the pirfenidone 2403mg/day treatment group. The lower dose of pirfenidone 1197mg/day was included to explore a dose-response relationship and was not adequately powered to demonstrate efficacy, thus, the discussion of efficacy for this treatment group will be limited. The primary efficacy endpoint in the phase 3 trials was the absolute change in percent predicted FVC from Baseline to Week 72. The results in Table 4 show that pirfenidone was significantly different than placebo in only one trial (PIPF-004). The effect size was an absolute difference in change from baseline percent predicted FVC of 4.4%.

Table 4 Primary Efficacy Endpoint				
Mean Change in Percent Predicted FVC from Baseline to Week 72*				
	Pirfenidone 1197mg/day	Pirfenidone 2403mg/day	Placebo	Difference from Placebo (p value)[†]
PIPF-004	-9.9 (n=87)	-8.0 (n=174)	-12.4 (n=174)	4.4 (p < 0.001)
PIPF-006		-9.0 (n=171)	-9.6 (n=173)	0.6 (p=0.501)
* Missing data imputed: if patient died, then 0 imputed; if patient alive imputation by the sum of squared differences method (SSD)				
[†] comparison for pirfenidone 2403mg/day group; rank ANCOVA with imputation of missing data				

In considering the results for the primary efficacy variable, the following issues will be discussed further below: a) the treatment effect throughout the duration of the trial, b) clinical significance of the effect size, and c) effects of imputation of missing data.

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 the figure below. The pirfenidone groups performed similarly in both trials and the difference was in the placebo treatment groups. In PIPF-006, there was a separation of the treatment groups between weeks 24 up to week 60, but after week 60, the results for treatment groups were similar.

Figure 1 Mean Change in Percent Predicted FVC from Baseline*



* pre-specified imputation for missing data; Rank ANCOVA

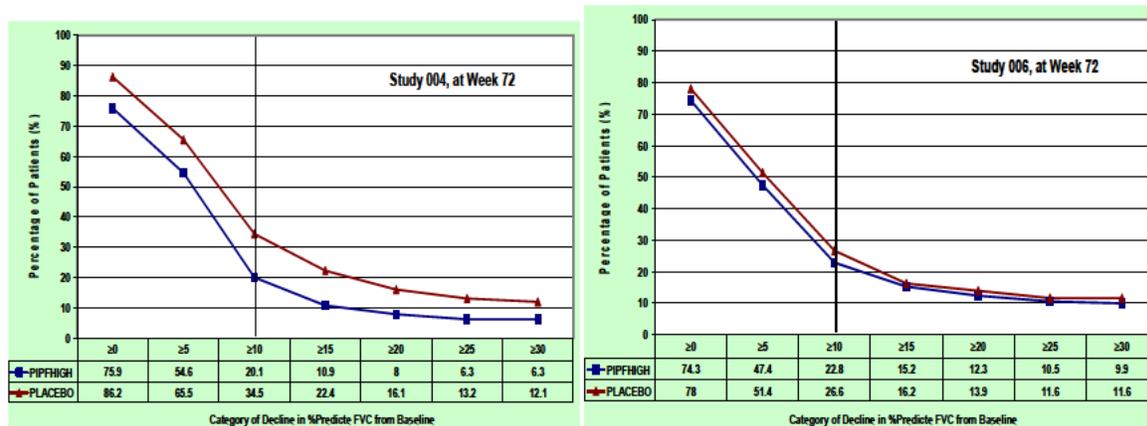
InterMune proposes that a difference in albuterol (salbutamol) use in the treatment groups in PIPF-006 may have contributed to the lack of treatment effect in PIPF-006. In PIPF-006, 28% of patients in the pirfenidone group and 41% in the placebo group reported use of salbutamol during the trial; however, InterMune noted that the majority of albuterol use was per protocol for PFT testing. Per protocol, patients were to be excluded if they were responsive to bronchodilators. It is unlikely that this post-hoc observation of difference in albuterol use explains the lack of treatment effect at Week 72 in PIPF-006. InterMune also proposes that a difference in duration of diagnosis of IPF between patients in PIPF-004 and PIPF-006 also may have been a factor in the results. Approximately 40% of patients in PIPF-006 and 52% in PIPF-004 were diagnosed with IPF greater than 1 year before study entry with the idea that a longer duration of diagnosis would portend a greater FVC progression. While the difference between the trials is noted, the treatment groups in each trial were balanced with regards to time of diagnosis and thus does not explain the lack of a treatment effect in PIPF-006.

While the results for the primary endpoint in PIPF-004 are statistically significant for the pre-defined primary endpoint, a discussion of the effect size is important. When discussing the primary efficacy variable of FVC for the phase 3 trials in pre-submission interactions, the Agency raised the concern regarding what would constitute a clinically meaningful outcome. According to the ATS Consensus Statement², vital capacity (VC) can be considered one of the factors to assess response to therapy as follows: favorable response to therapy is a $\geq 10\%$ increase in VC over 3 to 6 months, stable response is a 10% change in VC over 3 to 6 months, and a failure to respond to therapy is a $\geq 10\%$ decrease in VC over 3 to 6 months. In addition, some literature suggests the significance of a decrease $\geq 10\%$

threshold for FVC^{4,5}. The mean treatment effect of 4.4% predicted FVC in a single trial raises the question of the clinical significance of the results.

A responder analysis was 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, the results between pirfenidone and placebo groups were similar in PIPF-006. In PIPF-004, 20% of patients treated with pirfenidone had a decline greater than 10% compared to 35% of patients in the placebo group.

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.

Another way to evaluate the clinical significance of the treatment effect is to evaluate the change from baseline in FVC in milliliters. Based upon the observed data, the mean absolute change from baseline in FVC at week 72 without imputation in PIPF-004 and PIPF-006 was 75mL and 2.0mL, respectively. Using data imputation, the mean absolute change from baseline in FVC at week 72 in PIPF-004 and PIPF-006 was 157mL and -5mL, respectively.

The primary analysis included imputation of missing data. There are multiple methods for evaluating the primary efficacy variable with and without imputation of data. The statistician has evaluated the data using various methods and the overall results are similar in that PIPF-004 remains statistically significant, while PIPF-006 does not. The one difference using the different imputation methods is a difference in the effect size. For example, using the observed percent predicted FVC data, the treatment differences in PIPF-004 and PIPF-006 were 2.1 and 0.2, respectively. The statistical review has more details regarding the various sensitivity analyses of the primary efficacy variable.

⁴ King TE, Safrin S, Starko KM, et al. Analysis of Efficacy End Points in a Controlled Trial of Interferon-γ1b for Idiopathic Pulmonary Fibrosis. CHEST 2005; 127: 171-177.

⁵ 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.

Efficacy Results - Secondary Efficacy Variables

Based upon the statistical analysis plan, if the primary efficacy analyses from PIPF-004 and PIPF-006 each showed efficacy, then the secondary outcome variables were to be analyzed using pooled data from both studies as well as the individual study analyses. Although the results from PIPF-006 were not significant for the primary endpoint, a discussion of the secondary endpoints is warranted given the patient population and the fact that clinical trial endpoints in IPF patients are not well-established.

Although there are numerous secondary efficacy variables, only a few will be highlighted in this memo – death, progression free survival, and worsening of IPF. These efficacy variables were chosen because death is the most clinically meaningful endpoint and the other two endpoints represent composites of various definitions of disease progression.

In PIPF-004, the only secondary endpoint that was statistically significant was progression free survival. In Study PIPF-006, the only secondary endpoint that was statistically significant was the 6MWT distance, but because PIPF-006 did not meet the primary endpoint, results of secondary endpoints need to be interpreted carefully.

Death

The one secondary endpoint that warrants discussion is survival. As stated in Section 2, mortality is the ideal primary efficacy variable in an IPF program. The Agency analyzed survival using the On-Treatment and the Vital Status at the End of Study datasets. We also performed an analysis with inclusion of patients who underwent lung transplant. The rationale for inclusion of lung transplantation was that without this procedure, death was presumed to be imminent. That analysis is not presented below because the inclusion of lung transplants did not have an impact on the results. Death was not adjudicated in the clinical trials. However, investigators were asked to indicate via a checkbox on the mortality CRF whether the deaths were IPF-related. InterMune has included a post-hoc analysis of death based upon this assessment of IPF-related death. The results for the Agency's analysis of all cause death and IPF-related death are shown in the table below.

Table 5 Survival Analysis on Death				
	Number of Events (%)			Hazard Ratio [†] (95% CI), p value [‡]
	Pirfenidone 1197mg/day	Pirfenidone 2403mg/day	Placebo	
All cause death IPF related*				
PIPF-004	N=87	N=174	N=174	
On Treatment	8 (9.2)	10 (5.8)	14 (8.0)	0.71 (0.32, 1.60), p=0.413
IPF related*	6 (6.9)	5 (2.9)	11 (6.3)	0.45 (0.16, 1.31), p=0.143
Vital Status – End of Study	10 (11.5)	14 (8.0)	20 (11.5)	0.68 (0.34, 1.34), p=0.268
IPF related*	7 (8.0)	8 (4.6)	15 (8.6)	0.51 (0.22, 1.21), p=0.127
PIPF-006		N=171	N=173	
On Treatment		9 (5.3)	15 (8.7)	0.59 (0.26, 1.36), p=0.217
IPF related*		7 (4.1)	14 (8.1)	0.49 (0.20, 1.23), p=0.129
Vital Status – End of Study		18 (10.5)	17 (9.8)	1.06 (0.55, 2.07), p=0.856
IPF related*		14 (8.2)	15 (8.7)	0.94 (0.45, 1.95), p=0.863
Pooled PIPF-004 and 006		N=345	N=347	
On Treatment		19 (5.5)	29 (8.4)	0.65 (0.37, 1.16), p=0.146
IPF related*		12 (3.5)	25 (7.2)	0.48 (0.24, 0.95), p=0.035
Vital Status – End of Study		32 (9.3)	37 (10.7)	0.85 (0.53, 1.37), p=0.509
IPF related*		22 (6.4)	30 (8.6)	0.72 (0.42, 1.25), p=0.246

† 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
* post-hoc, unadjudicated

Neither trial demonstrated a mortality benefit; however, the results for On-Treatment survival numerically favored pirfenidone treatment in both trials. When looking at vital status on all patients at the end of the study, PIPF-004 was numerically favorable for pirfenidone, but PIPF-006 did not show any difference between treatment groups. Because the trials were similar in design, pooling to evaluate death is reasonable and the results show that the On-Treatment survival was numerically favorable. The post-hoc, unadjudicated IPF-related mortality generally had similar results, except that pooled On-Treatment results were statistically significant. This should be interpreted cautiously, however, as there are limitations of this post-hoc analysis. The primary limitation is the lack of adjudication. Review of the case narratives raises questions regarding the consistency of the determination of the cause of death. Finally, there does not appear to be a dose-response with pirfenidone with regards to death as the pirfenidone 1197mg/day treatment group had numerically similar proportion of deaths compared to placebo.

Progression Free Survival

The Treatment Period dataset was used for the efficacy analysis discussed below. As a reminder, progression free survival was defined as time to first occurrence of either:

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

As shown in the table below, the results for progression-free survival were statistically significant in PIPF-004 and numerically favorable in PIPF-006. The results appear to be driven primarily by the disease progression criterion of 10% decline in percent predicted FVC.

Table 6 Survival Analysis Progression-Free Survival during the Treatment Period				
	Pirfenidone 1197mg/day	Pirfenidone 2403mg/day	Placebo	Hazard Ratio^c (95% CI) p-value^b
	N of Event^a (%)	N of Event^a (%)	N of Event^a (%)	
PIPF-004				
N of Randomized	87	174	174	
Death or Disease Progression ^d	28 (32.2)	45 (26.2)	62 (35.8)	0.64 (0.44, 0.95), 0.023
Decline %predicted FVC \geq 10%	16 (18.4)	28 (16.3)	39 (22.5)	--
Decline %predicted DL _{CO} \geq 15%	5 (5.7)	9 (5.2)	9 (5.2)	--
Death before disease progression ^e	7 (8.0)	8 (4.7)	14 (8.1)	--
PIPF-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>				

Worsening of IPF

As a reminder, time to worsening of IPF was defined as the time to:

- acute IPF exacerbation
- IPF-related death
- lung transplantation
- respiratory hospitalization

Neither phase 3 trial demonstrated a significant benefit with regards to worsening of IPF, although there was a numerical difference favoring pirfenidone, primarily in PIPF-004. In both trials, worsening of IPF was driven primarily by respiratory hospitalization.

Table 7 Survival Analysis on Worsening of IPF during the Treatment Period				
	Pirfenidone 1197mg/day	Pirfenidone 2403mg/day	Placebo	Hazard Ratio^c (95% CI) p-value^d
	N of Event (%)	N of Event (%)	N of Event (%)	
PIPF-004				
N of Randomized	87	174	174	--
Worsening IPF ^a	10 (11.5)	26 (14.9)	30 (17.2)	0.84 (0.50, 1.42), 0.515
Acute IPF exacerbation	1 (1.1)	2 (1.1)	3 (1.7)	--
Lung transplantation	0	2 (1.1)	2 (1.1)	--
Respiratory hospitalization	9 (10.3)	21 (12.1)	24 (13.8)	--
IPF-related death ^b	0	1 (0.6)	1 (0.6)	--
PIPF-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>				

Efficacy Conclusions

In accord 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 efficacy⁶. Although IPF is an orphan disease, the requirements to establish effectiveness are not different, with the exception that the overall database may be smaller.

Clinical programs in patients with IPF are challenging because of the lack of validated surrogate endpoints, need for long term, placebo controlled clinical trials, and lack of regulatory precedence. The Agency noted concerns with FVC as the efficacy variable, including the uncertainty of what constitutes a clinically meaningful effect size. In addition, it should be noted that the proposed indication is specific regarding a reduction in lung function in patients with IPF; thus, FVC would need to be deemed adequate to support such a claim. In the submitted program, one trial (PIPF-004) met the primary endpoint of absolute change from baseline in percent predicted FVC with an effect size of 4.4% favoring pirfenidone over placebo and one trial (PIPF-006) did not meet the primary endpoint. Some secondary efficacy variables were numerically supportive. A survival benefit was not established for all cause on-treatment mortality, although the results

⁶ FDA Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products

generally numerically favored the pirfenidone treatment group. The results of PIPF-004 and PIPF-006 do not provide substantial evidence of efficacy to support the proposed indication to reduce decline in lung function in patients with IPF. Dr. Karimi-Shah recommends a Complete Response action based upon lack of sufficient efficacy data and I concur with her recommendation.

8 Safety

The safety database for pirfenidone comes primarily from PIPF-004 and PIPF-006. While other smaller phase 2 trials were submitted, these trials did not contribute substantially to the safety database. Because the phase 3 trials were similar in design, the safety results will be discussed for the pooled safety database. Safety assessments in the phase 3 clinical trials included adverse events (AEs), physical examinations, vital signs, electrocardiograms, and laboratories.

There were a total of 343 patients treated with pirfenidone (87 in the 1197 mg/day group and 345 in the 2403 mg/day group) and 347 patients treated with placebo. The mean treatment duration was similar between the treatment groups and was 71 weeks in PIPF-004 and 75 weeks in PIPF-006 with a maximum treatment duration of 118 weeks. More patients discontinued study medication in the pirfenidone treatment groups (20-22%) than in the placebo groups (18%). The primary reason for discontinuation of study medication was adverse events. Discontinuation of study medication due to AEs occurred in 13% of patients in the pirfenidone 2403mg/day group compared to 8% of patients in the placebo group. The main AEs leading to treatment discontinuation were IPF, rash, nausea, bladder cancer, photosensitivity reaction, and respiratory failure. Dose reduction for AEs occurred more frequently in the pirfenidone 2403mg/day group (39%) compared to the placebo group (16%).

Deaths were discussed in detail in the efficacy discussion. Generally, there were numerically fewer deaths in the pirfenidone groups than in the placebo group. On-Treatment all cause death occurred in 8 (9.2%), 19 (5.5%), and 29 (8.4%) patients in the pirfenidone 1197mg/day, pirfenidone 2403 mg/day, and placebo groups, respectively. The cause of death was not adjudicated, but per investigator judgment, the primary cause of death was IPF. Refer to Table 5 for more discussion of the deaths in the pirfenidone program.

Approximately one third of patients experienced a serious adverse event (SAE) in the pirfenidone phase 3 trials, which is not surprising given the long duration of the trials and the older population with a severe disease and co-morbidities. Overall, SAEs were balanced between treatment groups. SAEs that were reported more frequently in the pirfenidone 2403 mg/day group compared to placebo included the following: coronary artery disease, chest pain, pneumothorax, bladder cancer, fall, and syncope. A review of the 1197 mg/day pirfenidone group does not suggest a dose response for these particular SAEs.

Over 97% of patients treated with pirfenidone and 94% of patients treated with placebo reported AEs. Early clinical trials with pirfenidone have shown certain safety signals that appear to be related to study medication, including: hepatic laboratory abnormalities,

photosensitivity reaction and rash, gastrointestinal events (nausea, vomiting, diarrhea, dyspepsia, pain, etc.), dizziness, fatigue, anorexia, and syncope. Table 8 shows some of the common AEs reported.

Table 8 Common AEs Reported On-Treatment			
(Reported in >8% of patients on pirfenidone 2403mg/day and 2% more than on placebo)			
Preferred Term	Number of Patients, n(%)		
	Pirfenidone 1197mg/day (N=87)	Pirfenidone 2403mg/day (N=345)	Placebo (N=347)
Gastrointestinal Disorders			
Nausea	22 (25.3)	125 (36.2)	60 (17.3)
Diarrhea	22 (25.3)	99 (28.7)	67 (19.3)
Dyspepsia	12 (13.8)	66 (19.1)	26 (7.5)
Vomiting	11 (12.6)	47 (13.6)	15 (4.3)
GERD	11 (12.6)	36 (10.4)	26 (7.5)
Abdominal Distention	3 (3.4)	33 (9.6)	20 (5.8)
Stomach Discomfort	4 (4.6)	29 (8.4)	6 (1.7)
General Disorders and Administration Site Conditions			
Fatigue	25 (28.7)	104 (30.1)	71 (20.5)
Infections and Infestations			
Sinusitis	7 (8.0)	48 (13.9)	40 (11.5)
Investigations			
Weight Decreased	8 (9.2)	28 (8.1)	12 (3.5)
Metabolism and Nutrition Disorders			
Anorexia	9 (10.3)	37 (10.7)	13 (3.7)
Musculoskeletal and Connective Tissue Disorders			
Arthralgia	9 (10.3)	36 (10.4)	24 (6.9)
Nervous System Disorders			
Headache	14 (16.1)	65 (18.8)	56 (16.1)
Dizziness	14 (16.1)	63 (18.3)	35 (10.1)
Psychiatric Disorders			
Insomnia	13 (14.9)	34 (9.9)	23 (6.6)
Respiratory, Thoracic, and Mediastinal Disorders			
Dyspnea	22 (25.3)	64 (18.6)	77 (22.2)
Skin and Subcutaneous Tissue Disorders			
Rash	15 (17.2)	111 (32.2)	40 (11.5)
Photosensitivity Reaction	6 (6.9)	42 (12.2)	6 (1.7)

Rash, fatigue, and nausea were reported in >30% of patients treated with pirfenidone 2403mg/day. InterMune also noted AEs of interest based upon previous studies with pirfenidone. In addition to most of the above AEs, the AEs of interest included cardiac disorders (arrhythmias- supraventricular, ventricular, bundle branch block, AV block), increased ALT and AST, hyponatremia, and injuries (fractures, falls). Dr. Karimi-Shah has a more extensive discussion of the safety results. Few events led to hospitalization or discontinuation (see discontinuation and SAE discussion above). Some of the AEs led to dose modification as allowed in the protocols. Below is a brief discussion of some events of interest.

In terms of gastrointestinal adverse events, this was the most common system organ class for AEs, with events such as nausea, vomiting, dyspepsia, and diarrhea. The majority of

events were generally mild to moderate in severity. There were 8 patients with GI SAEs in the pirfenidone 2403mg/day treatment group and 13 (3.7%) in the placebo group. Some events (nausea, diarrhea, and vomiting) led to dose adjustment. Few GI AEs led to discontinuation of study medication, with nausea being the primary GI AE leading to discontinuation of study medication.

Abnormalities in liver laboratories were more common in the pirfenidone 2403mg/day treatment group compared to placebo. For example, 14 (4.1%) of patients in the pirfenidone group had AST or ALT > 3 x ULN compared to 2 (0.6%) in the placebo group. There is one patient who had a question of meeting Hy's Law criteria. The patient appeared to meet the laboratory criteria at a local laboratory, but not at the central laboratory and another medication was suspected as the cause. There were no deaths related to liver abnormalities. There were 5 liver related SAEs (hepatitis, LFTs abnormal, ALT/AST elevated): 1 in the 1197mg/day, 3 in the 2403mg/day, and 1 in the placebo group. Liver test abnormalities generally resolved without sequelae.

As shown in Table 8, rash and photosensitivity reaction AEs were more common in the pirfenidone 2403mg/day treatment group compared to placebo. The majority of the AEs were mild to moderate in severity. There was one patient with a rash SAE and one patient with a photosensitivity SAE in the pirfenidone 2403mg/day treatment group. There were no cases of Stevens-Johnson syndrome or toxic epidermal necrolysis.

Three patients in each of the pirfenidone treatment groups and one placebo patient had a hyponatremia AE. One patient in the pirfenidone 2403mg/day treatment group was hospitalized for hyponatremia (SAE). Eight (2.4%) of patients in the pirfenidone 2403mg/day treatment group compared to 1 (0.3%) in the placebo group had a decrease in sodium to 120-130mmol/L. Ten (2.9%) of patients treated with pirfenidone 2403mg/day experienced falls compared to three (0.9%) of placebo patients. Two of the pirfenidone patients experienced a hip fracture and one placebo patient had a concussion and one had a fractured coccyx. Six (1.7%) of patients treated with pirfenidone 2403mg/day experienced a serious fracture compared to none in the placebo group. Dizziness may play a role in falls and fractures.

Because the animal carcinogenicity studies are positive, a discussion of neoplasms in the clinical trials is warranted, although the studies were not powered or specifically designed to evaluate neoplasms. Overall, neoplasms occurred in 9-11% of patients. The most common neoplasm was basal cell carcinoma. The numbers of specific neoplasms were generally small in each treatment group and generally balanced across groups. No obvious signal or imbalance in neoplasms was noted.

Safety Summary

The two 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. The clinical program suggests that pirfenidone has some safety signals, including gastrointestinal AEs, liver laboratory abnormalities, photosensitivity, and rash. As shown in Table 9, other AEs were reported more frequently

with pirfenidone compared to placebo. These safety signals should be considered in the risk benefit assessment.

9 Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee meeting was held on March 9, 2010. Presentations of the efficacy and safety data were given by InterMune and the Agency. The open public hearing was filled with patients desperate for a treatment for IPF. Questions were asked about 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). Two individuals who voted that there was not sufficient efficacy data voted for approval of pirfenidone.

10 Pediatrics

Idiopathic pulmonary fibrosis is a disease of adults and does not occur in the pediatric population. As an orphan drug program, pediatric studies are not required.

11 Other Relevant Regulatory Issues

The Applicant conducted the clinical trials using Good Clinical Practices and the Applicant provided the required financial disclosure information for investigators. The financial disclosure information did not suggest a conflict with the investigators. A DSI audit was requested for 3 clinical sites based upon high enrollment and favorable outcome for pirfenidone. 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. The clinical data was deemed reliable.

A Regulatory Briefing was held on April 16, 2010, to discuss the efficacy data in the NDA and the recommendation for approval from the advisory committee meeting. The general feedback from the majority of the panel members indicated that substantial evidence of efficacy had not been met.

12 Labeling

The Applicant submitted a product label in the new PLR format, which is appropriate. Labeling negotiations were initiated with the Applicant. Main areas of revision included the clinical trials section to include the results of both clinical trials. Other labeling changes included simplification of the dose titration table, data regarding the liver and photosensitivity findings, and extensive revisions of the clinical pharmacology sections.

13 Recommendations/Risk Benefit Assessment

- Recommended regulatory action

The recommended regulatory action is **Complete Response**. From a clinical standpoint, the Applicant has not provided substantial evidence of efficacy of pirfenidone. In the submitted program, one trial (PIPF-004) met the primary endpoint of absolute change from baseline in percent predicted FVC with an effect size of 4.4% favoring pirfenidone over placebo and one trial (PIPF-006) did not meet the primary endpoint. Some secondary efficacy variables were numerically supportive. Given the fact that FVC is not an established surrogate for mortality in patients with IPF, replication of the findings is warranted. A survival benefit was not established for all cause on-treatment mortality, although the results generally numerically favored the pirfenidone treatment group. Overall, the results of PIPF-004 and PIPF-006 do not provide substantial evidence of efficacy to support the proposed indication to reduce decline in lung function in patients with IPF.

- Risk Benefit Assessment

The efficacy of pirfenidone is not adequately established for the reasons outlined above. The two phase 3 trials are adequate to assess the safety of pirfenidone for this patient population. The clinical program suggests that pirfenidone has some safety signals, including gastrointestinal AEs, liver laboratory abnormalities, photosensitivity, and rash. Without assurance of efficacy, the benefits of pirfenidone are not established and a risk/benefit assessment is not favorable.

- Recommendation for Postmarketing Risk Management Activities

Although the recommendation is Complete Response, a Risk Evaluation and Mitigation Strategy (REMS) was discussed during the review period. The Applicant voluntarily submitted a REMS for hepatotoxicity, which included a Medication Guide and Communication Plan. Meetings were held with DRISK and while DPARP generally agreed with the plan for a REMS to address the risks of photosensitivity, hepatotoxicity, and medication errors due to complex dose titration and modification, further discussion of the REMS will be deferred until the next cycle. Additional clinical data is being required and the additional safety data could affect the decision regarding a REMS, the goals, and the elements.

- Recommendation for other Postmarketing Study Commitments

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

- Recommended Comments to Applicant

Deficiency

The submitted data do not provide sufficient evidence of efficacy of pirfenidone for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function. One trial (PIPF-004) met the primary FVC endpoint and the results were not replicated in the second trial (PIPF-006). Because of the uncertainty of FVC as a surrogate for mortality, replication of efficacy is necessary. Mortality is the ideal primary endpoint in clinical trials in patients with IPF. The submitted data did not demonstrate a statistically significant benefit in all-cause mortality. Without independent substantiation of the FVC primary efficacy results or a significant benefit in all-cause mortality, the submitted application does not provide substantial evidence of the efficacy of pirfenidone.

Information Needed to Resolve Clinical Deficiencies

To support the approval of pirfenidone for patients with IPF, conduct a placebo controlled clinical trial that demonstrates a statistically significant benefit in all-cause mortality with pirfenidone. Alternatively, to support approval of pirfenidone for patients with IPF to reduce decline in lung function, conduct a clinical trial with FVC as the primary endpoint which replicates the efficacy of pirfenidone compared to placebo. The findings must be robust and provide evidence of a clinically meaningful response, including a responder analysis that favors pirfenidone. Mortality must be supportive and when the mortality data are pooled with the results from PIPF-004 and PIPF-006, the pooled data should support a benefit in all cause mortality.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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/s/

SALLY M SEYMOUR
04/23/2010

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	22-535
Priority or Standard	Priority
Submit Date(s)	November 4, 2009
Received Date(s)	November 4, 2009
PDUFA Goal Date	May 4, 2009
Division / Office	Division of Pulmonary and Allergy Products/Office of Drug Evaluation 2
Reviewer Name(s)	Banu A. Karimi-Shah, MD
Review Completion Date	April 1, 2010
Established Name	Pirfenidone
(Proposed) Trade Name	Esbriet
Therapeutic Class	Pyridone
Applicant	InterMune, Inc.
Formulation(s)	267mg Immediate Release Capsule
Dosing Regimen	3 Capsules Three Times a Day
Indication(s)	Treatment of idiopathic pulmonary fibrosis to reduce the decline in lung function
Intended Population(s)	Adults with idiopathic pulmonary fibrosis

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Brief Overview

InterMune submitted a 505(b)(1) New Drug Application (NDA) for pirfenidone capsules for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function. IPF is a chronic progressive, diffuse parenchymal lung disease of unknown etiology. It is characterized by scarring of the lungs, non-productive cough, and progressive dyspnea. Median survival time in patients with IPF is estimated to be from 3 to 5 years, with respiratory failure being the most frequent cause of death. IPF affects approximately 100,000 patients in the United States and therefore has been granted orphan drug designation. Pirfenidone for IPF was approved for the treatment of IPF in Japan in October 2008, in a different dose and formulation.

Currently, there are no FDA-approved therapies for an IPF indication. Hence, there is no regulatory precedent for an IPF clinical development program. The lack of regulatory precedent stems from the difficulty in choosing appropriate endpoints in IPF clinical trials. As IPF is a chronic progressive disease with survival estimated to be from 3 to 5 years, mortality is the ideal primary efficacy variable in IPF clinical trials. Mortality is also the preferred primary endpoint in IPF clinical trials because there are no prospectively validated surrogate endpoints for survival. Using a lung function parameter, such as forced vital capacity (FVC), as a primary endpoint in clinical trials for IPF, is logical, given the progressive respiratory decline that occurs in this disease, however there are several issues that make it difficult to interpret the clinical meaning of FVC decline. First, it is unclear how the FVC should be analyzed, whether as a difference in mean declines between treatment groups, a difference in the slope of decline in treatment groups, or more of responder analysis where certain thresholds of decline are measured among individual patients. Second, there is no agreed upon clinically important difference in any of these scenarios as to what might constitute a clinically meaningful benefit of active treatment. Although some literature suggests that a decrease $\geq 10\%$ in FVC is evidence of disease progression and may correlate with mortality, these have been retrospective subgroup types of analyses, with small numbers of patients, or produced by expert consensus, rather than prospectively validated (1-4).

In NDA #22-535, InterMune submitted the results of two 72-week, placebo-controlled, clinical trials with pirfenidone in patients with IPF (Trials PIPF-004 and PIPF-006). The primary efficacy endpoint was the absolute change in mean decline in percent predicted FVC from Baseline to Week 72. The results of the phase 3 trials showed that one trial (004) met the primary outcome and the second trial (006) did not. While trial 006 did not show a difference at Week 72, some earlier timepoints showed a favorable effect of pirfenidone on the percent predicted FVC. The treatment effect (pirfenidone – placebo) in trial 004 was a difference of 4.4 in percent predicted FVC. The treatment effect was quantitatively small and the clinical significance of this effect size is unclear. When the change in FVC was considered as a

responder analysis (responders were considered as those who dropped their percent predicted FVC $\geq 10\%$), a statistically significant difference between pirfenidone and placebo was shown in only one trial (PIPF-004).

Mortality was assessed and numerically favored pirfenidone in both trials although the results did not reach statistical significance even when pooled. Mortality was assessed on treatment (within 28 days of treatment discontinuation) and vital status was obtained for patients who discontinued (vital status at the end of study). Cause of death was not adjudicated, but InterMune did a post-hoc analysis of deaths considered related to IPF by the investigators. In the post-hoc pooled analysis for on-treatment IPF-related deaths, there was a statistically significant difference in the pooled trials, favoring pirfenidone; however, the Division noted many concerns with this analysis at the Pulmonary-Allergy Drugs Advisory Committee meeting (see below).

On March 9, 2010, the Division and InterMune discussed the findings from the pirfenidone NDA at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting. The open public hearing was filled with patients desperate for a treatment for IPF. Questions were asked about 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 given the fatal prognosis of IPF. As a result, the committee voted (9 yes, 3 no) that the safety data were adequate for patients with IPF. When asked whether pirfenidone should be approved for the proposed indication, the results were in favor of approval (9 yes, 3 no). Two individuals who voted that there was not sufficient efficacy data voted in favor of pirfenidone's approval.

Recommended Regulatory Action

Based upon my review of the submitted data in this NDA, the Applicant has not provided substantial evidence of the efficacy of pirfenidone. The basis for my opinion lies in the fact that the Applicant has not demonstrated replication of efficacy results for pirfenidone for the proposed indication. Of the two pivotal trials, only one trial achieved the primary endpoint, which was an absolute change from baseline to Week 72 in percent predicted FVC. As stated above, use of FVC as the primary endpoint in IPF clinical trials poses challenges on multiple levels. Given the issues with FVC analysis and interpretation, independent substantiation and replication of efficacy outcomes in two trials is necessary, in the opinion of this reviewer. A robust statistically significant finding of improved survival is one instance in which a single study (or in this case the pooled studies given their identical design) might be relied upon to provide substantial evidence of efficacy. However, neither trial individually, nor pooled, showed a statistically significant benefit in all-cause mortality. The pooled analysis of the two pivotal trials did reveal a statistical improvement in on-treatment IPF-related mortality, however there were several limitations with this analysis. Without independent substantiation of the efficacy results (in two trials) or a statistically significant benefit in all-cause mortality, the Applicant has not provided substantial evidence of the efficacy of pirfenidone. Therefore, from the standpoint of this clinical reviewer, the recommended regulatory action is a **Complete Response**.

Clinical Deficiency leading to Recommendation for a Complete Response

The efficacy of pirfenidone for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function has not been adequately established. The submitted clinical trials did not provide independent substantiation and replication of efficacy with respect to the primary endpoint, absolute difference between pirfenidone and placebo treatment groups in the mean decline in percent predicted FVC at week 72. Use of FVC as a primary endpoint is problematic on multiple levels. As FVC is an unvalidated surrogate for more clinically meaningful outcomes (i.e. mortality), replication of results using FVC as an endpoint is necessary. In addition, neither of the pivotal trials, individually or pooled, demonstrated a statistically significant benefit in all-cause mortality, the most clinically meaningful of endpoints in patients with IPF. Without independent substantiation of the primary efficacy results or a benefit in all-cause mortality, the submitted application does not provide substantial evidence of the efficacy of pirfenidone.

Information Needed to Resolve Clinical Deficiencies

To support the approval of pirfenidone for patients with IPF to reduce decline in lung function, conduct a clinical trial with FVC as the primary endpoint which demonstrates the efficacy of pirfenidone compared to placebo. Alternatively, a single well-designed trial that demonstrates a statistically significant benefit in all-cause mortality could also provide substantial evidence of efficacy.

1.2 Risk Benefit Assessment

In order to frame the discussion regarding a risk-benefit assessment, a brief summary of the efficacy and safety of pirfenidone is warranted.

Efficacy Results

Two pivotal trials, PIPF-004 and PIPF-006, were submitted by the Applicant to support the efficacy of pirfenidone to reduce the decline in lung function in patients with IPF. Both trials were almost identically designed as randomized, double-blind, placebo-controlled clinical trials to assess the efficacy and safety of treatment with pirfenidone compared with placebo in patients with IPF. In trial 004, patients were randomized 2:2:1 to receive pirfenidone 2403 mg/day, placebo, or pirfenidone 1197 mg/day, respectively. In trial 006, patients were randomized 1:1 to receive either pirfenidone 2403 mg/day or placebo. All patients were to remain on study treatment from the time of their randomization until approximately 72 weeks after the last patient had been randomized into the study. Therefore, duration of blinded therapy for each patient differed depending on when the patient was randomized into the study.

The pivotal trials enrolled patients aged 40–80 years who had a clinical, radiographic, and/or pathologic diagnosis of IPF, without evidence or suspicion of an alternative diagnosis for interstitial lung disease, and who had evidence of disease progression. Eligible patients were to

have mild to moderate disease severity as evidenced by percent predicted FVC $\geq 50\%$ at Screening and Day 1, a DLco $\geq 35\%$ at Screening, and no evidence of improvement in FVC over the year preceding study entry. For the most part, concomitant medications being used to treat IPF were prohibited; allowances were made in the case of acute respiratory decompensation, acute IPF exacerbation, and progression of disease.

The primary efficacy parameter was the absolute change in percent predicted forced vital capacity (FVC) from Baseline to Week 72. The primary efficacy comparison was between pirfenidone 2403 mg/d and placebo; the pirfenidone 1197 mg/d group was included only to explore a dose-response relationship. Important secondary efficacy parameters included progression free survival, time to IPF worsening, and mean change from baseline in percent predicted DLco, all measured at Week 72. Death was an exploratory endpoint. Survival was examined on-treatment (up to 28 days after treatment discontinuation) and at the end of the entire study period (vital status assessment). Safety assessments included adverse events (AEs), physical examinations, vital signs, electrocardiograms, and clinical laboratories.

A total of 779 IPF patients were randomized in the two phase 3 trials; 435 and 344 patients were enrolled at 64 and 46 sites in North America, Europe, and Australia, in PIPF-004 and PIPF-006, respectively. Baseline characteristics were generally balanced across treatment groups. Baseline characteristics across the two trials were also generally similar, except for a larger proportion of patients in trial 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 PIPF-004 and PIPF-006, over 80% of patients completed study treatment and over 90% completed the study, when deaths and lung transplant patients are classified as completers.

In trial 004, the mean decline from Baseline to Week 72 in percent predicted FVC was significantly reduced in patients receiving pirfenidone 2403 mg/day compared to placebo (-8.0% vs. -12.4%), with an absolute difference of 4.4 and a relative reduction of 35% ($p=0.001$). Additionally, a reduced decline from Baseline was statistically significant at every earlier timepoint in trial 004 as well. Trial 006 showed no difference between the pirfenidone and placebo groups at 72 weeks (-9.0% vs. -9.6%) with an absolute difference of 0.6 and a relative reduction of 6.5% ($p = 0.501$). However, in trial 006, there were statistically significant reductions in the mean decline of % predicted FVC in the pirfenidone group as compared with placebo at Weeks 24, 36, and 48 with a diminished effect at Week 60.

Multiple secondary efficacy endpoints were investigated. In trial 004, the only secondary endpoint that was statistically improved with pirfenidone treatment was progression-free survival. The Six-Minute Walk Test (6MWT) distance was the only secondary endpoint in favor of pirfenidone in trial 006, with a nominal p-value <0.05 . However, the significance of this

secondary endpoint should be interpreted with caution in the face of trial 006 failing to achieve the primary endpoint.

Survival was designated as an exploratory endpoint, but given the severity of IPF, unmet need in this population, and the fact that only one study met its primary endpoint, mortality was examined in detail, to determine whether either study showed a significant mortality benefit. The Agency typically requires two studies to provide independent substantiation and replication of results; however, there are situations where one study may be adequate. The Agency's Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products describes the situations in which FDA relies upon a single adequate and well-controlled efficacy study to support approval e.g., a multicenter study of excellent design with highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival.

Neither study demonstrated a benefit in all-cause on-treatment mortality, although both trials 004 and 006 trended towards a numerical mortality benefit in the pirfenidone treatment group. When deaths were counted at the end of the study period (vital status assessment), the results in trial 004 numerically continued to favor pirfenidone, however, there was no numerical benefit in trial 006. Additionally, when lung transplants were counted as “deaths”, again, no mortality benefit was demonstrated. When on-treatment IPF-related mortality was examined, the results of the pooled analysis of trials 004 and 006 were statistically significant in favor of pirfenidone. However, this analysis was performed post-hoc, and the cause of death was unadjudicated. As a result, assignment of relation to IPF may have not been consistent in all cases, as it was made by the individual investigators. Therefore, the statistical significance of the reduction in IPF-related mortality should be interpreted carefully with these limitations in mind.

Safety Results

The safety of pirfenidone 2403 mg/day is evaluated primarily in the two pivotal trials 004 and 006. Pooling of data across trials 004 and 006 to examine the emergence of any safety signals was deemed acceptable as these trials were identically designed and the patient population was comparable in terms of demographics, baseline characteristics, and dose of pirfenidone. Safety assessments in these two trials included adverse events, physical examinations, vital signs, ECGs, and clinical laboratory testing. For the purposes of the safety discussion, on-treatment results are emphasized.

There were a total of 432 patients treated with pirfenidone (87 in the 1197 mg/day group and 345 in the 2403 mg/day group) and 347 patients treated with placebo. The mean treatment duration was similar between the treatment groups. Overall, there were numerically fewer on-treatment deaths in the pirfenidone 2403 mg/day treated patients (5.5%) vs. placebo-treated patients (8.4%). There were a total of 56 on-treatment deaths in both trials, and the percentage of deaths was lowest in the pirfenidone 2403 mg/day group compared with the placebo and pirfenidone 1197 mg/day groups (19 patients, 5.5%; 29 patients, 8.4%; and 8 patients, 9.2%, respectively). In PIPF-004, where two doses of pirfenidone were explored, no numerical dose response was

demonstrated. Cause of death was not adjudicated centrally, but rather reported by the individual investigator. IPF (as a MedDRA preferred term) was the most common cause of death overall. Of the 19 treatment-emergent deaths in the pirfenidone 2403 mg/day group, the largest number were classified as due to IPF (n=6, 1.7%). Other cases were also classified as IPF-related deaths by individual investigators. Death is discussed in detail as an exploratory endpoint in the efficacy section of this review.

Serious adverse events (SAEs) occurred in about a third of patients in all three treatment groups. SAEs that were reported more frequently in the pirfenidone 2403 mg/day group as compared with placebo were: coronary artery disease, chest pain, pneumothorax, bladder cancer, fall, and syncope. No dose repose was noted in the pirfenidone 1197 mg/day group with respect to SAEs.

Overall, more patients discontinued study treatment secondary to an AE in the pirfenidone groups than in the placebo group. Idiopathic pulmonary fibrosis was the most frequently reported AE leading to discontinuation of study treatment (2.9% pirfenidone-treated; 2.6% placebo). The greatest differences in number of patients that discontinued secondary to an adverse event between the pirfenidone and placebo groups, respectively, were due to the AEs of rash, nausea, and bladder cancer. Dose interruption or modification rates were also higher in the two pirfenidone treatment groups. Adverse events of the skin (photosensitivity/rash) and gastrointestinal tract (nausea, diarrhea, and vomiting) led to the highest rates of dose modification.

Before unblinding trials 004 and 006, the Applicant identified a number of clinically important events AEs of interest. These events of interest were identified based upon relevant non-clinical findings as well as human experience in previously conducted pirfenidone IPF clinical trials. After unblinding the safety data from trials 004 and 006, the Applicant refined the AEs of interest to include only those AEs that occurred with an increased frequency in patients receiving pirfenidone. These AEs of interest can be divided into five major categories: 1) General Disorders: anorexia, decreased appetite, fatigue, 2) Cardiac Disorders: primarily arrhythmias, syncope, 3) GI events: diarrhea, nausea, vomiting, 4) Hepatic laboratory abnormalities: increase in transaminases, and 5) Skin events: photosensitivity reaction and rash. Most of these adverse events of interest were without significant clinical sequelae, although they did lead to dose reduction or discontinuation of study treatment in a minority of cases.

Safety data showed that pirfenidone is most commonly associated with nausea, diarrhea, dyspepsia, vomiting, fatigue, anorexia, dizziness, rash, and photosensitivity reaction, consistent with what had been described as adverse events of interest based upon previous clinical experience with pirfenidone. Overall, the two phase 3 trials were adequate to assess the safety of pirfenidone.

Risk-Benefit Assessment

The benefit to risk analysis of pirfenidone is complex, given that the science in the field of IPF is evolving, there are no effective therapies, and no regulatory precedent exists for this indication. One trial out of two demonstrated a statistically significant, albeit quantitatively small and

clinically unclear, benefit of pirfenidone over placebo. Further, the clinical meaning of the chosen primary endpoint (FVC) has not been established in a definitive manner. So, although the safety findings reported in the pirfenidone clinical development program do not preclude approval of pirfenidone for a life-threatening indication such as IPF, it is the unproven benefit in this patient population that negatively impacts my assessment of the risk-to-benefit-ratio. In my opinion, if the Applicant were able to provide substantial evidence of efficacy (i.e. by performing another trial with a statistically significant outcome in either this primary endpoint or all-cause mortality), the risk-benefit assessment of pirfenidone for the treatment of this fatal disease would be more favorable.

1.3 Recommendations for Post-market Risk Evaluation and Mitigation Strategies

The safety review of pirfenidone identified several safety signals that would warrant consideration for a REMS. The risks of concern are the following: hepatotoxicity, photosensitivity, and medication errors due to complex dose titration and dose modification recommendations. To help minimize that risks, a medication guide is recommended so that patients are aware of the risks and the dosing titration and modification. A communication plan would also be helpful to ensure that practitioners are familiar with the toxicities, dosing issues, and liver monitoring.

1.4 Recommendations for Post-market Requirements and Commitments

I have no recommendations for post-market requirements or commitments from a clinical perspective.

2 Introduction and Regulatory Background

2.1 Product Information

The chemical name for pirfenidone is 5-methyl-1-phenyl-2-(1H)-pyridone. The proposed trade name is Esbriet®. Pirfenidone is a new molecular entity in a new pharmacological class. The exact mechanism of action is uncertain, however the Applicant proposes, based upon in vitro and animal data, that pirfenidone has both anti-fibrotic and anti-inflammatory properties.

The proposed indication is the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function in patients 40 to 80 years of age. The proposed dosing regimen is 2403 mg/day divided into 3 doses (3 x 267 mg by mouth TID). For the purposes of this clinical development program, all pirfenidone and placebo capsules were supplied in opaque, hard, white gelatin capsules. Pirfenidone was supplied in either 267 mg or 133 mg capsules for the 2403 mg/day or 1197 mg/day doses, respectively. Each pirfenidone capsule contained the following excipients: croscarmellose sodium, microcrystalline cellulose, povidone, and

magnesium stearate. Each placebo capsule contained microcrystalline cellulose, pre-gel starch, magnesium stearate, and bitrex. The proposed to-be-marketed dosage strength is the 267 mg capsule, and this was the formulation used in the phase 3 clinical program.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are no FDA-approved treatments for any aspect of IPF. However, the following table provides a brief list of those drugs which are commonly used off-label to treat IPF in clinical practice.

Active Ingredient	Brand Name
Azathioprine	Imuran, Azasan
Bosentan	Tracleer
Cyclophosphamide	Cytoxan
Interferon-gamma 1 β	Actimmune
Methotrexate	Trexall, Rheumatrex
Methylprednisolone	Many generics
N-acetylcysteine	OTC supplement
Prednisone	Many generics
Sildenafil	Viagra

2.3 Availability of Proposed Active Ingredient in the United States

Pirfenidone is a new molecular entity and is not currently marketed in the United States.

2.4 Summary of Pre-submission Regulatory Activity Related to Submission

The regulatory history of pirfenidone dates back to the 1970s when its development was first begun by Marnac, Inc. The regulatory history is briefly outlined below.

- Mid 1970's: Marnac, Inc. initiated development of pirfenidone
 - Marnac conducted several small uncontrolled studies
 - In the 1990s, Marnac initiated compassionate use and Phase 2 controlled trials in IPF and pulmonary fibrosis patients
 - The formulation was a 400 mg capsule with dosing based on body weight.

- 1997: Shionogi acquires rights to develop pirfenidone in Japan, S. Korea, and Taiwan
 - Shionogi completed 2 randomized, double-blind, placebo-controlled trials of 1800 mg/day (Trials SP2 and SP3)
 - October 2008: Pirespa (pirfenidone 200 mg tablet) was approved for marketing by the Japanese Ministry of Health

- March 2002: InterMune acquired the worldwide rights from Marnac (with the exception of Japan, S. Korea, and Taiwan, which were owned by Shionogi)

- April 2003: IND 67,284 for pirfenidone became active
 - InterMune terminated the compassionate use protocols and limited Phase 2 IPF trials conducted by Marnac due to poor patient enrollment and lack of compliance with good clinical practices.

- March 2005: End of Phase 2 Meeting (EOP2)

The following key issues/comments were discussed:

 - The Agency cautioned that dose/dosing interval were not thoroughly explored in Phase 2. To circumvent this issue, the Agency suggested that an additional dose arm be added to Phase 3.
 - The Agency noted that a single study would not be adequate unless results were “highly clinically and statistically persuasive” and that all available data would be examined to either support or weaken reliance on a single trial
 - The Agency noted the lack of knowledge regarding mechanism of action as a limitation.
 - The proposed primary endpoint (EP) was time to death or to disease progression (relative decline in the % predicted FVC of $\geq 10\%$ on 2 consecutive visits). The applicant also proposed to use $FVC \geq 10\%$ as a surrogate for mortality.
 - Agency voiced concerns regarding surrogate endpoint and stated that mortality would be the ideal endpoint
 - Agency said that if the sponsor proceeded with the proposed primary EP, the efficacy of pirfenidone would not be based solely on winning on the primary EP, but what drives the EP. If the EP was driven mostly by the decrease in FVC, this would be less compelling.

- May 2005: Agency Comments PIPF-004 and PIPF-006

The protocols were powered to detect a difference of 3.5% in predicted FVC between treatment groups. The Agency commented that although this number could be used to aid in the adequate powering of their studies, the Agency did not necessarily agree that this was the minimally important difference.

- September 2008: pre-NDA meeting
 - The Agency reiterated its concern with the primary endpoint
 - The Agency re-emphasized that decline in FVC was not an established surrogate for mortality and further, that the clinically meaningful difference in FVC is unknown.
 - The Agency stated that since the applicant had chosen to use FVC as the primary endpoint, the totality of the data would be examined to determine what was driving the primary endpoint. It would also be important for the secondary endpoints (many of which are clinically meaningful to patients) to support the primary endpoint
 - Because of the difference in trial design, dosing regimens, etc, the Marnac studies should not be incorporated into the Integrated Summary of Efficacy, but a safety summary from these trials should be included in the Integrated Summary of Safety.
 - PIPF-004 and PIPF-006 were to be the pivotal clinical trials.

2.5 Other Relevant Background Information

Pirfenidone (Pirespa®, Shionogi & Co., Ltd.) formulated as a 200 mg tablet, was approved for the treatment of IPF in Japan in October 2008. Post-marketing safety reporting from this foreign market is discussed in 8 Post-market Experience.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The original NDA dated November 4, 2009, was submitted in electronic common technical document (eCTD) format, well-organized, and easily navigated by this reviewer. There were no issues with respect to submission quality and/or integrity. The Division has requested an audit by the Division of Scientific Investigation (DSI) for this NDA, since pirfenidone is new molecular entity proposed for an indication for which there are no FDA-approved therapies. Three sites were recommended for audit based on high enrollment and demonstration of outcomes that were in favor of pirfenidone. Preliminary report of the DSI inspections has revealed that the sites operated by Drs. Allen and Golden had minor deficiencies which included incomplete/inaccurate record documentation, not following proper informed consent procedures, or deficiencies in study drug accountability monitoring. Dr. Nathan's clinical site inspection met Good Clinical Practices (GCP) and required no action (NAI). Refer to the details of Dr. Anthony Orenca's report for further details.

3.2 Compliance with Good Clinical Practices

Before patient enrollment, the protocol, protocol amendments, patient informed consent form(s) (ICFs), and any advertisements were reviewed and approved by the Independent Ethics Committee (IEC)/Institutional Review Board (IRB) governing each participating study center. Documentation of this approval was to be provided to the sponsor or its designee. The studies were conducted in accordance with good clinical practices (GCP) as described in the United States of America (USA) Food and Drug Administration (FDA) regulations (21 CFR 50, 54, 56, and 312) and the International Conference on Harmonization (ICH) document “Guidance for Industry—E6 Good Clinical Practice: Consolidated Guidance,” dated April 1996 (ICH 1997), which are consistent with the principles stated in the Declaration of Helsinki.

3.3 Financial Disclosures

Of the 64 sites at which patients were enrolled, only one investigator, (b) (6) reported any significant payments from the sponsor. In May 2006, InterMune issued a research grant in the amount of \$25,000 payable to (b) (6) to support a study to be conducted by (b) (6) as the principal investigator. The title of the study was, “Characterization of Pulmonary Arterial Hypertension in Patients with Idiopathic Pulmonary Fibrosis”. The nature of the study was a retrospective review of the existing data from IPF patients who were previously evaluated and transplanted by the (b) (6). In addition, (b) (6) received an honorarium in the amount of \$2,500, for an updated total as of June 2009 of \$27,500. (b) (6) was the primary investigator at site (b) (6) in trial PIPF-004, which enrolled 10 patients. The treatment difference at Week 72 (LS mean difference, treatment-placebo, by ANCOVA, in absolute change from baseline of % predicted FVC) was much larger in this group of patients (12.05) than the average treatment difference (4.4). This site was therefore the subject of a DSI audit to confirm that this financial arrangement between the Applicant and (b) (6) did not compromise the integrity or quality of the results in trial PIPF-004. From a preliminary standpoint, the DSI inspection did not note any deficiencies.

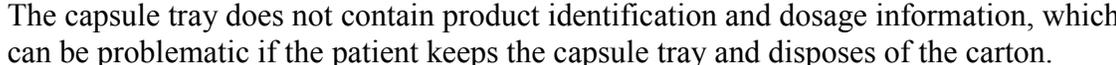
4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Pirfenidone is a small, synthetic, non-peptide molecule, and is a new molecular entity. The proposed commercial drug product for pirfenidone is a 267 mg immediate release capsule. The active pharmaceutical ingredient is a white to pale yellow powder. The product will be packaged

in bulk bottles of 270 capsules and in blister trays for a 14-day titration period or a 4-week maintenance period.

The CMC reviewer has identified several issues with the carton and container labeling.

- The directions are not easily read due to contrast/font issues
-  (b) (4)
- 
- The capsule tray does not contain product identification and dosage information, which can be problematic if the patient keeps the capsule tray and disposes of the carton.

The CMC review team recommends approval of this application pending response to an information request regarding an impurity which contains a structural alert. The CMC reviewer has asked for the drug master file for this impurity, and that the amount of the impurity be controlled to within accepted parameters for potential genotoxic impurities. If the Applicant is unable to do so, the impurity will need to be qualified via a bacterial mutagenicity assay. The response to the CMC request for information is pending at the time this review is finalized.

4.2 Preclinical Pharmacology/Toxicology

InterMune submitted a complete pharmacology/toxicology program to support the chronic use of pirfenidone. The program included chronic, repeat-dose, toxicology studies in rats and dogs as well as other short-term toxicology studies. Reproductive toxicology assessment in rats and rabbits, and carcinogenicity studies in rats and mice were submitted. Photosafety tests in guinea pigs and mice were also conducted.

In a 6-month rat toxicology study with doses up to 1000 mg/kg/day and 9-month dog toxicology studies with doses up to 200 mg/kg/day, the target organ of toxicity was the liver, with increased liver weights and hepatic centrilobular hypertrophy, but no effects on ALT, AST, and bilirubin.

Genotoxicity studies with pirfenidone were negative. The 2-year carcinogenicity study in mice showed an increase in liver neoplasms – hepatocellular adenoma, carcinoma and hepatoblastoma. The carcinogenicity study in rats showed an increase in hepatocellular adenoma, uterine tumors (adenoma, adenocarcinoma) and thyroid gland follicular cell carcinoma. In the photo-safety tests, phototoxicity and irritation were noted in the guinea pigs after administration of pirfenidone and exposure to UVA light. The severity was decreased by sunscreen application.

4.3 Clinical Pharmacology

4.4.1 Mechanism of Action

The mechanism of action of pirfenidone has not been fully established. However, existing data from in vitro and animal models suggest that pirfenidone exerts both anti-inflammatory and anti-fibrotic effects. Pirfenidone is capable of reducing the production of pro-inflammatory cytokines

including tumor necrosis factor α (TNF- α) and interleukin-1-beta (IL-1 β). Pirfenidone has also been shown to reduce the accumulation of inflammatory cells in response to various stimuli (5). The Applicant has also demonstrated that pirfenidone attenuates the production of profibrotic cytokines, including platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF- β), and reduces the accumulation of extracellular matrix components, particularly collagen (6).

Reviewer's comment: As the MOA of pirfenidone has not been fully established by the Applicant, and the efficacy thus far is marginal, [REDACTED] (b) (4) [REDACTED] if pirfenidone is to be approved, it will simply be described by its chemical structure (pyridone).

4.4.2 Pharmacodynamics

The Applicant conducted a thorough QT study. Review of clinical pharmacology data and discussions with the clinical pharmacology reviewer, Dr. Elizabeth Shang, suggest that the information regarding prolongation of the QT interval is limited. Effects of multiple doses of proposed therapeutic (801 mg TID) and supra-therapeutic doses (1335 mg TID) of pirfenidone upon QT prolongation were studied in 80 healthy subjects and compared to placebo and moxifloxacin. Overall, the thorough QT study failed to demonstrate the positive control's anticipated effect, and therefore cannot be interpreted.

Reviewer's comment: The limited supra-therapeutic dose and lack of positive control effect are the reasons for the clinical pharmacology recommendation of a repeat thorough QT study as a post-marketing requirement. It is of note, that there was extensive ECG monitoring in the phase 3 clinical trials, with centralized reading and interpretation, that did not reveal any issues with QTc prolongation. From a clinical perspective, I don't think another TQT study is necessary, as no signal was apparent in the phase 3 program.

4.4.3 Pharmacokinetics

Following single oral administration of 801 mg, pirfenidone is absorbed quickly with a mean peak plasma concentration of 16.4 mg/L reached at approximately 0.5 hour. The terminal elimination half-life (T_{1/2}) of pirfenidone is about 3 hours. Food decreased the absorption of pirfenidone, however, it is recommended for administration with food, to reduce the frequency of adverse events.

Mean protein binding of pirfenidone is ~58% at concentration range of 1 to 10 mg/L. Pirfenidone is primarily metabolized by CYP1A2. 5-Carboxy-pirfenidone is the major metabolite found in human plasma and excreted in urine. Pharmacokinetics of pirfenidone is affected by renal impairment, hepatic impairment, and co-administration of strong CYP1A2 inhibitors or inducers. Refer to the Biopharmaceutics Review of Dr. Elizabeth Shang for further details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 2: Summary of Pirfenidone Clinical Studies Included in NDA					
Study Number	Phase	Study Design	Objective	Population	# Exposed Pirf/Control
Subjects					
InterMune-Sponsored					
PIPF-005	1	Uncontrolled	PK	Healthy	41/-
PIPF-007	1	RDBPC/AC	Thorough QTc	Healthy	81/81
PIPF-008	1	RDBPB	MTD/Safety	Healthy	16/4
PIPF-009	1	Uncontrolled	Renal Impairment	Renal or Healthy	26/-
PIPF-010	1	Uncontrolled	DDI/PK	Healthy	54/-
PIPF-011	1	Uncontrolled	Hepatic Impairment	Hepatic or healthy	24/-
Patients					
InterMune-Sponsored					
PIPF-002	2	Uncontrolled	Safety and Efficacy	IPF/PF	83/-
PIPF-004	3	RDBPC	Safety and Efficacy	IPF	261/174
PIPF-006	3	RDBPC	Safety and Efficacy	IPF	171/173
PIPF-012*	3	Uncontrolled	Safety	IPF	603/-
Marnac-Sponsored					
PIPF-001	2	RDBAC	Safety and Efficacy	IPF/PF	26/26
PIPF-003	2	RDBPC	Safety and Efficacy	IPF/PF	27/25
IPP/Exception	2	Uncontrolled	Safety	IPF/PF	34/-
Shionogi-Sponsored					
SP2	2	RDBPC	Safety and Efficacy	IPF	73/36
SP3	3	RDBPC	Safety and Efficacy	IPF	164/107
AC: active control; DDI: drug-drug interaction; MTD: maximum tolerated dose; PF: pulmonary fibrosis; PK: pharmacokinetics; RDBPC: randomized, double blind, placebo controlled; *: PIFP-012 treated 603 patients from the phase 3 studies 004 and 006 of whom 274 had received placebo and 329 had received pirfenidone, data from this study will be included in the safety update. Source: Table 2.5-1, pg. 4, Clinical Overview, Module 2.					

Table 3: Pivotal Studies				
Study #	Study Type/ Design Total N	Age (yrs)	Treatment Groups (N)	Duration Centers/Sites
004	Efficacy/Safety R, DB, PC, PG N=435	45-81	Pirf 2403 mg/d [3 x 267 mg TID] (174) Pirf 1197 mg/d [3 x 133 mg TID] (87) Placebo (174)	72 weeks 64 sites in US, Europe, Australia
006	Efficacy/Safety R, DB, PC, PG N = 344	45-80	Pirf 2403 mg/d (3 x 267 mg TID) (171) Placebo (173)	72 weeks 46 sites in US, Europe, Australia
R: Randomized; DB: Double blind; PC: placebo-controlled; PG: parallel group; TID: three times daily				

5.2 Review Strategy

The pivotal trials, 004 and 006, have been reviewed in detail to determine if the Applicant has provided substantial evidence of the efficacy and safety of pirfenidone for the proposed indication. To orient the reader, the review has been organized in the following manner. The protocols for trials 004 and 006 are discussed in detail in Section 5.3 Discussion of Individual Studies/Clinical Trials. The efficacy results for each trial (patient disposition, demographics, primary and secondary outcomes) are presented in Section 6 Review of Efficacy; the safety results for the pivotal trials (extent of exposure, deaths, serious adverse events, adverse events) are presented in Section 7 Review of Safety.

Trial SP3 was sponsored by Shionogi, Inc, the Japanese company that acquired the rights (from Marnac, see 2.4 Summary of Pre-submission Regulatory Activity Related to Submission) to develop pirfenidone in Japan, South Korea, and Taiwan. SP3 provided the evidence that formed the primary basis for approval of the pirfenidone 200 mg tablet in Japan in October 2008. SP3 was a randomized, double-blind, placebo-controlled trial of pirfenidone 1800 mg/day (N=110), 1200 mg/day (N=56), and placebo (N=109) in 275 Japanese patients with IPF. The trial was conducted at 73 sites in Japan, with a treatment duration of 52 weeks. A definitive diagnosis of IPF was made based on the criteria set forth by the Ministry of Health, Labor and Welfare Specific Diffuse Pulmonary Disease Research Group (revision 4). The primary efficacy outcome in SP3 was defined as a change from baseline in vital capacity at week 52. In the primary efficacy analysis, the mean decline from baseline in VC at week 52 was reported by the Applicant to be significantly reduced in patients receiving pirfenidone 1800 mg/day compared to placebo (-0.09 L vs. -0.16 L, relative difference 44%; $p=0.042$, ANCOVA). There was also a reduced mean decline in percent predicted VC at week 52 in the pirfenidone 1800 mg/d group compared with placebo (-2.91% vs. -5.13%; $p=0.044$, ANCOVA).

The Applicant has submitted an English translation of the Japanese clinical study report for trial SP3. The Applicant asserts that this “phase 3 study conducted by Shionogi contributes significantly to the totality of the data supporting the safety and efficacy of pirfenidone,” and therefore, “was more fully integrated into the NDA than was initially proposed at the Pre-NDA meeting.” However, the Applicant has not provided any patient-level data to support the information presented in the SP3 clinical study report (e.g. case report forms, narratives, and SAS data sets). Given that the results of SP3 were presented in the NDA submission with unexpected emphasis, this information was requested from the Applicant on December 11, 2009. The Applicant notified the Agency on December 14, 2009 that they did not in fact have this Shionogi-owned data, and that the SP3 study report was submitted only to serve as supportive information in this NDA. Without the data to review and confirm the analysis, the Agency cannot rely upon the results of SP3 to evaluate the efficacy and safety of pirfenidone. Therefore, the SP3 study and results will not be reviewed further in this document. In addition, there are several noteworthy differences between SP3 and trials 004/006, which would limit the applicability of the SP3 data to the overall development program. Notable differences include: IPF diagnostic criteria, dose, formulation, primary endpoint, and treatment duration.

5.3 Discussion of Individual Studies/Clinical Trials

Trials 004 and 006 were identically designed trials, with the exception of the inclusion of a low-dose treatment group in trial 004, PK sampling in trial 004, and HRCT at baseline and week 72 in trial 006.

PIPF-004

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-Arm Study of the Safety and Efficacy of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Study Dates: July 14, 2006 – November 7, 2008

Study Sites: 64 sites in the United States, Canada, Mexico, United Kingdom, France, Italy, Poland, and Australia

PIPF-006

Study Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of the Safety and Efficacy of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Study Dates: April 27, 2006 – October 31, 2008

Study Sites: 46 sites in the United States, Australia, Belgium, Germany, Ireland, Spain, and Switzerland.

Description

PIPF-004 and -006 were phase 3, randomized, double-blind, placebo-controlled clinical trials designed to assess the safety and efficacy of treatment with pirfenidone compared with placebo in patients with IPF. Additional clinical objectives included assessment of a lower dose (1197 mg/day), in PIPF-004 only. In trial 004, patients were randomized 2:2:1 to receive pirfenidone 2403 mg/day, placebo, or pirfenidone 1197 mg/day, respectively. In trial 006, patients were randomized 1:1 to receive either pirfenidone 2403 mg/day or placebo. Following a 15-day dose escalation phase, study medication was administered orally as 3 capsules three times per day (TID) with food for a total of 9 capsules per day. Patients received study treatment from randomization until approximately 72 weeks after the last patients had been randomized into the study.

Study Schedule

The study consisted of three study periods: Washout, Screening, and Treatment. All patients were also required to have a final follow-up visit three to four weeks after their treatment completion visit (See Figure 1).

Figure 1: Study Design - PIPF-004 and PIPF-006

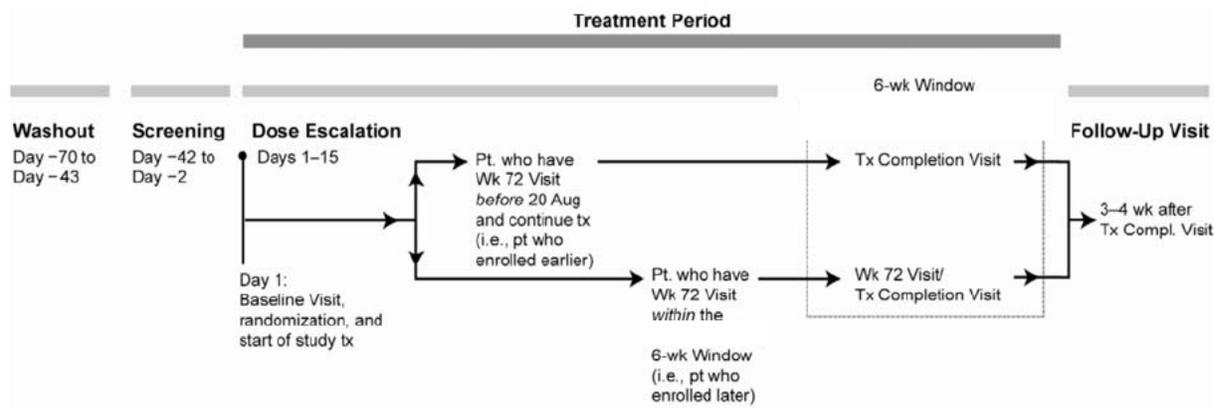


Figure 9-1 Study Flow Diagram

Compl. = Completion; pt = patient(s); tx = treatment; wk = week(s)

Source: Figure 9-1, p. 40, PIPF-004 CSR, Module 5.

During the washout period (at least 28 days before the start of screening), patients were required to discontinue any prohibited medication that they were taking, including therapy targeted to treat IPF. Study assessments during the washout period included: history, ECG, and a review of lung biopsy/transbronchial biopsy/BAL data.

Screening assessments included: history, physical exam, vital signs, ECG, review of lung biopsy/transbronchial biopsy/BAL data, HRCT, PFTs (lung volumes, spirometry, and DLco), 6MWT, and clinical laboratories. Patients who met all the eligibility criteria during the screening period were then randomized to one of the three treatment groups. Additional Day 1 assessments included a repeat of spirometry measurement (could not vary from screening by more than 10%), arterial blood gas, and UCSD SOBQ. The dose of study treatment was escalated from 1 capsule TID to a full maintenance dose of 3 capsules TID over the first 15 days of the study, as tolerated.

During the treatment period, patients were monitored at Week 1, via a telephone assessment, and during study visits scheduled at Weeks 2, 4, 6, 12, and then every 12 weeks until the treatment completion visit. All patients were to remain on study treatment from the time of their randomization until approximately 72 weeks after the last patient had been randomized into the study. Therefore, duration of blinded therapy for each patient differed depending on when the patient was randomized into the study. However, all patients were to complete study treatment by September 30 or September 25, 2008, for trials 004 and 006, respectively. All patients were required for their final follow-up visit three to four weeks after the treatment completion visit (See Table 4).

Table 4: Schedule of Study Assessments during the Treatment Period: PIPF-004 and -006

Study Assessments	Weeks										
	1	2	4	6	12	24	36	48*	72A	72B and /or TCV	Final F/U (4 weeks after TCV)
Phone Call	X										
Directed History		X	X	X	X	X	X	X		X	X
PE, VS, Weight		X	X	X	X	X	X	X		X	X
ECG		X		X	X		X	q 24 Wks		X	X
Body Plethysmography							X			X	
Spirometry (pre- and post-BD) ^a					X	X	X	X	X	X	X
DLco or TLco					X	X	X	X		X	X
6MWT					X	X	X	X		X	
ABG (at rest for 20 minutes)										X	
Clinical Labs		X	X	X	X	X	X	X		X	X
PK		X					X			X	
UCSD SOBQ, SGRQ, WHO QOL					X	X	X	X		X	

Source: Table 9-3, p. 65, PIPF-004 CSR, Module 5.

*: and every 12 weeks

a: Patients who had a FVC decline of 10% or a DLco decline of 15% had to have a confirmatory test performed at least 6 weeks later or at the final f/u visit.

TCV: treatment completion visit; F/U: follow up; PE: physical exam; VS: vital signs; PK: pharmacokinetics;

72A and 72B: If patients completed their Week 72 visit before August 20, 2008, they were to return for their TCV before Sept. 30, 2008. If patients completed their 72 week visit between August 20 and September 30, the Week 72 visit served as the TCV. All patients were to complete study treatment by September 30, 2008.

Population

For PIPF-004, the planned enrollment: 400 patients, randomized 2:2:1 to pirfenidone 2403 mg/day (N=160), placebo (N=160), or pirfenidone 1197 mg/day (N=80). The actual enrollment was 435 patients (174 pirfenidone 2403 mg/d, 174 placebo, 87 pirfenidone 1197 mg/d). In PIPF-006, the planned enrollment was 320 patients, randomized 1:1 to pirfenidone 2403 mg/day or placebo. The actual enrollment was 344 patients (171 pirfenidone, 173 placebo).

Patients aged 40–80 years who had a confident clinical, radiographic, and/or pathologic diagnosis of IPF without evidence or suspicion of an alternative diagnosis for interstitial lung disease, and who had evidence of disease progression were eligible to participate in the study. Eligible patients were to have mild to moderate disease severity as evidenced by percent predicted FVC \geq 50% at Screening and Day 1, a DLco \geq 35% at Screening, and no evidence of improvement in FVC over the year preceding study entry.

- Summary of Inclusion Criteria:

- **Diagnosis of IPF**

- Age 40-80 years, inclusive.

- Clinical symptoms consistent with IPF, including insidious onset of otherwise unexplained dyspnea on exertion of ≥ 3 months duration
- Diagnosis of IPF, defined as the first instance a patient was informed of having IPF, within 48 months of randomization
- HRCT scan showing a pattern of disease consistent with a confident (definite) radiographic diagnosis of usual interstitial pneumonia (UIP)/IPF. For patients with surgical lung biopsy showing definite or probable UIP, the HRCT criterion of probable UIP/IPF was sufficient.
- For patients < 50 years of age: open or video-assisted thoracoscopic surgical (VATS) lung biopsy showing a definite or probable UIP within 48 months of randomization. In addition, there were no features that supported an alternative diagnosis on transbronchial biopsy or bronchoalveolar lavage (BAL), if performed.
- For patient ≥ 50 years of age: at least of the following diagnostic findings, as well as the absence of any features on specimens resulting from these procedures, which supported an alternative diagnosis within 48 months of randomization:
 - Open or VATS lung biopsy that showed definite or probable UIP
 - Transbronchial biopsy that hosed no features of an alternative diagnosis
 - BAL that showed no features of an alternative diagnosis

IPF disease severity and progression

- Percent predicted FVC $\geq 50\%$ at screening and Day 1 (before randomization). The change in FVC between screening and Day 1 must have been $\leq 10\%$ relative difference.
 - Hemoglobin (Hgb)-corrected carbon monoxide diffusing capacity/carbon monoxide transfer capacity (DLco) $\geq 35\%$ of predicted value at screening only
 - Either FVC or Hgb-corrected DLco $\leq 90\%$ of predicted value at screening
 - No evidence of improvement in measures of IPF disease severity over the year preceding study entry
 - Distance walked ≥ 150 meters (492 feet) with O₂ saturation $\geq 83\%$ on ≤ 6 L/minute of O₂ during the 6-Minute Walk Test (6MWT) oxygen titration procedure performed at screening.
- Summary of Exclusion Criteria
 - Disease-Related Exclusions**
 - FEV₁/FVC ratio of < 0.7 after administration of bronchodilator at the Screen Visit and Day 1 before randomization
 - Bronchodilator response defined by an absolute increase of $\geq 12\%$ and an increase of 200 mL in the predicted FEV₁ or FVC or both after bronchodilator use compared to the values seen before bronchodilator at the Screen Visit and Day 1 before randomization
 - Residual volume (RV) $> 120\%$ of predicted (before administration of bronchodilator)
 - History of clinically significant environmental exposure known to cause pulmonary fibrosis (including but not limited to drugs, asbestos, beryllium, radiation, domestic birds).

- Known explanation for ILD, including but not limited to radiation, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, HIV, viral hepatitis, and cancer.
- Diagnosis of any connective tissue disease, including but not limited to scleroderma, systemic lupus erythematosus, and rheumatoid arthritis
- Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis
- In the clinical opinion of the investigator, the patient was expected to need and be eligible for a lung transplantation within 72 weeks after randomization

Reviewer's comment: Patients who were imminently in need of lung transplantation would have been excluded based on this criterion. However, in a disease such as IPF, with an unpredictable stepwise pattern of decline, it is difficult to garner a clinical opinion of which patient would not be expected to require a lung transplant in the next 72 weeks.

- Unable to undergo pulmonary function testing, which included meeting the following reproducibility standards:
 - At Screening, the 2 highest acceptable FVC values were within 0.100 liter
 - At Day 1, the 2 highest acceptable FVC values were within 0.100 liter
 - At Screening, 2 of the 3 acceptable DLco values were within 2 units (for carbon monoxide transfer capacity [TLco], within 0.67 SI units) of each other

Medical Exclusions

- Any history of malignancy likely to have resulted in death or significant disability or likely to have required significant medical or surgical intervention within 2 years after study entry. This did not include minor surgical procedures for localized carcinoma (e.g., basal cell carcinoma)
- Any condition other than IPF which, in the opinion of the investigator, was likely to result in the death of the patient within 2 years after study entry
- History of advanced cirrhosis or clinically significant liver disease
- History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within 6 months before study entry, including but not limited to the following:
 - Myocardial infarction, unstable angina pectoris, coronary artery bypass surgery, or coronary angioplasty
 - Congestive heart failure requiring hospitalization
 - Uncontrolled arrhythmias
 - Asthma or chronic bronchitis requiring hospitalization in the 6 months before study entry
- Any condition, which, in the opinion of the investigator, might have been significantly exacerbated by the known side effects associated with the administration of pirfenidone
- Poorly-controlled diabetes (defined by glycosylated hemoglobin [HbA1c] >10)

- Pregnancy or lactation. Women of childbearing capacity were required to have a negative serum pregnancy test before treatment and must have agreed to maintain highly effective methods of contraception by practicing abstinence or by using at least two methods of birth control from the date of consent through the end of the study. If abstinence was not practiced, then one of the two methods of birth control should have been an oral contraceptive (e.g., oral contraception and a spermicide).
- History of any condition or habit associated with altered consciousness and a risk of aspiration in the 2 years before study entry

Laboratory Exclusions

- Any of the following liver function test (LFT) criteria above specified limits: total bilirubin >2.5 _ ULN; aspartate or alanine aminotransferase (AST or ALT) >2.5x ULN; alkaline phosphatase >2.5x ULN
- Screening or Day 1 electrocardiogram (ECG) with a QTcB (Bazett's corrected QT) interval >500 milliseconds (ms)

Concomitant Therapy Exclusions:

- Prior use of pirfenidone or known hypersensitivity to any of the components of study treatment
- Patients were excluded if they required the following therapies within 28 days before screening:
 - Investigational therapy defined as any drug that was not approved for marketing for any indication in the country of the participating site
 - Any cytotoxic, immunosuppressive, cytokine modulating, or endothelin receptor antagonist agents including but not limited to: azathioprine, bosentan, cyclophosphamide, corticosteroids, cyclosporine, etanercept, iloprost, infliximab, leukotrienes, methotrexate, mycophenolate mofetil, sildenafil (daily), tetrathiomolybdate, TNF- α inhibitors, N-acetylcysteine (NAC), imatinib mesylate, Interferon gamma-1b (IFN- 1b), and tyrosine kinase inhibitors.
- Concomitant medications being used for the treatment of IPF (including but not limited to: angiotensin-converting enzyme [ACE]-inhibitors, colchicine, warfarin, heparin, sildenafil, and hepatic 3-methylglutaryl coenzyme A reductase [HMG-CoA] inhibitors). These drugs could have been used if given for a non-IPF indication if there was no clinically acceptable alternative therapy for the same indication.

Reviewer's comment: The inclusion/exclusion criteria as outlined in both protocols are acceptable.

Treatments

- Study Treatments

Eligible patients were randomized to receive pirfenidone 2403 mg/day (3 x 267 mg capsules TID), placebo equivalent, or pirfenidone 1197 mg/day (3 x 133 mg capsules TID in 004 only) via oral administration in three divided doses with a meal. Study treatments were escalated from 1 capsule TID on Days 1-7, to 2 capsules TID on Days 8-14, to a full maintenance dose of 9 capsules per day (3 capsules TID) beginning on Day 15. If patients followed a different dose escalation schedule, they were not considered protocol deviations. If patients missed scheduled dose, they were instructed to skip that dose and resume regular dosing with the next scheduled dose. Any interruption of study treatment for a period of ≥ 2 consecutive weeks was to be reported. If the investigator and medical monitor agreed that the patient should resume study treatment, the dose was re-escalated over 15 days as described.

Dose modification guidelines were provided for commonly seen AEs with pirfenidone, that have included fatigue, gastrointestinal side effects, a photosensitivity rash, and liver function test abnormalities. The dose of study treatment was modified at the investigator's discretion in the event of adverse effects or intolerability after discussion with the medical monitor. Dose modification was recorded in the case report forms. Strategies for dealing with the commonly observed AEs were as follows (arrows denote symptom persistence for 7 days):

- Fatigue/GI side effects: Dose reduced to 2 capsules TID → dose reduced to 1 capsule TID → dose reduced to 1 capsule BID or interrupted for 1-2 weeks to allow resolution of symptoms
- Mild to moderate photosensitivity rash (CTC Grade 1 or 2): dose reduced to 1 capsule TID → treatment interruption for 15 days
- Severe photosensitivity rash (CTC Grade 3 or higher): treatment interrupted; patient instructed to avoid all sun exposure.
- Elevations in ALT/AST/Bilirubin:
 - Grade 1: discontinue confounding medications, reduce dose of study treatment. Upon resolution, rechallenge patient with 3 capsules TID (full dose) at the discretion of the investigator.
 - Grade 2: discontinue confounding medications, reduce dose of study drug. Upon resolution, rechallenge with not more than 2 capsules TID if there was a reasonable suspicion that the abnormalities were related to study drug.
 - Grade 3: permanently discontinue study drug. Patients were not rechallenged.

• Permitted Medications

Concomitant medications for other medical conditions were allowed at the discretion of the investigator and were recorded in the CRF. Allowances were made in the case of acute respiratory decompensation, acute IPF exacerbation, and progression of disease (See Table 5).

Table 5: Permitted IPF Therapies			
	Pre-defined Criteria	Permitted Therapy ^b	Permitted Duration
Acute Respiratory Decompensation	Meet all criteria within 4 weeks: <ul style="list-style-type: none"> • Worsening PaO₂ or significant increase or new use of supplemental O₂ • Clinically significant worsening dyspnea • New or worsening radiographic abnormalities on CXR or HRCT 	Pulse-dose steroids	14 days
Acute IPF Exacerbation	Meet all criteria within 4 weeks: <ul style="list-style-type: none"> • Worsening of PaO₂ ≥ 8 mm Hg drop from the most recent value • Clinically significant worsening of dyspnea • New, superimposed ground-glass opacities on HRCT in one or more lobes • All other causes, such as cardiac, thromboembolic, aspiration, or infectious processes, were ruled out 	Azathioprine or Cyclophosphamide with or without corticosteroids [*]	12 weeks ^{**}
Progression of Disease ^c	<ul style="list-style-type: none"> • ≥10% absolute ↓ in % predicted FVC^a or • ≥ 15% absolute ↓ in % predicted DLco^a 	Azathioprine or Cyclophosphamide NAC+AZA+corticosteroids	

Source; Sections 9.4.7.3.1 – 3, p. 59-61, PIPF-004 CSR, Module 5.
^{*}Study drug was to be continued if possible
^{**} After the permitted duration of treatment, every effort was to be made to taper patients from the additional drugs.
 a: decrease as compared with mean of the highest FVC values obtained at Screen and Day 1 on two consecutive visits at least 6 weeks apart
 b: doses of ATS/ERS recognized permitted therapies were administered in accordance with the ATS guidelines
 c: Patients were only eligible for progression of disease therapy after Week 72

- Prohibited Medications

The following medications were prohibited within 28 days of screening: pirfenidone, any cytotoxic, immunosuppressive, cytokine modulating or receptor antagonist agent, any investigational therapy, or any medication being used for the treatment of IPF (including but not limited to ACE-inhibitors, colchicine, warfarin, heparin, sildenafil, and MGH-CoA reductase inhibitors). All prohibited medications that required tapering were to be tapered during the Washout Period.

Patient Discontinuation/Withdrawal Criteria

Study treatment was discontinued due to:

- unacceptable toxicity
- patient request
- pregnancy
- protocol violation (at the sponsor's discretion)
- investigator discretion
- study termination by sponsor
- lung transplantation

Patients who withdrew from the study underwent an early withdrawal evaluation which included assessment of spirometry, DLco, and other secondary efficacy parameters. These patients were also encouraged to permit Vital Status Assessments every 6 months and at study completion.

Primary Efficacy Analyses

The primary efficacy parameter was the absolute change in percent predicted forced vital capacity (FVC) from Baseline to Week 72. Baseline FVC was defined as the mean of the maximum acceptable FVC measurements obtained during the Screening and Day 1 Visits. The FVC at Week 72 was defined as the mean of the maximum acceptable FVC measurements obtained on two separate days at the Week 72 Visit (Week 72A and 72B). The primary analysis of the primary endpoint was a rank ANCOVA. The test of significance for the primary analysis of the primary efficacy outcome variable used a two-sided alpha of 0.0498. When data were ranked, data that were missing as a result of death were to be ranked “worse” than data missing for reasons other than death. Missing data due to reasons other than death for physiologic measurements (i.e. percent predicted FVC) were replaced with imputed data based on the average measurements for “similar” patients at the given time point. Similar patients were those whose data had the smallest sum of squared deviations from that patient for all visits before the one with the missing data.

Spirometry measurements were conducted in a uniform fashion across time and study sites in accordance with procedural guidelines described in the PFT Procedures Manual, which was based upon spirometry procedural guidelines defined by the ATS.

Reviewer's comment: The Applicant states that their initial spirometry procedure was more stringent than ATS criteria, and thus, as the trial progressed it became clear that the criteria initially proposed for the trials were too strict and not uniformly achievable by IPF patients. The strict enforcement of these guidelines would have led to inappropriately excluding quality and clinically valid spirometry data, in the opinion of the Applicant. As a result, the definition of 'acceptable' maneuvers as broadened to be more consistent with the ATS Guideline Statement and with accepted clinical practice. The final PFT manual was amended to reflect these changes.

Secondary Efficacy Analyses

If the primary efficacy analyses (absolute change in percent predicted FVC) from 004 and 006 each showed efficacy ($p \leq 0.0498$), then the secondary outcome variables were analyzed using pooled data from both studies in addition to the individual study analyses.

The secondary efficacy outcome variables were tested only in the pirfenidone 2403 mg/d and placebo groups as follows:

- Time to worsening of IPF: time to acute IPF exacerbation, IPF-related death, lung transplantation or hospitalization, whichever came first.
- Progression-free survival: time to first occurrence of either a 10% absolute decline in percent predicted FVC, a 15% decline in percent predicted DLco, or death. In the case of FVC and DLco, the decline must have been confirmed at 2 consecutive visits at least 6 weeks apart.
- Categorical assessment of absolute change from baseline to week 72 in percent predicted FVC. The changes were categorized as severe decline ($\downarrow \geq 20\%$, death, or lung transplantation), moderate decline ($\downarrow 10-20\%$), mild decline ($\downarrow 0-10\%$), mild improvement ($\uparrow 0-10\%$), or moderate improvement ($\uparrow \geq 10\%$).

The following secondary efficacy variables were analyzed as changed from baseline to week 72:

- Dyspnea: as measured by the University of California at San Diego Shortness-of-Breath Questionnaire (USCD SOBQ).
- Percent predicted HgB-corrected DLco.
- Worst oxygen saturation measured during the 6MWT.
- Distance walked during the 6MWT

The following were exploratory analyses measured as a change from baseline to week 72:

- St. George Respiratory Questionnaire (SGRQ)
- A-a gradient
- Absolute % predicted TLC
- World Health Organization Quality of Life Questionnaire
- Borg Scale difference before and after 6MWT

Other exploratory analyses included:

- Overall survival time, as measured by time from randomization to death
- Time from randomization to first requirement for outpatient oxygen
- Number of days alive without a respiratory hospitalization through Week 72

Protocol Amendments

There were 2 amendments to the original protocol (27 January 2006), Amendment 1 (19 March 2007), Amendment 2 (21 December 2007) which called for the following changes:

- The duration of blinded therapy was extended to 72 weeks, and the visit schedule after the first 72 weeks was adjusted. The original protocol required 60 weeks of therapy for all patients. The extension provided additional blinded safety and efficacy data and was thought likely to increase the power for the secondary endpoints including the “time to event” analyses. All patients would remain on blinded therapy until 72 weeks after the last patient was randomized. As a consequence of this change, patients randomized early in the enrollment period would remain on blinded therapy for approximately 32 months. The primary outcome of the study remained unchanged.
- The study sample size was increased by 75 patients from 325 to 400. During the enrollment period of trials 004 and 006, Shionogi concluded a Phase 3 trial of pirfenidone in IPF patients in Japan and InterMune had the opportunity to review the efficacy data. Based on this review of external data, they decided to modify the study design to provide appropriate powering for primary and secondary efficacy outcome measures.
- The DMC requested a stopping rule to guide their recommendations in the event of strongly favorable efficacy results around survival. This stopping rule was to be invoked if an analysis of survival time utilizing pooled data from both studies (004 and 006) in the 2403 mg group versus the placebo group was highly statistically significant using nominal alpha for survival of 0.0001 (two-sided) at either the second or third DMC meeting. The significance level for the primary analysis of the absolute change in %Predicted FVC for each study was to be 0.0498 based on an adjustment for the two DMC mortality analyses. This stopping rule was based on the need to have unambiguous evidence of efficacy on a clinically significant single endpoint if these studies were to stop early as the other endpoints would then be largely not evaluated; this stopping rule was not based on power calculations or an expectation that the study would be likely to stop early.
- A pooled analysis from both studies was specified because if the primary FVC analysis was significant in both studies all of the specified efficacy endpoints and the safety data would be required to help determine the risk/ benefit profile of

pirfenidone, of primary interest for this determination is the effect size for the efficacy endpoints which, per the Applicant, would be best estimated with the larger sample size of a combined analysis.

There were two amendments to the original SAP (8 August 2007), Amendment 1 (14 July 2008), Amendment 2 (6 January 2009) which called for the following changes:

- Modifications were made in the planned statistical analysis plan in Protocol Amendment 1, which consisted of changes in the sample size and power considerations, the method for evaluating efficacy (from ANCOVA to rank ANCOVA, where appropriate), the definition of categorical assessment (from relative change to absolute change in %Predicted FVC in secondary efficacy outcome variables), the range of individual categories in %Predicted FVC to more evenly distribute patients, and the methods for handling missing data.
- Addition of a description of study design to help with definition of time to event analyses which included two periods (study period and treatment period). The Study Period consisted of a Treatment Period and a Follow-up Period. The duration of the Treatment Period (duration of intended blinded therapy) for each patient differed depending on when the patient was randomized into the study. Study treatment was to stop during a 6-week window, 72 weeks after the last patient was randomized. All patients still undergoing study assessments at the start of the 6 week window were required to return to the clinic for a “Treatment Completion Visit” or a “Week 72” visit, or both, during the six week window; this visit was the last visit during the Treatment Period. For patients that discontinued regular study assessments prior to the six week window (no visit either within 12 weeks of window or in window) the Treatment Period was to end at the start of the 6 week window. Following the completion of the Treatment Period, patients entered the Follow-up Period.

6 Review of Efficacy

Efficacy Summary

Two pivotal trials, PIPF-004 and PIPF-006, were submitted by the Applicant to support the efficacy of pirfenidone to reduce the decline in lung function in patients with idiopathic pulmonary fibrosis (IPF). Both trials were designed as randomized, double-blind, placebo-controlled clinical trials to assess the efficacy and safety of treatment with pirfenidone compared with placebo in patients with IPF. In trial 004, patients were randomized 2:2:1 to receive pirfenidone 2403 mg/day, placebo, or pirfenidone 1197 mg/day, respectively. In trial 006, patients were randomized 1:1 to receive either pirfenidone 2403 mg/day or placebo. All patients were to remain on study treatment from the time of their randomization until approximately 72 weeks after the last patient had been randomized into the study. Therefore, duration of blinded therapy for each patient differed depending on when the patient was randomized into the study. However, all patients were to complete study treatment by a specified date. All patients were

required for their final follow-up visit three to four weeks after the treatment completion visit (see Table 4 and Figure 1).

The pivotal trials enrolled patients aged 40–80 years who had a confident clinical, radiographic, and/or pathologic diagnosis of IPF without evidence or suspicion of an alternative diagnosis for interstitial lung disease, and who had evidence of disease progression were eligible to participate in the study. Eligible patients were to have mild to moderate disease severity as evidenced by percent predicted FVC $\geq 50\%$ at Screening and Day 1, a DLco $\geq 35\%$ at Screening, and no evidence of improvement in FVC over the year preceding study entry. For the most part, concomitant medications being used to treat IPF were prohibited; allowances were made in the case of acute respiratory decompensation, acute IPF exacerbation, and progression of disease (See Table 5).

The primary efficacy parameter was the absolute change in percent predicted forced vital capacity (FVC) from Baseline to Week 72. The primary efficacy comparison was between pirfenidone 2403 mg/d and placebo; the pirfenidone 1197 mg/d group was included only to explore a dose-response relationship. The treatment effect was tested using the Mantel-Haenszel mean score chi-square test. For missing values, the Applicant imputed data for patients who did not contribute FVC measurements at particular timepoint(s). If the patient died on or before the protocol-specified measurement date, a zero 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. For those patients with missing values due to reasons other than death, data for percent predicted FVC was imputed by the sum of squared differences (SSD) method. This method replaces missing data with imputed data based on the average measurements for “similar” patients at the given time point. Similar patients were those whose data had the smallest sum of squared deviations from that patient for all visits before the one with the missing data. The pre-specified primary analysis of the primary endpoint was a rank ANCOVA model stratified by geographic region, with Baseline percent predicted FVC included as a covariate. The Agency has also conducted an analysis of the primary endpoint, using the same rank ANCOVA model, without imputation of data (either for missing values or death). The Agency’s analysis using non-imputed data will also be presented and discussed in tandem with the Applicant’s analysis (for full details of this analysis, see the Biometrics Review by Dr. Feng Zhou).

Important secondary efficacy parameters included progression free survival, time to IPF worsening, and mean change from baseline in percent predicted DLco, all measured at Week 72. Survival was examined on-treatment (up to 28 days after treatment discontinuation) and at the end of the entire study period (vital status assessment).

A total of 779 IPF patients were randomized in the two phase 3 trials; 435 and 344 patients were enrolled at 64 and 46 sites in North America, Europe, and Australia, in PIPF-004 and PIPF-006, respectively. Baseline characteristics were generally balanced across treatment groups. Baseline characteristics across the two trials were also generally similar, except for a larger proportion of patients in trial 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 PIPF-004 and PIPF-006, over 80% of patients completed study treatment and over 90% completed the study, when deaths and lung transplant patients are classified as completers.

In trial 004, the mean decline from Baseline to Week 72 in percent predicted FVC was significantly reduced in patients receiving pirfenidone 2403 mg/day compared to placebo (-8.0% vs. -12.4%), with an absolute difference of 4.4 and a relative reduction of 35% ($p=0.001$). Additionally, a reduced decline from Baseline was statistically significant at every earlier timepoint in trial 004 as well (See Table 12). Trial 006 showed no difference between the pirfenidone and placebo groups at 72 weeks (-9.0% vs. -9.6%) with an absolute difference of 0.6 and a relative reduction of 6.5% ($p = 0.501$).

As detailed above, the Applicant’s pre-specified primary analysis included imputation of missing data. The Agency’s statistical reviewer, Dr. Feng Zhou, conducted multiple analyses of the primary efficacy endpoint to investigate the robustness of the data, and the impact that different statistical estimates and imputation methods (including no imputation at all) would have on the magnitude of the treatment effect. These analyses are summarized in Table 6.

Table 6: Estimate of Treatment Effect in Percent Predicted FVC at Week 72, Trials 004 and 006						
	Trial 004			Trial 006		
	Pirfenidone 2403 mg/d	Placebo	Absolute Diff.	Pirfenidone 2403 mg/d	Placebo	Absolute Diff.
Protocol specified imputation (SSD)						
Mean (STD)	-8.0 (16.5)	-12.4 (18.5)	4.4	-9.0 (19.6)	-9.6 (19.1)	0.6
Median (range)	-5.8 (-91, 13)	-6.9 (-83, 10)	1.1	-4.2 (-99, 18)	-5.3 (-88, 19)	1.1
LOCF with imputing death to 0						
Mean (STD)	-7.9 (16.5)	-12.2 (18.5)	4.3	-9.0 (19.6)	-9.6 (19.2)	0.6
Median (range)	-5.3 (-91, 13)	-6.8 (-83, 10)	1.5	-4.2 (-99, 18)	-5.1 (-88, 19)	0.9
Observed data						
Mean (STD)	-4.4 (6.5)	-6.5 (6.9)	2.1	-3.7 (7.2)	-3.9 (7.1)	0.2
Median (range)	-4.8 (-25, 13)	-6.3 (-29, 10)	1.5	-3.6 (-27, 18)	-3.8 (-21, 19)	0.2
LOCF without imputing death to 0						
Mean (STD)	-4.7 (7.5)	-6.7 (7.6)	1.9	-4.1 (7.6)	-4.9 (7.8)	0.8
Median (range)	-4.7 (-52, 13)	-6.2 (-33, 10)	1.5	-3.6 (-27, 18)	-4.3 (-36, 19)	0.7
Repeated measure model without imputation^a						
LS Mean (SE)	-5.0 (0.59)	-7.2 (0.60)	2.2	-3.8 (0.67)	-4.6 (0.67)	0.7
95% CI	--	--	(0.6, 3.9)	--	--	(-1.0, 2.4)

Source: Table 10, Biometrics Review, Dr. Feng Zhou
 a: Mixed Linear model comparing Pirfenidone 2403 mg/d to Placebo, with change from baseline as the outcome variable. Treatment, geographical region (USA and ROW), assessment week, and treatment by assessment week interaction as fixed effects; covariates of baseline %Predicted FVC, and a repeated effect of assessment week, unstructured covariance structure and patient as the subject factor.

Although the statistical models and methods of imputation are different, the results from trial 004 consistently showed a statistically significant benefit of pirfenidone 2403 mg/day over placebo (Biometrics Review, Dr. Feng Zhou, not shown in Table 6). It is noteworthy, however, that the magnitude of the treatment effect varies from 1.1 to 4.4 depending on the analysis method (see Table 6). It is also notable that none of the statistical analyses performed can produce a statistically significant result for pirfenidone over placebo in trial 006. Although trial 004 demonstrated statistical significance with respect to analysis of mean change in FVC from Baseline to week 72, an absolute change of 4.4 in percent predicted FVC is of uncertain clinical significance.

Assessment of the absolute change in FVC volume from baseline to 72 weeks is another way of examining the primary efficacy variable. In trial 004, the mean decline from Baseline at Week 72 in FVC volume was significantly reduced in patients receiving pirfenidone 2403 mg/day compared to placebo (-318mL vs. -475mL), with an absolute difference of 157mL and a relative reduction of 33% ($p=0.005$). Additionally, a reduced decline from Baseline was statistically significant at every earlier timepoint in trial 004 as well (See Table 14). Trial 006 showed no difference between the pirfenidone and placebo groups at 72 weeks (-379mL vs. -373mL) with an absolute difference of -6mL (in favor of placebo). When the analysis was performed without imputation of data in trial 004, the mean decline from Baseline at Week 72 in FVC volume was significantly reduced in patients receiving pirfenidone 2403 mg/day compared to placebo (-169mL vs. -244mL), with an absolute difference of 75mL and a relative difference of 30.8% ($p=0.015$). Although the size of the treatment effect decreased (absolute difference = 157mL using imputed data), it continued to be statistically significant in trial 004. The difference between pirfenidone and placebo were not statistically significant at Week 72 in trial 006, however, several earlier timepoints (Weeks 12, 24, and 48) demonstrated statistical significance, similar to the analysis in which imputed data was used. However, similar to the Applicant's analysis using imputed data, there was no evidence of treatment effect in trial 006 at 72 weeks (-147mL vs. -149mL), with an absolute difference of 2mL and a relative difference of 1.3% ($p=0.705$).

A responder analysis was also performed using the primary efficacy variable (see

Figure 5 and Figure 6). Using an absolute decline in % predicted FVC of 10% to define a responder, the results were similar in PIPF-006. In PIPF-004, 20.7% of patients treated with pirfenidone had a decline greater than 10% compared to 33% of patients in the placebo group.

Multiple secondary efficacy endpoints were investigated (see Table 16). In trial 004, the only secondary endpoint that was statistically improved with pirfenidone treatment was progression-free survival (**Error! Reference source not found.**). The Six-Minute Walk Test (6MWT) distance was the only secondary endpoint in favor of pirfenidone in trial 006, with a nominal p-value <0.05. However, the significance of this secondary endpoint should be interpreted with caution in the face of trial 006 failing to achieve the primary endpoint.

Survival was designated as an exploratory endpoint, but given the severity of IPF, unmet need in this population, and the fact that only one study met its primary endpoint, mortality was examined in detail, to determine whether either study showed a significant mortality benefit. Survival was examined on-treatment and at the end of the study (vital status assessment). Neither study demonstrated a benefit in on-treatment mortality, although numerically, both trials 004 and 006, trended towards an on-treatment mortality benefit in the pirfenidone treatment group. In trial 004, a total of 10 (5.8%) patients in the pirfenidone 2403 mg/day group compared with 14 (8.0%) patients in the placebo group died on-treatment (see Table 19) [HR = 0.72, 95% CI (0.32, 1.62), p=0.422]. In trial 006, 9 (5.3%) in the pirfenidone 2403 mg/day group compared with 15 (8.7%) in the placebo group died on-treatment [HR = 0.59, 95% CI (0.26, 1.36) p = 0.216). When deaths were counted at the end of the study period (vital status assessment), the results in trial 004 numerically continued to favor pirfenidone, however, there was no numerical benefit in trial 006. Additionally, when lung transplants were counted as “deaths”, again, no mortality benefit was demonstrated (Table 20). When on-treatment IPF related mortality was examined, the results of the pooled analysis of trials 004 and 006 were statistically significant in favor of pirfenidone [(HR: 0.48 (0.24, 0.95), p=0.036]. However, this analysis was performed post-hoc, and the cause of death was unadjudicated. As a result, assignment of relation to IPF was not consistent in all cases (Table 22), as it was made by the individual investigators. Therefore, the statistical significance of the reduction in IPF-related mortality should be interpreted carefully with these limitations in mind.

Based upon the review of this NDA, the Applicant does not have replication of efficacy for pirfenidone for the treatment of IPF to reduce decline in lung function. Of the two pivotal trials, only PIPF-004 achieved the primary endpoint, however, the clinical significance of the treatment effect size is uncertain. A robust statistically significant finding of improved survival might be one instance in which a single study might be relied upon to provide substantial evidence of efficacy. However, neither trial showed a statistically significant benefit in all-cause mortality. The pooled analysis of the two pivotal trials did reveal a statistical improvement in IPF-related mortality, however there were several limitations with this analysis. Therefore, in the opinion of this reviewer, the Applicant has not provided substantial evidence to support the efficacy of pirfenidone for the proposed indication.

6.1 Indication

The Applicant proposes that pirfenidone is an anti-fibrotic and anti-inflammatory indicated for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function.

6.1.1 Methods

The pivotal trials, 004 and 006, conducted by InterMune have been reviewed in detail to determine if the Applicant has provided substantial evidence of the efficacy of pirfenidone for the proposed indication. Trial SP3, conducted by Shionogi Inc., has not been reviewed, as Applicant has not submitted the patient-level data to the Agency. Without the data to review and confirm the analysis, the Agency cannot rely upon the results of SP3 to evaluate the efficacy and safety of pirfenidone. Therefore, the SP3 study and results will not be reviewed further in this document. In addition, there are several noteworthy differences between SP3 and trials 004/006, which would limit the applicability of the SP3 data to the overall development program. Notable differences include: IPF diagnostic criteria, dose, formulation, primary endpoint, and treatment duration.

Efficacy analyses performed by both the applicant and the Agency will be presented in this section. The Agency has no issue with the way in which the pre-specified analyses were conducted. Different statistical models and imputation strategies were utilized by the Agency only to explore the robustness of the data. A summary of these varied methods will be presented in the following review of efficacy. For full details of these sensitivity analyses, refer to the Biometrics Review by Dr. Feng Zhou.

All analyses presented in this review have been conducted using the modified intent-to-treat population (MITT). The MITT population comprises all patients who received any amount of study treatment. Because all randomized patients in the study were treated with study treatment, the MITT population is identical to the ITT population, and thus this population is also referred to as “all randomized patients”. The MITT population included a total of 779 patients: 345 pirfenidone 2403 mg/day patients (174 in trial 004, 171 in trial 006), 87 pirfenidone 1197 mg/day patients (trial 004, only), and 347 placebo patients (174 in trial 004, 173 in trial 006).

Because many patients were treated beyond 72 weeks and patients were encouraged to stay in the study after discontinuing study medication, there are many ways to evaluate the data collected in the phase 3 trials. Before discussion of the results, it is important to discuss the different datasets used for analysis of the efficacy and safety data in this review as the results may vary based upon the dataset.

- Treatment Period – data for all patients up to the September 2008 cutoff used by InterMune; some patients would have > 72 weeks treatment; this is the dataset used for the efficacy analyses (at 72 weeks)
- On-Treatment - data for all patients while on study medication and 28 days after the last dose of study medication; primary dataset for safety endpoints, but also used in the survival analysis

- Vital Status at End of Study – data including the Treatment Period (Sept 2008 cut-off) and subsequent follow up; used for vital status only.

6.1.2 Demographics

Patient demographics for all randomized (ITT) patients are summarized for both trials 004 and 006 in Table 7.

Demographic Parameter	PIPF-004			PIPF-006	
	Pirf LD N = 87	Pirf HD N = 174	Placebo N = 174	Pirf HD N = 171	Placebo N = 173
Geographic Region, n (%)					
USA	58 (66.7)	114(65.5)	114 (65.5)	148 (87)	150 (87)
ROW	29 (33.3)	60 (34.5)	60 (34.5)	23 (14)	23 (13)
Age (years)					
Range (Min, Max)	45, 81	45, 80	40, 79	45, 80	42, 80
Mean (SD)	68.0 (7.6)	65.7 (8.2)	66.3 (7.5)	66.8 (7.9)	67.0 (7.8)
Age distribution (years), n (%)					
< 55	5 (5.7)	16 (9.2)	10 (5.7)	11 (6.4)	10 (5.8)
55-64	23 (26.4)	59 (33.9)	63 (36.2)	59 (34.5)	51 (29.5)
65-74	39 (44.8)	72 (41.4)	69 (39.7)	64 (37.4)	83 (48.0)
≥ 75	20 (23.0)	27 (15.5)	32 (18.4)	37 (21.6)	29 (16.8)
Sex, n (%)					
Male	65 (74.7)	118 (67.8)	128 (73.6)	123 (71.9)	124 (71.7)
Female	22 (25.3)	56 (32.2)	46 (26.4)	48 (28.1)	49 (28.3)
Race, n (%)					
White	83 (95.4)	168 (96.6)	168 (96.6)	169 (98.8)	171 (98.8)
Black or African American	1 (1.1)	2 (1.1)	2 (1.1)	1 (0.6)	2 (1.2)
Asian	3 (3.4)	2 (1.1)	4 (2.3)	1 (0.6)	0
American Indian/Alaskan Native	0	2 (1.1)	0	0	0

Pirf LD: 1197 mg/day; Pirf HD: 2403 mg/day; ROW: rest of world
Source: Table 11.1, pg. 112-3, PIPF-006 CSR and Table 11.1, pg. 118-9, PIPF-004 CSR.

A total of 779 patients were randomized in the two phase 3 trials, 435 patients in trial 004, and 344 patients in trial 006. Within each study, demographic characteristics were comparable between treatment groups with respect to geographic region, age, gender, and race. Specifically, demographic characteristics in the pirfenidone LD group were similar to those reported for the pirfenidone HD group. In both trials, most patients were male (>67%), white (>96%), and of similar age (mean age, 65.7-67 years, range 40-80 years). Demographics between the two trials were also well-balanced, with the exception of geographic region, for which fewer patients were enrolled at US sites in trial 004 than 006. When demographics were compared by geographic region, sex, race, age, and ethnicity were well-balanced between the US and the ROW. A slight imbalance was observed in weight, in that both men and women in the US were generally heavier than patients outside the US (Table 7.5, Integrated Summary of Efficacy, Module 5, NDA 22-535).

Reviewer's comment: The limited number of non-Caucasian patients, female patients, and patients < 55 is expected given that IPF is a rare disease that occurs most commonly in white males over the age of 65.

Baseline characteristics for all randomized (ITT) patients are summarized in Table 8.

Table 8: Other Baseline Characteristics (All Randomized Patients, Trials 004 and 006)

Baseline Characteristic	PIPF-004			PIPF-006	
	Pirf LD N = 87	Pirf HD N = 174	Placebo N = 174	Pirf HD N = 171	Placebo N = 173
FVC (% predicted)					
Mean (SD)	76.4 (14.4)	74.5 (14.5)	76.2 (15.5)	74.9 (13.2)	73.1 (14.2)
Median	75.8	73.0	73.6	74.5	70.3
Range (Min, Max)	52, 116	52, 124	48, 136	50, 108	52, 128
DLco (% predicted)					
Mean (SD)	47.2 (8.2)	46.4 (9.5)	46.1 (10.2)	47.8 (9.8)	47.4 (9.2)
Median	47.3	45.4	43.7	45.6	46.2
Range (Min, Max)	34, 71	30, 81	30, 90	31, 81	33, 78
Supplemental Oxygen Use n (%)					
Yes	15 (17.4)	29 (16.7)	25 (14.4)	48 (28.1)	49 (28.3%)
No	71 (82.6)	145 (83.3)	149 (85.6)	123 (71.9)	124 (71.7%)
Time (yrs): IPF Dx to Randomization					
Mean (SD)	1.4 (1.2)	1.3 (1.0)	1.4 (1.1)	1.2 (1.1)	1.1 (1.0)
Median	0.9	1.0	1.1	0.7	0.7
Range (Min, Max)	>0, 4	>0, 4	>0, 4	>0, 4	>0, 4
IPF Diagnosis by HRCT, n (%)					
Definite IPF	83 (95.4)	159 (91.4)	164 (94.3)	149 (87.6)	158 (91.3)
Probable IPF	4 (4.6)	14 (8.0)	10 (5.7)	20 (11.8)	15 (8.7)
Uncertain IPF	0	1 (0.6)	0	1 (0.6)	0
Surgical Lung Biopsy, n (%)					
Number of Patients w/ lung Biopsy	32 (36.8)	86 (49.4)	85 (48.9)	94 (55.0)	94 (54.3)
Definite UIP	31	81	83	90	87
Probable UIP	1	4	2	3	6
Uncertain UIP	0	1	0	1	1
IPF Diagnostics Performed, n (%)					
Surgical lung biopsy (SLBx)	23 (26.4)	58 (33.3)	57 (32.8)	76 (44.4)	86 (49.7)
Bronchoalveolar lavage (BAL)	45 (51.7)	74 (42.5)	73 (42.0)	40 (23.4)	33 (19.1)
Transbronchial biopsy (TBBx)	2 (2.3)	4 (2.3)	1 (0.6)	8 (4.7)	11 (6.4)
SLBx and BAL	4 (4.6)	15 (8.6)	12 (6.9)	4 (2.3)	1 (0.6)
SLBx and TBBx	2 (2.3)	2 (1.1)	4 (2.3)	3 (1.8)	5 (2.9)
BAL and TBBx	8 (9.2)	10 (5.7)	15 (8.6)	29 (17.0)	35 (20.2)
SLBx, BAL, and TBBx	3 (3.4)	11 (6.3)	12 (6.9)	11 (6.4)	2 (1.2)
Smoking Status at Screening, n (%)					
Never smoker ^a	27 (31.0)	56 (32.2)	51 (29.3)	59 (34.5)	64 (37.0)
Previously smoker ^b	57 (65.5)	110 (63.2)	114 (65.5)	112 (65.5)	101 (58.4)
Current smoker	3 (3.4)	8 (4.6)	9 (5.2)	0	8 (4.6)

Pirf LD: 1197 mg/day; Pirf HD: 2403 mg/day
 a. Never smoker: < 100 cigarettes over lifetime
 b. Previous smoker: ≥ 100 cigarettes over lifetime
 FVC: forced vital capacity; DLco: diffusion capacity; Dx: diagnosis; HRCT: high resolution computed tomography; UIP: usual interstitial pneumonia
 Source: Table 11.2, pg. 115-6, PIPF-006 CSR and Table 11.2, pg. 121-2, PIPF-004 CSR.

Baseline mean values were comparable across the studies and the treatment groups in percent predicted FVC and percent predicted DLco. More than 87% of all patients in both studies across all treatment groups had a definite diagnosis of IPF by HRCT; the proportion of patients who had had a surgical lung biopsy ranged from 36.8 -55%. Among patients who had a surgical lung biopsy performed, >90% had a definite diagnosis of UIP. There was a slight imbalance in the median time from IPF diagnosis to randomization, in that it was slightly shorter in trial 006 than in 004 (0.7 years vs. 1 year, respectively). More patients in trial 006 than in 004 were diagnosed with IPF within 1 year prior to study entry (60% vs. 40%). A larger proportion of patients in trial 006 were treated with supplemental oxygen (28% in 006 vs. 14-17% in trial 004).

Reviewer's comment: The baseline characteristics of the patients with regard to IPF diagnostic criteria (HRCT or surgical lung biopsy finding of UIP) demonstrate that patients enrolled in these trials had confident IPF diagnoses.

Reviewer's comment: The Applicant asserts that the greater proportion of patients with a diagnosis of IPF that was made within 1 year of study entry may have attenuated the treatment effect in 006, because this is associated with "less FVC progression and a smaller pirfenidone treatment effect". (p. 18, Clinical Overview, Module 2.5, NDA 22-535). However, the pirfenidone treatment group in trial 006 had a similar change from Baseline in FVC at each time point as compared with the pirfenidone treatment group in trial 004 (see Figure 3). It was the placebo group in trial 006 that did not decline to the same degree as the placebo group in trial 004. Since both the pirfenidone and placebo groups in trial 006 had relatively similar times from IPF diagnosis to randomization, in the opinion of this reviewer, this difference does not explain the failure of trial 006 to achieve the primary endpoint.

More than half of the patients in both studies in all treatment groups were previous smokers, but current smoking was not common (0-5.2%). Supplemental oxygen use was comparable between treatment groups within each study, respectively, but a lower proportion of patients in trial 004 used supplemental oxygen at baseline than in 006 (16% vs. 28%, respectively).

When baseline characteristics were examined by region (not shown in Table 6), imbalances between patients in the US and ROW in both studies were observed for supplemental oxygen use and surgical lung biopsy. In each study, more than four times as many patients at sites in the US (range 20.2%-32.4%) than in the ROW (range 0-5%) used supplemental oxygen at baseline. Additionally, in each study, surgical lung biopsy was performed more often in patients enrolled at US sites (range 54-61%) than in the ROW (25-40%). In both studies, the majority of patients in the US (>86%) and the ROW (>88%) had a definite diagnosis of IPF by HRCT and a definite diagnosis of UIP by surgical lung biopsy (if performed), and more than half of the patients in both regions were previous smokers (Table 7.9, Integrated Summary of Efficacy, Module 5, NDA 22-535).

Selected concomitant medications (used during the treatment period) are summarized in Table 9.

Baseline Characteristic	PIPF-004			PIPF-006	
	Pirf LD N = 87	Pirf HD N = 174	Placebo N = 174	Pirf HD N = 171	Placebo N = 173
	n (%)			n (%)	
Drugs for Acid-Related Disorders^a	52 (59.8)	126 (72.4)	109 (62.6)	123 (71.9)	111 (64.2)
Bronchodilators/COPD drugs	39 (44.8)	84 (48.3)	87 (50.0)	89 (52.0)	97 (56.1)
Salbutamol Sulfate	27 (31.0)	45 (25.9)	53 (30.5)	48 (28.1)	70 (40.5)
Salmeterol xinafoate ^b	6 (6.9)	23 (13.2)	28 (16.1)	5 (2.9)	4 (2.3)
Ipratropium/albuterol ^c	3 (3.4)	11 (6.3)	11 (6.3)	1 (0.6)	2 (1.2)
Tiotropium bromide	1 (1.1)	2 (1.1)	1 (0.6)	1 (0.6)	3 (1.7)
Systemic Corticosteroids	24 (27.6)	38 (21.8)	52 (29.9)	42 (24.6)	50 (28.9)
Immunosuppressants	0	3 (1.7)	2 (1.1)	1 (0.6)	1 (0.6)
Azathioprine	0	2 (1.1)	2 (1.1)	1 (0.6)	1 (0.6)
Cyclophosphamide	0	1 (0.6)	0	0	0
Anti-oxidants	1 (1.1)	4 (2.3)	3 (1.7)	0	1 (0.6)
N-acetylcysteine	1 (1.1)	4 (2.3)	3 (1.7)	0	1 (0.6)

Pirf LD: 1197 mg/day; Pirf HD: 2403 mg/day
 a: Proton-pump inhibitors
 b: Includes Seretide marketed in Europe
 c: Includes combination marketed in Italy known as Breva
 Source: Table 11.3, pg. 125-6, and Table 14.1-19, p. 542-7, PIPF-004 CSR ; Table 11 3, pg. 119-20, and Table 14.1-19, p. 499-502, PIPF-006 CSR.

The Applicant has provided a complete listing of all concomitant medications used by study subjects during the treatment period. The above-listed medications were chosen by this reviewer either because they are used in clinical practice to treat IPF and/or an imbalance between treatment groups was noted. As is shown in Table 9, there was an imbalance in trial 004 in patients taking drugs for acid-related disorders (72.4% in the Pirfenidone HD group and 62.6% in the placebo group). An imbalance in the use of salbutamol was observed in trial 006 (28.1% in the Pirfenidone HD vs. 40.5% Placebo).

Reviewer's comment: The Applicant asserts in the clinical study reports that the imbalance in the use of salbutamol had the potential to bias the FVC outcomes against the pirfenidone HD group in favor of placebo. However, they do state that salbutamol was used in most patients only for bronchodilator challenge during PFTs, and in others more chronically for symptomatic relief of difficulty breathing. In the opinion of this reviewer, the imbalance of salbutamol use in trial 006 is likely to have had minimal impact on FVC outcomes because, a) enrollment criteria excluded those patients who were bronchodilator responsive, and b) bronchodilators were held prior to pulmonary function testing. For these reasons, it is my opinion that the failure of trial 006 to achieve the primary endpoint is unlikely to be due to this imbalance in salbutamol use.

6.1.3 Patient Disposition

Patient disposition for trials 004 and 006 is summarized in Table 10.

Table 10: Patient Disposition (All Randomized Patients, Trials 004 and 006)					
Disposition, n (%)	PIPF-004			PIPF-006	
	Pirf LD N = 87	Pirf HD N = 174	Placebo N = 174	Pirf HD N = 171	Placebo N = 173
	n (%)			n (%)	
Patients Who Completed the Study	73 (83.9)	146 (83.9)	144 (82.8)	139 (81.3)	146 (84.4)
Patients Who Withdrew Early	14 (16.1)	28 (16.1)	30 (17.2)	32 (18.7)	27 (15.6)
Reasons for Withdrawal					
Adverse Event	3 (3.4)	8 (4.6)	3 (1.7)	5 (2.9)	4 (2.3)
Death	9 (10.3)	12 (6.9)	18 (10.3)	15 (8.8)	14 (8.1)
Lung Transplant	0	3 (1.7)	4 (2.3)	4 (2.3)	4 (2.3)
Subject's Decision	2 (2.3)	4 (2.3)	5 (2.9)	6 (3.5)	5 (2.9)
Sponsor's Decision ^b	0	0	0	1 (0.6)	0
Other ^c	0	1 (0.6)	0	1 (0.6)	0

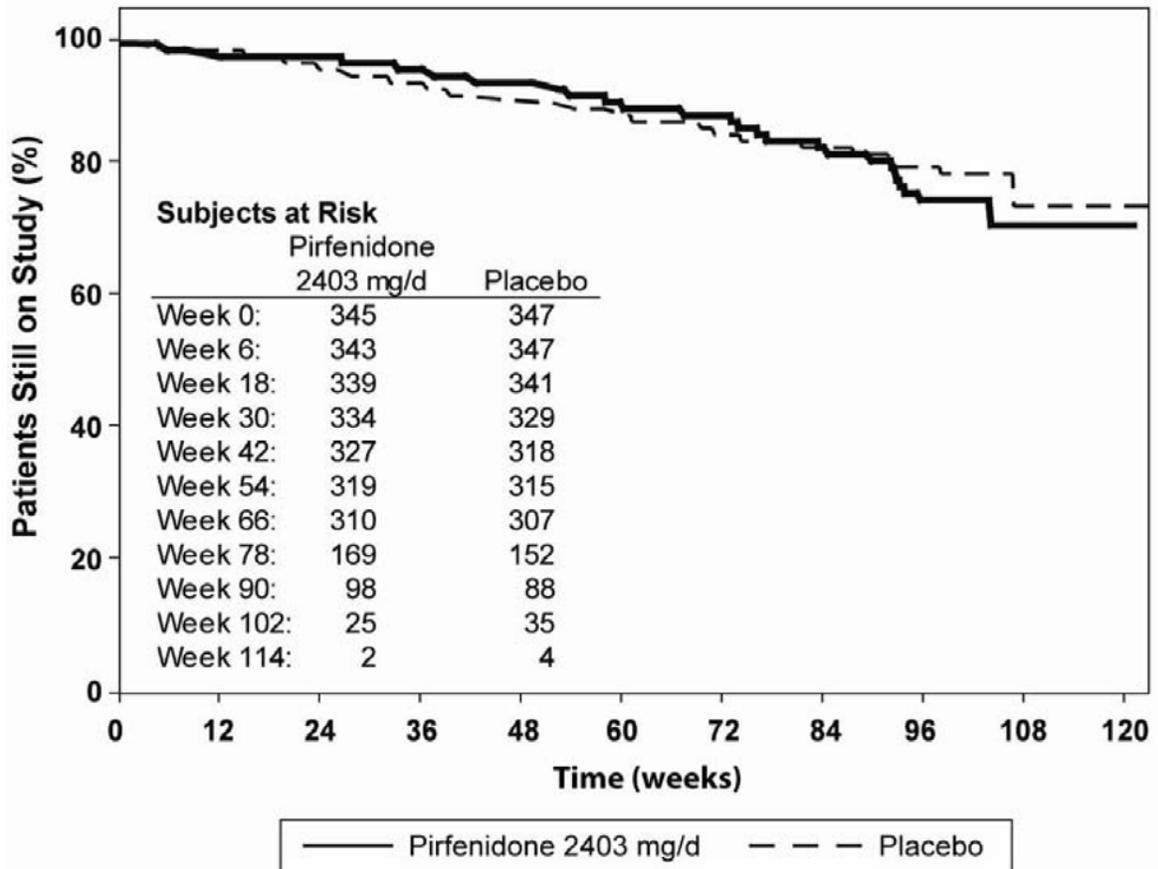
Pirf LD: 1197 mg/day; Pirf HD: 2403 mg/day
 a. Patients who completed their scheduled treatment completion visit; these patients may have discontinued treatment, but continued with study assessments
 b: Investigator removed patient due to LFT elevation
 c: Other reasons included: deportation (trial 004) and placement on lung transplant schedule (trial 006)
 Note: The number of deaths summarized in this table differs from the deaths described in the safety section, because this disposition analysis includes only those patients who were ON study when they died. The safety table includes patients who had withdrawn from study but were being followed for vital status only.
 Source: Table 10-2, pg. 111, PIPF-004 CSR ; Table 10-2, pg.107 PIPF-006 CSR.

Overall, most patients across the studies and across the treatment groups completed the study (81-85%). The most common reasons for patients prematurely withdrawing in each study were adverse events (AEs) and death. In trial 004, a higher percentage of patients withdrew from the study because of an AE in the pirfenidone 2403 mg/day group than in the placebo group, respectively (4.6% vs. 1.7%), while in trial 006, a similar number of patients in each treatment group withdrew from the study because of an AE (2.9% and 2.3%). In addition, in PIPF-004, fewer patients withdrew from study because of death in the pirfenidone 2403 mg/d group than in the placebo group (6.9% vs. 10.3%), while in PIPF-006, a similar number of patients in each treatment group withdrew from study due to death (8.8% and 8.1%). Lung transplants were similar across treatment groups, with the exception of the low dose pirfenidone group in trial 004 in which there were no patients who were transplanted. When patients who prematurely withdrew from study due to death or lung transplantation are classified as having completed the study, 92.5% and 95.4% of patients in the pirfenidone 2403 mg/day and placebo completed the study in trial 004; 92.4% and 94.8% of patients are considered to have completed the study in trial 006.

Reviewer's comment: It is the Applicant's assertion that the high proportion of patients completing the study substantially discounts the potential for bias due to missing data that could affect the interpretation of efficacy. I agree with this statement.

In the pooled analysis of trials 004 and 006, the time to premature withdrawal was similar (See Figure 2).

Figure 2: Time to Premature Withdrawal from Study (Pooled analysis trials 004 and 006, Kaplan-Meier Estimates (All Randomized Patients))



Note: Time to event was defined as event date or censoring date minus randomization date plus one. Patients who completed the study or were ongoing were censored at the date of last study visit.

Source: Figure 7.4, p. 84, Integrated Summary of Efficacy, Module 5.

Compliance

Treatment compliance for all randomized patients in trials 004 and 006 is summarized in Table 11.

Table 11: Treatment Compliance (All Randomized Patients, Trials 004 and 006)					
	<i>PIPF-004</i>			<i>PIPF-006</i>	
Treatment Compliance	Pirf LD N = 87	Pirf HD N = 174	Placebo N = 174	Pirf HD N = 171	Placebo N = 173
	n (%)			n (%)	
Patients who Received Any Amount of Study Treatment					
N (%)	87 (100)	174 (100)	174 (100)	171 (100)	173 (100)
Percent Compliance per Patient ^a					
Mean (SD)	91.2 (17.1)	88.9 (23.1)	93.8 (14.6)	91.4 (17.9)	93.7 (16.2)
Median (Range)	98.1 (18-100)	98 (2 – 100)	99 (1 – 100)	98 (10 – 100)	98 (0 – 100)
N (%)					
80% to 100%	77 (88.5)	151 (86.8)	161 (92.5)	152 (88.9)	162 (93.6)
60% to < 80%	5 (5.7)	7 (4.0)	5 (2.9)	6 (3.5)	2 (1.2)
40% to <60%	1 (1.1)	1 (0.6)	4 (2.3)	4 (2.3)	3 (1.7)
<40%	4 (4.6)	15 (8.6)	4 (2.3)	9 (5.3)	6 (2.5)
Treatment Duration (weeks)					
Mean (SD)	73.0 (19.7)	70.3 (22.5)	71.1 (20.7)	75.0 (22.4)	74.6 (22.2)
Median (Range)	72.7 (13,109)	72 (1 - 104)	72 (0 - 110)	75 (6 – 118)	73 (1 – 120)
Pirf LD: 1197 mg/day; Pirf HD: 2403 mg/day					
a Compliance with dosing was calculated as a percentage using the number of capsules prescribed from the first dose until Week 72 minus the number of capsules not taken divided by the number of capsules prescribed from the first dose until Week 72 or, for patients with lung transplantation or death, the date of the last study treatment.					
Source: Biometrics Review, Table 6, Table 11-6, p. 132 and Table 14.1-15, p. 429, PIPF-004 CSR, Module 5.					

Mean compliance with study treatment was comparable between trials 004 and 006. In both trials, the proportion of patients who were $\geq 80\%$ compliant was slightly lower in the pirfenidone groups, than in the placebo groups. In trial 004, there was no appreciable difference between the low dose and high dose pirfenidone groups with respect to compliance.

6.1.4 Analysis of the Primary Endpoint

The primary efficacy parameter was the absolute change in percent predicted forced vital capacity (FVC) from Baseline to Week 72. Baseline percent predicted FVC was defined as the mean of the maximum acceptable FVC measurements obtained during the Screening and Day 1 Visits. The percent predicted FVC at Week 72 was defined as the mean of the maximum acceptable FVC measurements obtained on two separate days at the Week 72 Visit (Week 72A and 72B). The primary efficacy comparison was between pirfenidone 2403 mg/d and placebo; the pirfenidone 1197 mg/d group was included only to explore a dose-response relationship.

The treatment effect was tested using the Mantel-Haenszel mean score chi-square test. For missing values, the Applicant imputed data for patients who did not contribute FVC measurements at particular timepoint(s). If the patient died on or before the protocol-specified

measurement date, a zero 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. For those patients with missing values due to reasons other than death, data for percent predicted FVC was imputed by the sum of squared differences (SSD) method. This method replaces missing data with imputed data based on the average measurements for “similar” patients at the given time point. Similar patients were those whose data had the smallest sum of squared deviations from that patient for all visits before the one with the missing data. At week 72, imputation was applied to missing data on 12 patients in the 2403 mg/day group and 8 patients in the placebo group for reasons other than death in trial 004. Similarly, the data were imputed for 10 patients in 2403 mg/day group and 9 patients in the placebo group in trial 006.

Reviewer’s comment: It is worth noting here that based on the method of imputation, the mean FVC at Week 72 was influenced by those patients that died, because 0 was imputed for their assessment. Therefore change from Baseline was [0 – Baseline]. In trial 004, data (zero) was imputed due to death in 8 patients in the pirfenidone 2403 mg/day group and in 16 patients in the placebo group; in trial 006, data (zero) was imputed due to death in 13 patients in the pirfenidone 2403 mg/day group and in 15 patients in the placebo group (at week 72) [Biometrics Review, Table 8, Dr. Feng Zhou].

Reviewer’s comment: It is also notable that so few patients required imputation of data for reasons other than death. As is seen later in this review, when the analysis is conducted without imputation of data for either missing values or death, there is a decrease in the magnitude of the treatment effect size.

The pre-specified primary analysis of the primary endpoint was a rank ANCOVA model stratified by geographic region, with Baseline percent predicted FVC included as a covariate. The test of significance for the primary analysis of the primary efficacy outcome variable used a two-sided alpha of 0.0498. When data were ranked, patients who died were ranked worse than patients with missing data who remained alive. Data for patients who died were ranked according to the number of days from randomization until death, with the shortest time until death as the worst rank. The Agency has also conducted an analysis of the primary endpoint, using the same rank ANCOVA model, without imputation of data (either for missing values or death). The Agency’s analysis using non-imputed data will also be presented and discussed in tandem with the Applicant’s analysis (for full details of this analysis, see the Biometrics Review by Dr. Feng Zhou).

The Applicant also conducted three pre-specified supportive analyses of the change from baseline in percent predicted FVC: 1) a repeated measures analysis, 2) cumulative distribution plots, and 3) an LOCF method of imputation. These supportive analyses will be briefly presented (as confirmed by the Agency’s statistical review) in order to provide an assessment of robustness of the primary endpoint, as well as to assess the effect on the magnitude of the treatment effect, when statistical testing is varied. Finally, the Applicant conducted a post-hoc analysis of the mean change from baseline in FVC volume (mL). This analysis, using both

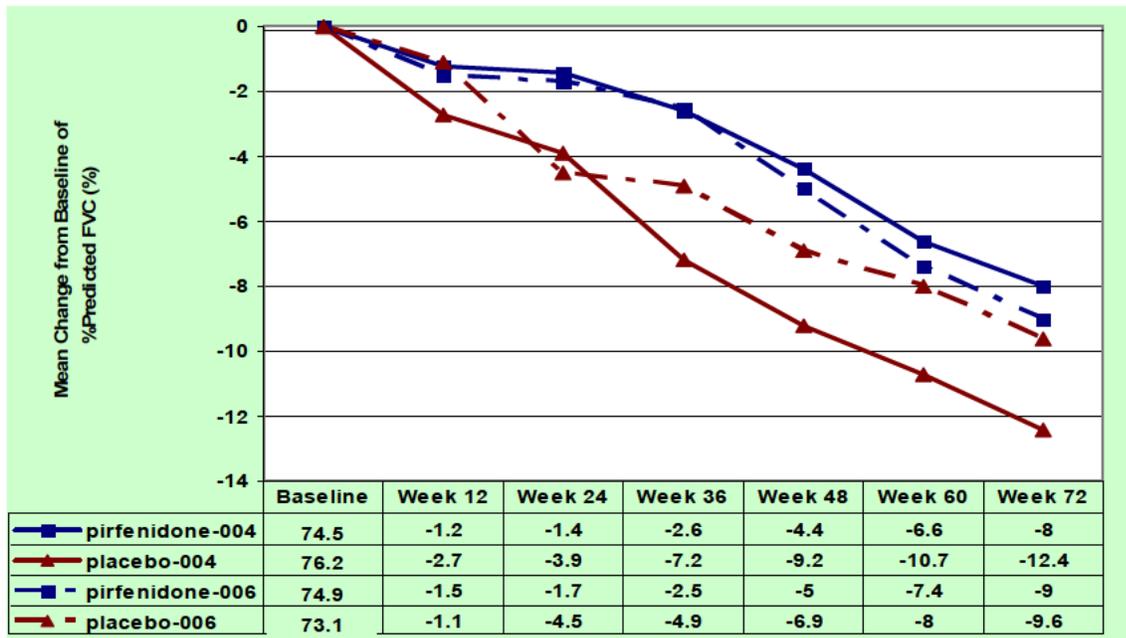
imputed (Applicant) and non-imputed (Agency) data, will be presented, as it provides another way in which to examine the primary endpoint.

Primary Efficacy Analysis: Absolute Change in Percent Predicted FVC from Baseline to Wk 72

A. Applicant’s Analysis Using Imputed Data

Figure 3 and Table 12 show the results of the comparison of the change from Baseline in percent predicted FVC in the pirfenidone 2403 mg/day and placebo treatment groups at Weeks 12, 24, 36, 48, 60, and 72 in both trials using the rank ANCOVA model and the pre-specified imputation method described above. The analysis depicted in Figure 2 was conducted by Dr. Feng Zhou, the Agency’s Biometrics Reviewer, and confirms the analysis as presented by the Applicant.

Figure 3: Mean Change from Baseline in Percent Predicted FVC in All Randomized Patients – Trials 004 and 006 (rank ANCOVA with imputation of missing data)



Source: Biometrics Review, Dr. Feng Zhou

Table 12: Mean Change from Baseline in Percent Predicted FVC in All Randomized Patients (rank ANCOVA with imputation)

	Pirfenidone 2403 mg/day	Placebo	Treatment Comparison		
Week	Mean Change in Percent Predicted FVC (SD) ^{a,b}		Absolute Difference ^c	Relative Difference ^d	p-value ^e
PIPF-004					
	N=174	N=174			
Baseline ^f	74.5 (14.5)	76.2 (15.5)	--	--	--
Week 12	-1.2 (6.8)	-2.7 (9.5)	1.5	55.6%	0.061
Week 24	-1.4 (7.5)	-3.9 (12.1)	2.5	64.1%	0.014
Week 36	-2.6 (9.1)	-7.2 (15.6)	4.6	63.9%	< 0.001
Week 48	-4.4 (12.1)	-9.2 (17.2)	4.8	52.2%	<0.001
Week 60	-6.6 (15.5)	-10.7 (17.6)	4.1	38.3%	<0.001
Week 72	-8.0 (16.5)	-12.4 (18.5)	4.4	35.5%	0.001
PIPF-006					
	N = 171	N = 173			
Baseline ^f	74.9 (13.2)	73.1 (14.2)	--	--	--
Week 12	-1.5 (10.7)	-1.1 (4.5)	0.5	27.7%	0.021
Week 24	-1.7 (11.2)	-4.5 (12.7)	2.8	62.2%	<0.001
Week 36	-2.5 (13.4)	-4.9 (15.0)	2.4	49.0%	0.011
Week 48	-5.0 (15.6)	-6.9 (15.4)	1.9	27.5%	0.005
Week 60	-7.4 (18.2)	-8.0 (17.2)	0.6	6.7%	0.172
Week 72	-9.0 (19.6)	-9.6 (19.1)	0.6	6.5%	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. Relative difference in mean change from baseline, 100*(pirfenidone-placebo)/absolute (placebo).
 e. 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.
 f. 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.

In trial 004, the mean decline from Baseline to Week 72 in percent predicted FVC was significantly reduced in patients receiving pirfenidone 2403 mg/day compared to placebo (-8.0% vs. -12.4%), with an absolute difference of 4.4 and a relative reduction of 35% (p=0.001). Additionally, a reduced decline from Baseline was statistically significant at every earlier timepoint in trial 004 as well (See Table 12). Trial 006 showed no difference between the pirfenidone and placebo groups at 72 weeks (-9.0% vs. -9.6%) with an absolute difference of 0.6 and a relative reduction of 6.5% (p = 0.501). However, in trial 006, there were statistically significant reductions in the mean decline of % predicted FVC in the pirfenidone group as compared with placebo at Weeks 24, 36, and 48 with a diminished effect at Week 60 (see Table 12).

Reviewer's comment: Although several earlier timepoints demonstrated that pirfenidone was statistically better than placebo, the insignificant difference at week 72 calls into question the durability of the efficacy response in trial 006. In addition, even though 006 was statistically significant at earlier timepoints, the treatment effect was not as large as in 004.

B. Agency's Analysis Without Imputation of Data

In order to examine the robustness of the data and the impact of data imputation on the magnitude of the treatment effect, Dr. Zhou conducted the same rank ANCOVA analysis of the primary endpoint without imputation (i.e. using observed data at each visit, rather than imputing zero for death and using the SSD method for missing data due to reasons other than death). These results are presented in Table 13.

Table 13: Mean Change from Baseline in Percent Predicted FVC in All Randomized Patients – Trials 004 and 006 (rank ANCOVA without imputation)							
	Pirfenidone 2403 mg/day		Placebo		Treatment Comparison		
Week	N observed (Death)	Mean^a Change (SD)	N observed (Death)	Mean^a Change (SD)	Absolute Difference^b	Relative Difference^c	p- value^d
PIPF-004							
Baseline ^e	174 (0)	74.5 (14.5)	174 (0)	76.2 (15.5)	--	--	--
Week 12	170 (1)	-0.8 (4.5)	166 (3)	-1.6 (4.7)	0.8	50.2	0.059
Week 24	168 (1)	-0.9 (5.6)	164 (5)	-2.1 (6.0)	1.2	55.3	0.026
Week 36	160 (2)	-1.5 (5.0)	156 (10)	-3.7 (6.3)	2.2	58.8	<.001
Week 48	159 (4)	-2.4 (5.4)	154 (13)	-4.6 (6.8)	2.2	48.7	0.002
Week 60	156 (7)	-3.6 (6.9)	148 (14)	-5.6 (7.3)	2.1	27.0	0.002
Week 72	154 (8)	-4.4 (6.5)	150 (16)	-6.5 (6.9)	2.1	32.3	0.007
PIPF-006							
Baseline ^e	171 (0)	74.9 (13.2)	173 (0)	73.1 (14.2)	1.7	--	--
Week 12	167 (2)	-0.4 (4.8)	168 (0)	-1.1 (4.6)	0.7	60.6	0.016
Week 24	168 (2)	-0.7 (5.9)	165 (5)	-2.5 (5.7)	1.9	73.4	<.001
Week 36	159 (4)	-0.9 (6.7)	158 (7)	-2.1 (6.4)	1.2	57.9	0.045
Week 48	157 (6)	-2.3 (6.4)	156 (8)	-3.7 (6.7)	1.4	37.6	0.011
Week 60	151 (10)	-3.2 (6.8)	148 (11)	-3.8 (7.0)	0.6	16.1	0.204
Week 72	148 (13)	-3.7 (7.2)	149 (15)	-3.9 (7.1)	0.2	5.1	0.717
a. Mean change from baseline is calculated as post minus baseline b. Absolute difference in mean change from baseline: pirfenidone – placebo; positive absolute difference favors pirfenidone; negative favors placebo c. Relative difference in mean change from baseline, 100*(pirfenidone-placebo)/absolute (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 9, Biometrics Review, Dr. Feng Zhou.							

When the analysis was performed without imputation of data in trial 004, the mean decline from Baseline at Week 72 in percent predicted FVC was significantly reduced in patients receiving pirfenidone 2403 mg/day compared to placebo (-4.4% vs. -6.5%), with an absolute difference of

2.1 and a relative difference of 32.3% ($p=0.007$). Although the size of the treatment effect decreased (absolute difference = 4.4 using imputed data), it continued to be statistically significant in trial 004. The difference between pirfenidone and placebo were not statistically significant at Week 72 in trial 006, however, several earlier timepoints (Weeks 12, 24, 36, and 48) demonstrated statistical significance, as was the case when imputed data was used. However, similar to the Applicant's analysis using imputed data, there was no evidence of treatment effect in trial 006 at 72 weeks (-3.7% vs. -3.9%), with an absolute difference of 0.2 and a relative difference of 5.1% ($p=0.717$) [Biometrics Review, Dr. Feng Zhou].

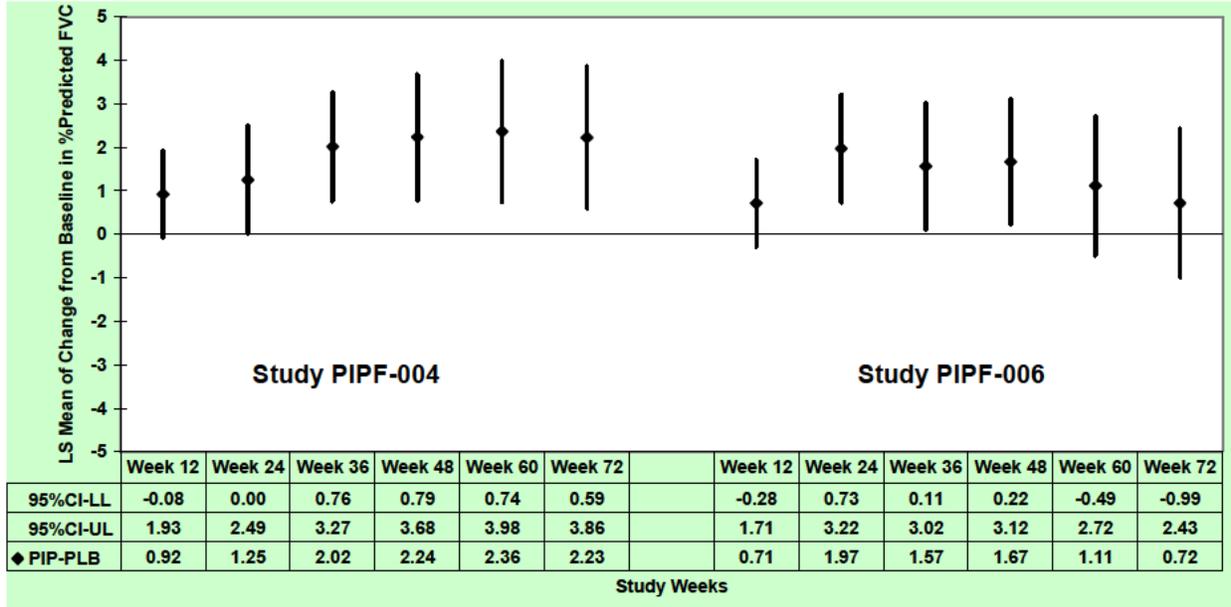
Supportive Analyses of the Primary Outcome Variable

1. Mean Change from Baseline in % Predicted FVC: Repeated Measures Mixed Linear Model
The Applicant conducted a repeated measures mixed linear model to assess the change in percent predicted FVC across all study visits. For this analysis, missing FVC data due to death were assigned a value of 30%; no other imputations were made. Per the Applicant's analysis, a strongly positive treatment effect of pirfenidone 2403 mg/day compared with placebo was apparent in reducing the overall decline from baseline in percent predicted FVC ($p=0.007$).

Reviewer's comment: This repeated measures analysis was prominently presented at the PADAC, and likely influenced the voting of the AC panel. It should be noted that although the repeated measures analysis was pre-specified, the data imputation method was changed post-hoc, when the unblinded data did not conform to the requirements of the statistical assumptions that had been made prior to seeing the data. This analysis takes the earlier timepoints into account more heavily, and thus the positive statistical outcome.

Dr. Zhou conducted the same analysis without imputation of data missing due to death or for other reasons. The Agency's analysis is depicted in Figure 4.

Figure 4: Treatment Comparison of Mean Change from Baseline to Week 72 in Percent Predicted FVC, All Randomized Patients – Trials 004 and 006 (Mixed Linear Model without Imputation)



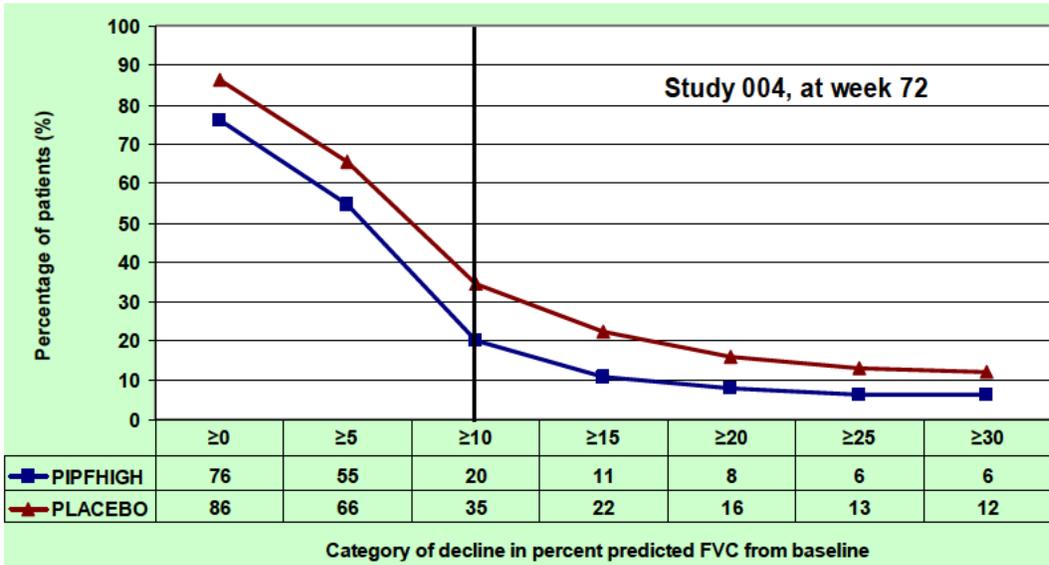
Note: Mixed Linear model comparing Pirfenidone 2403 mg/d to Placebo, with change from baseline as the outcome variable. Treatment, geographical region (USA and ROW), assessment week, and treatment by assessment week interaction as fixed effects; covariates of baseline %Predicted FVC, and a repeated effect of assessment week, unstructured covariance structure and patient as the subject factor.

In Figure 4, the Agency’s repeated measures mixed linear model without data imputation demonstrates that the treatment effect was statistically significant at all timepoints (with the exception of Week 12) in trial 004, and at Weeks 24, 36, and 48 in trial 006. At Week 72, the treatment effects were 2.23 [95% CI: 0.59, 3.86] and 0.72 [95% CI: -0.99, 2.43] at Week 72 in trials 004 and 006, respectively.

2. Cumulative Distribution of Change from Baseline in Percent Predicted FVC
 The Agency’s analysis is presented in

Figure 5 and Figure 6. In these plots, all patients who discontinued treatment due to death are considered the worst responders. With respect to missing values, the last available value for those who discontinued treatment for reasons other than death was carried forward. These figures were created to provide a visual display of the relative benefit of pirfenidone across the entire range of response at Week 72. The x-axis shows the reduction in percent predicted FVC from baseline to Week 72; the y-axis displays the corresponding percentage of patients who demonstrated that level of decline or greater. The positive treatment effect of pirfenidone 2403 mg/day was demonstrated by the consistent separation of the curves in trial 004. When patients with a FVC decline $\geq 10\%$ were considered “responders”, there was a greater percentage of patients in the placebo group that experienced this level of decline than in the pirfenidone group (35% vs. 20%). By this analysis, no treatment effect was seen in trial 006.

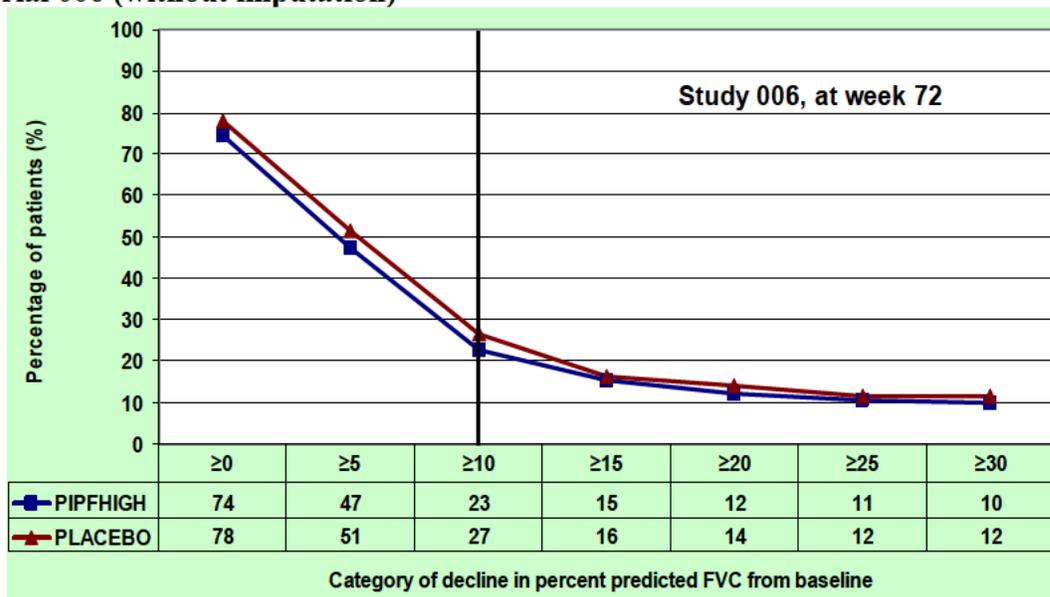
Figure 5: Cumulative Percent of Patients – Change From Baseline in % Predicted FVC – Trial 004 (without imputation)



Percent change from baseline = $100 * (\text{post baseline} - \text{baseline}) / \text{baseline}$.

Source: Biometrics Review, Dr. Feng Zhou

Figure 6: Cumulative Percent of Patients – Change From Baseline in % Predicted FVC – Trial 006 (without imputation)



Percent change from baseline = $100 * (\text{post baseline} - \text{baseline}) / \text{baseline}$.

Source: Biometrics Review, Dr. Feng Zhou

3. Mean Change from Baseline in Percent Predicted FVC - LOCF method

The Applicant performed a pre-specified sensitivity analysis using the rank ANCOVA model and LOCF methodology to impute missing values for change from Baseline in percent predicted

FVC at Week 72. In this analysis, missing values were imputed by the LOCF method instead of the SSD method if the patient was alive at Week 72, and zero was imputed for values missing due to death. With this imputation method, in trial 004, the mean decline from Baseline at Week 72 in percent predicted FVC was significantly reduced in patients receiving pirfenidone 2403 mg/day compared to placebo (-7.9 % vs. -12.2%), with an absolute difference of 4.3 and a relative reduction of 35% ($p < 0.001$). Trial 006 showed no difference between the pirfenidone and placebo groups at 72 weeks (-9.0% vs. -9.6%) with an absolute difference of 0.6% and a relative reduction of 6.5% ($p = 0.504$), similar to the primary analysis with SSD imputation. The Agency also conducted the same LOCF/rank ANCOVA analysis, without imputing zero for death. The treatment effect decreased to 1.9 and 0.8, in trials 004 and 006, respectively (Table 10, Biometrics Review, Dr. Feng Zhou).

Reviewer's comment: The Applicant states that the similar findings in the LOCF imputation method are not surprising due to the small number of patients that required imputed data: trial 004: 12 of 174, 6.9% of patients in the 2403 mg/day group and 8 of 174, 4.6% patients in the placebo; trial 006: 10 of 171, 5.85% patients in the pirfenidone 2403-mg/d group and 9 of 173, 5.20% patients in the placebo group). However, when the results are analyzed using non-imputed data for death (Agency's analysis), the magnitude of the effect size is certainly affected.

Analysis of Change from Baseline in FVC volume (post-hoc)

A. Applicant's Analysis Using Imputed Data

Table 14 show the results of the comparison of the change from Baseline in FVC volume (mL) in the pirfenidone 2403 mg/day and placebo treatment groups at Weeks 12, 24, 36, 48, 60, and 72 in both trials using the same rank ANCOVA model and imputation method as described in Section 6.1.4 Analysis of the Primary Endpoint. The analysis depicted in Table 13 was conducted by Dr. Feng Zhou, the Agency's Biometrics Reviewer, and confirms the analysis as presented by the Applicant.

Reviewer's comment: Although this is a post-hoc analysis, presentation of the data in terms of FVC in ml provides another way to examine the primary endpoint, and is therefore very relevant.

Table 14: Mean Change from Baseline in FVC volume in All Randomized Patients (rank ANCOVA with imputation)

	Pirfenidone 2403 mg/day	Placebo	Treatment Comparison		
Week	Mean Change in FVC (mL) ^{a,b}		Absolute Difference ^c	Relative Difference ^d	p-value ^e
PIPF-004					
	N=174	N=174			
Baseline ^f	2872	2914	42	--	--
Week 12	-47	-108	61	56.3%	0.025
Week 24	-62	-153	91	59.4%	0.034
Week 36	-111	-284	173	60.9%	0.001
Week 48	-181	-350	169	48.3%	0.002
Week 60	-266	-403	137	34.0%	0.001
Week 72	-318	-475	157	33.0%	p = 0.005
PIPF-006					
	N = 171	N = 173			
Baseline ^f	2940	2855	85	--	--
Week 12	-65	-39	-26	-67.8%	0.047
Week 24	-70	-175	105	60.0%	<0.001
Week 36	-108	-190	82	43.0%	0.021
Week 48	-220	-274	54	19.8%	0.006
Week 60	-316	-323	6	1.9%	0.174
Week 72	-379	-373	-5	-1.4%	p = 0.508

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. Relative difference in mean change from baseline, 100*(pirfenidone-placebo)/absolute (placebo).
 e. 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.
 f. 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 11-8, p. 139, PIPF-004 CSR, and Table 11-8, p. 130, PIPF-006 CSR, Module 5.

In trial 004, the mean decline from Baseline at Week 72 in FVC volume was significantly reduced in patients receiving pirfenidone 2403 mg/day compared to placebo (-318mL vs. -475mL), with an absolute difference of 157mL and a relative reduction of 33% (p=0.005). Additionally, a reduced decline from Baseline was statistically significant at every earlier timepoint in trial 004 as well (See Table 14). Trial 006 showed no difference between the pirfenidone and placebo groups at 72 weeks (-379mL vs. -373mL) with an absolute difference of -6mL (in favor of placebo). However, in trial 006, there were statistically significant reductions in the mean decline FVC volume in the pirfenidone group at earlier timepoints (see Table 14).

Reviewer's comment: Although several earlier timepoints demonstrated that pirfenidone was statistically better than placebo, the insignificant difference at week 72 calls into question the durability of the efficacy response in trial 006.

B. Agency’s Analysis Without Imputation of Data

In order to examine the robustness of the data and the impact upon the magnitude of the treatment effect, Dr. Zhou conducted the same rank ANCOVA analysis of the mean change in FVC volume without imputation (i.e. using observed data at each visit, rather than imputing zero for death and using the SSD method for missing data due to reasons other than death). These results are presented in Table 15.

Table 15: Mean Change from Baseline in FVC volume in All Randomized Patients - Trials 004 and 006 (rank ANCOVA without imputation)							
Week	Pirfenidone 2403 mg/day		Placebo		Treatment Comparison		
	N observed (Death)	Mean Change ^a	N observed (Death)	Mean Change ^a	Absolute Difference ^b	Relative Difference ^c	p-value ^d
PIPF-004							
Baseline*	174 (0)	2871.6	174 (0)	2913.6	-42.0	--	--
Week 12	170 (1)	-26.0	166 (0)	-63.4	37.4	59.0	0.034
Week 24	168 (1)	-38.0	164 (5)	-80.7	42.7	52.9	0.041
Week 36	160 (2)	-60.1	156 (10)	-143.7	83.6	58.2	0.003
Week 48	159 (4)	-94.2	154 (13)	-179.3	85.1	47.5	0.005
Week 60	156 (7)	-139.6	148 (14)	-213.2	73.6	34.5	0.004
Week 72	154 (8)	-168.6	150 (16)	-243.7	75.0	30.8	0.015
PIPF-006							
Baseline*	171 (0)	2940.5	173 (0)	2855.2	85.3	--	--
Week 12	167 (2)	-20.7	168 (0)	-39.4	18.7	47.3	0.032
Week 24	168 (2)	-25.0	165 (5)	-92.1	67.1	72.9	<.001
Week 36	159 (4)	-35.8	158 (7)	-77.5	41.7	53.8	0.055
Week 48	157 (6)	-96.2	156 (8)	-140.9	44.6	31.7	0.018
Week 60	151 (10)	-126.4	148 (11)	-140.2	13.8	9.8	0.229
Week 72	148 (13)	-147.0	149 (15)	-149.0	2.0	1.3	0.705

Footnotes a-e same as Table 13.
 Source: Table 11, Biometrics Review, Dr. Feng Zhou.

When the analysis was performed without imputation of data in trial 004, the mean decline from Baseline at Week 72 in FVC volume was significantly reduced in patients receiving pirfenidone 2403 mg/day compared to placebo (-169mL vs. -244mL), with an absolute difference of 75mL and a relative difference of 30.8% (p=0.015). Although the size of the treatment effect decreased (absolute difference = 157mL using imputed data), it continued to be statistically significant in trial 004. The difference between pirfenidone and placebo were not statistically significant at Week 72 in trial 006, however, several earlier timepoints (Weeks 12, 24, and 48) demonstrated statistical significance, similar to the analysis in which imputed data was used. However, similar to the Applicant’s analysis using imputed data, there was no evidence of treatment effect in trial 006 at 72 weeks (-147mL vs. -149mL), with an absolute difference of 2mL and a relative difference of 1.3% (p=0.705) [Table 11, Biometrics Review, Dr. Feng Zhou].

6.1.5 Analysis of Secondary Endpoints and Survival

The results of the Applicant’s secondary efficacy analyses and survival analysis (a pre-specified exploratory endpoint) are summarized in Table 16. Solid circles represent a result directionally favorable to pirfenidone (● $p > 0.05$; ●● $p < 0.05$). Open circles represent a result favoring placebo.

Table 16: Primary, Secondary, & Survival Endpoints (004 and 006) – Applicant’s Results

Outcome Variable	Study	Week					
		12	24	36	48	60	72
Primary Endpoint							
Percent Predicted FVC	PIPF-004	●	●●	●●	●●	●●	●●
	PIPF-006	●●	●●	●●	●●	●	●
Secondary and Survival Endpoints							
Categorical FVC	PIPF-004	●	●●	●●	●●	●●	●●
	PIPF-006	●	●●	●●	●	●	●
6MWT Distance	PIPF-004	●	●	●	●	●	●
	PIPF-006	●	●●	●●	●●	●●	●●
Percent Predicted DL _{CO}	PIPF-004	●	●	●	●	●	●
	PIPF-006	●	●	●	●	●	●
Worst SpO ₂	PIPF-004	●	●	●●	●	●	●
	PIPF-006	●	●	●	●	●	○
UCSD SOBQ	PIPF-004	○	●	●	●	●	●
	PIPF-006	○	●	○	●	●	●
Progression-Free Survival	PIPF-004	●●					
	PIPF-006	●					
Worsening of IPF	PIPF-004	●					
	PIPF-006	●					
Survival	PIPF-004	●					
	PIPF-006	●					

Source: NDA Section 5.3.5.3 ISE Tables 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17, 2.18, 2.19, 2.20; CSR PIPF-004; CSR PIPF-006

6MWT = Six-minute walk test, DL_{CO} = Carbon monoxide diffusing capacity; FVC = Forced vital capacity; SpO₂ = Oxygen saturation by pulse oximetry; UCSD SOBQ = University of San Diego Shortness of Breath Questionnaire

Source: Table 2.5-3, Clinical Overview, Module 2.

In trial 004, the only secondary endpoint that was statistically improved with pirfenidone treatment was progression-free survival (PFS). The Six-Minute Walk Test (6MWT) distance was the only secondary endpoint in favor of pirfenidone in trial 006, with a nominal p-value <0.05. However, the statistical significance of this secondary endpoint is debatable in the face of trial 006 failing to achieve the primary endpoint. This reviewer will therefore focus the discussion of secondary/exploratory endpoints on progression free survival and survival, with a brief summary of other endpoints (time to IPF worsening and DLco).

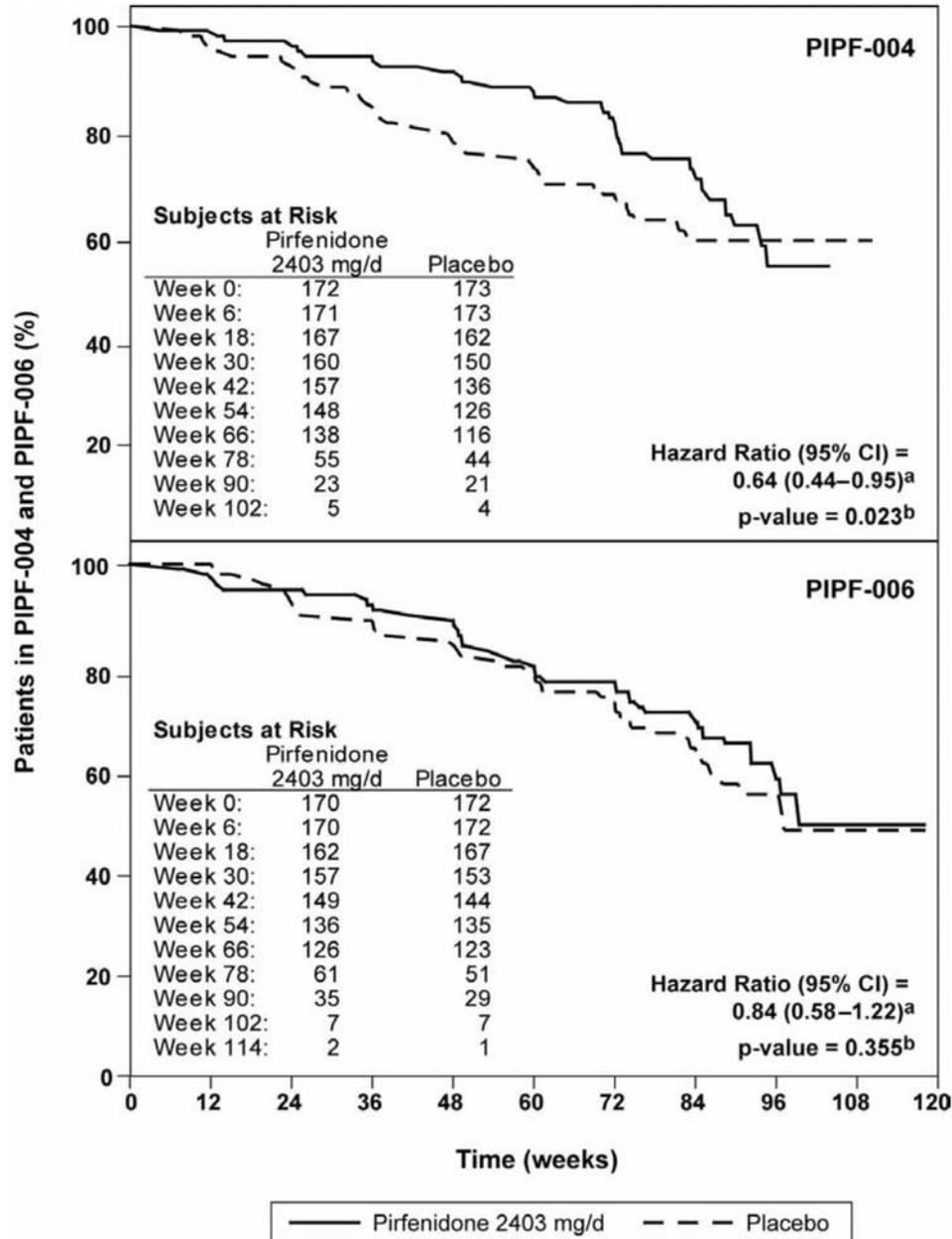
Time to Progression-Free Survival

Progression-free survival time was defined as the time to first occurrence of either a 10% absolute decline in percent predicted FVC, a 15% decline in percent predicted DLco, or death. In the case of FVC and DLco, the decline must have been confirmed at 2 consecutive visits at least 6 weeks apart. The Applicant's results of the progression-free survival analysis are summarized in Table 17 and Figure 7.

Table 17: Progression Free Survival in All Randomized Patients (004 and 006)				
	Pirfenidone 1197 mg/day	Pirfenidone 2403 mg/day	Placebo	Hazard Ratio ^c
		N of Event ^a (%)	N of Event ^a (%)	(95% CI) p-value ^b
PIPF-004				
N Randomized	87	174	174	--
Death or Disease Progression ^d	28 (32.2)	45 (26.2)	62 (35.8)	0.64 (0.44, 0.95), 0.023
Decline in %predicted FVC \geq 10%	16 (18.4)	28 (16.3)	39 (22.5)	--
Decline in %predictedDL _{CO} \geq 15%	5 (5.7)	9 (5.2)	9 (5.2)	--
Death before disease progression ^e	7 (8.0)	8 (4.7)	14 (8.1)	--
PIPF-006				
N Randomized		171	173	--
Death or Disease Progression ^d		54 (31.8)	60 (34.9)	0.84 (0.58, 1.22), 0.355
Decline in %predicted FVC \geq 10%		31 (18.2)	41 (23.8)	--
Decline in %predictedDL _{CO} \geq 15%		10 (5.9)	9 (5.2)	--
Death before disease progression ^e		13 (7.6)	10 (5.8)	--

[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
 [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.
 [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.
 Source: Biometrics Review, Dr. Feng Zhou, Table 7-21, p. 131, Integrated Summary of Efficacy, Module 5.

Figure 7: Time to Progression-Free Survival During the Treatment Period – Kaplan-Meier Estimates, All Randomized Patients (Trials 004 and 006)



Note: Time to event was the event date minus the randomization date plus one. The censoring date was defined as the last FVC or DLCO assessment during the Treatment Period. Deaths after this visit were counted if they occurred within 24 weeks of the visit. a p-value was based on the log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d with placebo.

b Hazard ratio was based on the Cox proportional hazard model.

Source: Figure 7-14, p. 130, ISE, Module 5.

Treatment with pirfenidone 2403 mg/day was associated with a 36% relative reduction in death or disease progression when compared with placebo ($p = 0.023$; HR [95% CI]: 0.64 [0.44–0.95]). This reduction was driven mainly by the $\geq 10\%$ decline in percent predicted FVC that occurred in 16.3% (28/172) of patients in the pirfenidone 2403-mg/d group compared with 22.5% (39/173) of patients in the placebo group (Table 17). There was evidence of a treatment effect of pirfenidone 2403 mg/d that began at approximately Week 12 and extended beyond Week 72. At and after Week 78, these plots need to be interpreted with caution due to the small numbers of patients remaining at risk (Figure 7). Progression-free survival was not statistically better in pirfenidone treated patients in trial 006. The low dose pirfenidone group did not demonstrate any dose response with respect to progression free survival.

Survival

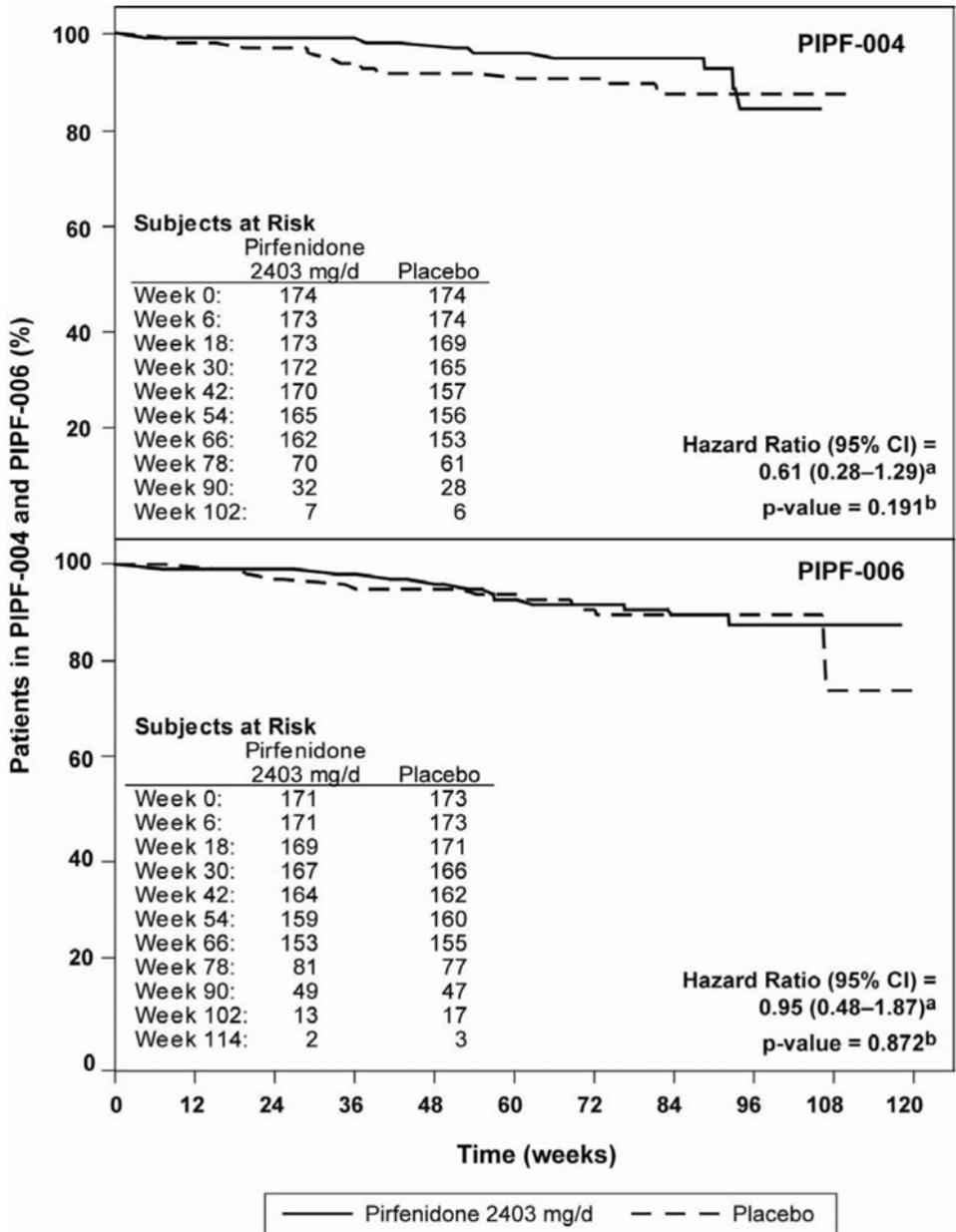
Deaths were classified in a number of different ways in this application:

- 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 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.

The Applicant presented an analysis of survival counting deaths (all cause mortality) that occurred by the end of the treatment period. The Applicant’s analysis is presented in Table 18 and Figure 8.

Table 18: All Cause Mortality – During the Treatment Period (Trials 004 and 006)			
	Pirfenidone 2403 mg/day	Placebo	
Fatal Adverse Event	N of Event ^a (%)	N of Event ^a (%)	Hazard Ratio ^c (95% CI) p-value ^b
PIPF- 004			
Patient Randomized	174	174	--
Patient Deaths ^a	11 (6.3)	17 (9.8)	0.61 (0.28, 1.29), 0.191
Patients Censored ^a	163 (93.7)	157 (90.2)	
PIPF- 006			
Patient Randomized	171	173	
Patient Deaths ^a	16 (9.4)	17 (9.8)	0.95 (0.48, 1.87), 0.872
Patients Censored ^a	155 (90.6)	156 (90.2)	
<p>a 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 available contact date or time of lung transplantation (if one occurred), or the end of the Treatment Period.(Sept 30 or 25, 2008, for PIPF 004 and PIPF-006 respectively).</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>Source: Biometrics Review, Dr. Feng Zhou and Table 7-35, p. 153, Integrated Summary of Efficacy, Module 5.</p>			

Figure 8: Overall Survival Time – Kaplan-Meier Estimates, All Randomized Patients (Trials 004 and 006)



Source: Figure 7-20, p. 152, ISE, Module 5.

When death was examined during the treatment period, neither study demonstrated a mortality benefit, although numerically, trial 004 trended towards a mortality benefit in the pirfenidone treatment group. In trial 004, a total of 11 (6.3%) patients in the pirfenidone 2403 mg/day group compared with 17 (9.8%) patients in the placebo group died by the end of the treatment period (HR 0.61 [95% CI, 0.28–1.29]; p = 0.191). The Kaplan-Meier estimates (Figure 8) show that the pirfenidone group was numerically better than placebo, until approximately Week 90, when the curves for the two treatment groups cross. In trial 006, there was no trend towards a mortality benefit in the pirfenidone group, with a similar proportion of deaths in both the pirfenidone and placebo groups (9.4% and 9.8%, respectively) (HR 0.95 [95% CI, 0.48, 1.87; p = 0.872).

Because the effect on mortality could vary based on when death was measured, the Agency performed survival analyses examining those deaths which occurred on-treatment or when a patient was followed for vital status. The pirfenidone low dose group is included only for exploration of dose response. The primary comparison is between pirfenidone 2403 mg/day and placebo. The Agency’s analysis is presented in Table 19.

Table 19: All-Cause Mortality - On-Treatment and Vital Status-End of Study (Trials 004 and 006)				
	Number of Events (%)			Hazard Ratio† (95% CI) p value‡
	Pirfenidone 1197mg/day	Pirfenidone 2403mg/day	Placebo	
<i>PIPF-004</i>				
N randomized	87	174	174	
On Treatment	8 (9.2)	10 (5.8)	14 (8.0)	0.72 (0.32, 1.62), p=0.422
Vital Status – End of Study	10 (11.5)	14 (8.0)	20 (11.5)	0.66 (0.33, 1.31), p=0.237
<i>PIPF-006</i>				
N randomized		171	173	
On Treatment		9 (5.3)	15 (8.7)	0.59 (0.26, 1.36), p=0.216
Vital Status – End of Study		18 (10.5)	17 (9.8)	1.05 (0.54, 2.04), p=0.879
<i>Trials 004 and 006 combined</i>				
N randomized		345	347	
On Treatment		19 (5.5)	29 (8.4)	0.65 (0.37, 1.16), p=0.149
Vital Status – End of Study		32 (9.3)	37 (10.7)	0.84 (0.52, 1.35), p=0.468
† Hazard ratio was based on the Cox proportional hazard model				
‡ p-value based on the log-rank test, stratified by geographic region comparing pirfenidone 2403 mg/d to placebo				

When deaths were examined using the on-treatment and vital status datasets, again, neither trial demonstrated a mortality benefit. However, when looking at on-treatment deaths, survival numerically favored pirfenidone 2403 mg/day in both trials (trial 004: 10 deaths pirfenidone 2403 mg/day, 14 deaths placebo; trial 006: 9 deaths pirfenidone 2403 mg/day, 15 deaths placebo). When death was examined using the vital status dataset, trial 004 numerically favored pirfenidone (14 deaths pirfenidone 2403 mg/day, 20 deaths placebo), but trial 006 did not show any difference between treatment groups (18 deaths pirfenidone 2403 mg/day, 17 deaths placebo). While the pirfenidone 1197 mg/day group was included only for dose exploration, it is notable that there did not appear to be any dose-response with increasing dose with respect to

death, as the low dose and high dose pirfenidone groups had similar proportions of death compared with the placebo group.

The Agency conducted a survival analysis treating both patients who died and those who received lung transplants as “deaths”. Lung transplantation was included as a fatal event because death was presumed to be imminent without this procedure. Table 20 demonstrates an analysis of overall survival, in which lung transplant is included as a fatal event, using the on-treatment and vital status datasets. The low dose pirfenidone group is not included, as there were no lung transplants in this group.

Table 20: All Cause Mortality (including Lung Transplant) On-treatment and Vital Status, End of Study – (Trials 004 and 006)			
Any Fatal Adverse Event (including lung transplant)	Pirfenidone 2403 mg/day	Placebo	Hazard Ratio ^b (95% C.I.), p-value ^c
	# events ^a (%)	# events ^a (%)	
PIPF-004			
N randomized	174	174	--
On-treatment	13 (7.5)	19 (10.9)	0.68 (0.34, 1.39), 0.292
Vital Status – End of Study	17 (9.8)	24 (13.8)	0.67 (0.36, 1.24), 0.204
PIPF- 006			
N Randomized	171	173	--
On-treatment	11 (6.4)	20 (11.6)	0.54 (0.26,1.13), 0.104
Vital Status – End of Study	22 (12.9)	22 (12.7)	1.00 (0.55, 1.80), 0.984
Trials 004 and 006 Combined			
N randomized	345	347	--
On-treatment	24 (7.0)	39 (11.2)	0.61 (0.37, 1.02), 0.058
Vital Status – End of Study	39 (11.3)	46 (13.3)	0.82 (0.54, 1.26), 0.369
a Based on occurrence of event (death (D) or lung transplant (L)), in specified time period: on-treatment: between 1 st day of randomization and 28 days post-study treatment discontinuation; or by vital status at the end of the study period. b Hazard ratio was based on the Cox proportional hazard model. c p-value was based on the log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d with placebo Source: Biometrics Review, Dr. Feng Zhou			

The number of patients receiving lung transplants during the study period was small and fairly well balanced across treatment groups. When lung transplants were counted as “deaths”, again, no mortality benefit was demonstrated.

The Applicant also presented an analysis of on-treatment IPF related mortality in the pooled 004 and 006 population. The Agency expanded this analysis to examine IPF-related mortality in each trial individually, using both the on-treatment and vital status datasets. These results are presented in Table 21.

Table 21: IPF-related Mortality* - On-Treatment and Vital Status-End of Study (Trials 004 and 006)				
	Number of Events (%)			Hazard Ratio† (95% CI) p value‡
	Pirfenidone 1197mg/day	Pirfenidone 2403mg/day	Placebo	
PIPF-004				
N randomized	87	174	174	
On Treatment	6 (6.9)	5 (2.9)	11 (6.3)	0.46 (0.16, 1.32), p=0.147
Vital Status – End of Study	7 (8.0)	8 (4.6)	15 (8.6)	0.51 (0.21, 1.20), p=0.147
PIPF-006				
N randomized		171	173	
On Treatment		7 (4.1)	14 (8.1)	0.49 (0.20, 1.23), p=0.128
Vital Status – End of Study		14 (8.2)	15 (8.7)	0.93 (0.45, 1.92), p=0.834
Trials 004 and 006 combined				
N randomized		345	347	
On Treatment		12 (3.5)	25 (7.2)	0.48 (0.24, 0.95), p=0.036
Vital Status – End of Study		22 (6.4)	30 (8.6)	0.71 (0.41, 1.24), p=0.229
* post-hoc analysis; unadjudicated cause of death				
† Hazard ratio was based on the Cox proportional hazard model				
‡ p-value based on the log-rank test, stratified by geographic region comparing pirfenidone 2403 mg/d to placebo				

As shown in Table 23, when IPF-related mortality was examined in the on-treatment pooled population, there was a statistically significant 52% reduction in IPF-related mortality in the pirfenidone 2403 mg/day group as compared with placebo [(HR: 0.48 (0.24, 0.95), p=0.036]. Neither trial individually demonstrated a statistically significant on-treatment IPF-related mortality benefit, however, both trials numerically favored pirfenidone. When IPF-related mortality was examined using the vital status dataset, there was a numerical benefit in trial 004, but not in 006. Further, the pooled IPF-related mortality measured using the vital status dataset did not achieve statistical significance [HR: 0.71 (0.41, 1.24), p=0.229].

It is important to note that death was not adjudicated in the pirfenidone pivotal clinical trials. Investigators were asked to indicate via a checkbox on the mortality case report form as to whether a death was considered “IPF-related”. As both the Applicant’s and Agency’s analysis rely on the investigators’ assessment as to cause of death, further discussion regarding this assessment is warranted. The cause of death (by preferred term) is listed in the table below, divided by treatment group. The number of cases in each treatment group and whether that death was assessed as being IPF-related is depicted in Table 22.

Table 22: Cause of On-Treatment Deaths – Pooled Population Trials 004 and 0006				
	Treatment Groups			
	Pirfenidone N = 345		Placebo N = 347	
	N	IPF- related?	N	IPF- related?
Cause of Death (Preferred Term)				
Acute Respiratory Distress Syndrome	--	--	1	Yes
Arteriosclerosis	--	--	1	No
Bladder Cancer	1	No	--	--
Cor Pulmonale Acute	--	--	1	No
Hypoxia	1	Yes	1	Yes
Idiopathic Pulmonary Fibrosis	6	Yes	14	Yes
Myocardial Infarction	1	No	1	No
			1	Yes
Pneumonia	2	No	2	Yes
Pulmonary Hemorrhage	1	No	--	--
Respiratory Failure/Arrest	5	Yes	6	Yes
Septic Shock	1	No	--	--
Small Cell Lung Cancer Metastatic	1	No	1	No
Total On-Treatment Deaths	19		29	
Total IPF-related Deaths	12		25	

Source: Table 5-37, p. 195, ISS.
 PTs of respiratory failure and respiratory arrest combined by this reviewer.

I have reviewed the narratives for each of the deaths presented in Table 22. As shown in Table 22, of the 19 on-treatment deaths in the pirfenidone 2403 mg/day group, 12 were assessed as being related to IPF. The diagnoses (by MedDRA preferred term) were hypoxia (n=1), idiopathic pulmonary fibrosis (n=6), and respiratory failure/arrest (n=5). In the placebo group, there were a total of 29 on-treatment deaths, with 25 being assessed as related to IPF. Causes of death (by preferred term) included ARDS (n=1), hypoxia (n=1), IPF (n=14), myocardial infarction (n=1), pneumonia (n=2), and respiratory failure/arrest (n=6).

Because the causes of death and relatedness to IPF were assessed by individual investigators and unadjudicated, the following inconsistencies/issues are worth noting:

- Pneumonia was not deemed as being IPF-related in the pirfenidone group, but was assessed to be IPF-related in the placebo group. In my review of the narratives, there was no apparent difference in the pneumonias in the pirfenidone and placebo groups that would justify the discrepant classification.
- Per the narrative, the patient with septic shock in the pirfenidone group developed sepsis due to pneumonia. This death, like the other cases of pneumonia in the pirfenidone group, was deemed to be unrelated to IPF.

- Pulmonary hemorrhage in the pirfenidone group was not deemed as being related to IPF. In review of this patient's case narrative, his primary event was a CVA, which led to development of a pneumonia and requirement for mechanical ventilation. He had a poor neurologic prognosis, and thus his family agreed to withdraw life support. The patient eventually died due to pulmonary hemorrhage. The narrative gives a detailed explanation as to why this pulmonary hemorrhage was not related to study drug. The main argument provided was that patients with IPF are at risk for pulmonary hemorrhage due to the physiology of their disease. It therefore, is unclear as to why this death would not be classified as IPF-related.

Given the manner in which IPF-related mortality was assessed, and the inconsistencies noted in assignment of IPF-relatedness, the statistically significant results of reduction in IPF-related mortality in the pooled 004 and 006 trial population should be interpreted with caution.

Reviewer's comment: Whether or not IPF-related mortality is the appropriate measure to examine in IPF clinical trials is uncertain. Literature/expert opinions in the field of IPF tend to favor all-cause mortality as the preferred outcome, as determining cause of death in these patients can often be difficult and somewhat subjective.

Time to IPF Worsening

Worsening of IPF was defined by the occurrence of any of the following: acute IPF exacerbation (as defined in Table 5), IPF-related death, lung transplantation, or respiratory hospitalization. The Applicant's analysis is summarized in Table 23.

Table 23: Time to IPF Worsening in All Randomized Patients (Trials 004 and 006)

	Pirfenidone 1197 mg/day	Pirfenidone 2403 mg/day	Placebo	Hazard Ratio ^c (95% CI) p-value ^d
		N of Event (%)	N of Event (%)	
PIPF-004				
N of Randomized	87	174	174	--
Worsening IPF ^a	10 (11.5)	26 (14.9)	30 (17.2)	0.84, (0.50, 14.2), 0.515
Acute IPF exacerbation	1 (1.1)	2 (1.1)	3 (1.7)	--
Lung transplantation	0	2 (1.1)	2 (1.1)	--
Respiratory hospitalization	9 (10.3)	21 (12.1)	24 (13.8)	--
IPF-related death ^b	0	1 (0.6)	1 (0.6)	--
PIPF-006				
N of Randomized		171	173	--
Worsening IPF ^a		24 (14.0)	32 (18.5)	0.73 (0.43, 1.24), 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)	--
^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. ^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. ^c Hazard ratio was based on the Cox proportional hazard model. ^d p-value was based on the log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d with placebo. Source: Table 16, Biometrics Review, Dr. Feng Zhou				

Neither trial demonstrated a statistical benefit in the time to worsening of IPF in patients treated with pirfenidone. In PIPF-004, in the analysis of time to worsening of IPF in patients taking pirfenidone 2403 mg/day relative to placebo, the HR was 0.84 (95% CI, 0.50–1.42; p = 0.515). A total of 26 (14.9%) patients in the pirfenidone 2403 mg/day group and 30 (17.2%) patients in the placebo group had worsening of IPF. There was no dose response noted for the lower dose pirfenidone group in PIPF-004. In PIPF-006, in the analysis of time to worsening of IPF in patients taking pirfenidone 2403 mg/d compared with placebo, the HR was 0.73 (95% CI, 0.43–1.24; p = 0.248). A total of 24 (14.0%) patients in the pirfenidone 2403 mg/d group and 32 (18.5%) patients in the placebo group had worsening of IPF. Worsening of IPF was primarily related to respiratory hospitalizations, which occurred in 21 (12.1%) and 24 (13.8%) patients in the pirfenidone 2403 mg/d and placebo groups, respectively, in PIPF-004, and in 17 (9.9%) and 23 (13.3%) patients in PIPF-006. Acute exacerbations, lung transplantation, and IPF-related death were uncommon (Table 23).

Mean Change from Baseline in Percent Predicted Hemoglobin Corrected DLco

The Agency’s analysis of the mean change from Baseline to Week 72 in percent predicted DLco is summarized in Table 24.

Table 24: Mean Change from Baseline in % Predicted DLco, All Randomized Patients (Trials 004 and 006) (rank ANCOVA without imputation)

week	Pirfenidone 2403 mg/d		Placebo ^a		Treatment Comparison		
	N Observed (Death)	Mean ^a	N Observed (Death)	Mean ^a	Absolute Difference ^c	Relative Difference ^d	p-value ^b
PIPF-004							
Baseline	174 (0)	46.4	172 (0)	46.1	0.3	--	--
Week 12	169 (1)	-1.1	164 (3)	-2.1	1.0	45.8	0.221
Week 24	166 (1)	-1.9	159 (5)	-2.4	0.5	19.9	0.518
Week 36	158 (2)	-2.6	150 (10)	-2.7	0.1	2.5	0.379
Week 48	157 (4)	-4.4	151 (13)	-4.9	0.5	11.1	0.581
Week 60	155 (7)	-4.9	145 (14)	-5.1	0.2	3.5	0.851
Week 72	152 (8)	-6.3	148 (16)	-6.6	0.3	5.2	0.584
PIPF-006							
Baseline	171 (0)	47.8	173 (0)	47.4	0.4	--	--
12	167 (2)	-1.3	166 (0)	-1.3	-0.0	-0.3	0.592
24	167 (2)	-2.3	165 (5)	-2.5	0.2	9.6	0.708
36	157 (4)	-3.6	158 (7)	-3.8	0.2	4.8	0.537
48	157 (6)	-4.7	154 (8)	-4.6	-0.1	-2.8	0.682
60	151 (10)	-6.1	148 (11)	-6.3	0.2	2.9	0.7716
72	147 (13)	-6.8	147 (15)	-5.9	-0.9	-14.4	0.808

[a] Mean change from baseline is calculated as post minus baseline.
 [b] Ranked Analysis of Covariance (ANCOVA), 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. Deaths are ranked worst.
 [c] Absolute difference in mean change from baseline, pirfenidone - placebo.
 [d] Relative difference in mean change from baseline, 100*(pirfenidone-placebo)/absolute (placebo).
 Source: Table 17, Biometrics Review, Dr. Feng Zhou

When the analysis of DLco change from baseline was performed without imputation of data the treatment differences between pirfenidone and placebo were 0.3 and -0.9, in trials 004 and 006, respectively. Neither the Applicant's nor the Agency's analysis demonstrated a statistically significant benefit in DLco change in pirfenidone treated patients.

Reviewers comment: To examine the treatment effect on a lung function parameter, non-imputed data were thought to provide the "most true" estimate, since the pre-specified imputation method weighs death heavily. The Applicant's analysis using imputed data did not demonstrate a statistical benefit in the mean change in DLCO from baseline to week 72 in pirfenidone treated patients: Trial 004 (-7.9% and -9.9%, respectively, p = 0.145) Trial 006 (-9.8% and -9.2%, respectively, p = 0.996).

Distance Walked During the 6MWT

The Agency's analysis of the mean change from Baseline to Week 72 in 6MWT distance is summarized in Table 25.

Table 25: Mean Change from Baseline in 6MWT Distance (meters), All Randomized Patients (Trials 004 and 006) (rank ANCOVA without imputation)

week	Pirfenidone 2403 mg/d		Placebo ^a		Treatment Comparison		
	N Observed (Death)	Mean ^a	N Observed (Death)	Mean ^a	Absolute Difference ^c	Relative Difference ^d	p-value ^b
PIPF- 004							
Baseline	170 (0)	411.1	170 (0)	410.0	1.1	--	--
Week 12	164 (1)	-7.5	166 (3)	-8.3	0.8	9.3	0.768
Week 24	163 (1)	-11.9	163 (5)	-20.2	8.3	41.1	0.628
Week 36	152 (2)	-13.3	151(10)	-11.4	-1.9	-16.5	0.986
Week 48	155 (4)	-27.3	152 (13)	-27.4	0.1	0.5	0.291
Week 60	150 (7)	-29.8	142 (14)	-37.3	7.5	20.1	0.206
Week 72	150 (8)	-43.7	148 (16)	-44.6	0.9	2.1	0.579
PIPF- 006							
Baseline	169 (0)	378.0	168 (0)	399.1	-21.1	--	--
12	161 (2)	-2.3	168 (0)	-9.0	6.7	74.9	0.794
24	164 (2)	-2.4	162 (5)	-17.8	15.4	86.4	0.048
36	155 (4)	-5.4	156 (7)	-24.8	19.5	78.5	0.038
48	154 (6)	-8.4	152 (8)	-31.0	22.6	72.8	0.018
60	150 (10)	-6.8	146 (11)	-34.6	27.8	80.5	0.015
72	145 (13)	-15.4	147 (15)	-50.0	34.7	69.3	<.001
[a] Mean change from baseline is calculated as post minus baseline.							
[b] Ranked Analysis of Covariance (ANCOVA), 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. Deaths are ranked worst.							
[c] Absolute difference in mean change from baseline, pirfenidone - placebo.							
[d] Relative difference in mean change from baseline, 100*(pirfenidone-placebo)/absolute (placebo).							
Source: Table 18, Biometrics Review, Dr. Feng Zhou							

When the analysis of 6MWT change from baseline was performed without imputation of data the treatment differences between pirfenidone and placebo were 0.9 m and 34.7, in trials 004 and 006, respectively. The result was statistically significant in trial 006 ($p < 0.001$). Similarly, in the Applicant's analysis, using imputed data, the treatment differences were 16.4 m and 31.8 m, in trials 004 and 006, respectively (Table 7-23, Integrated Summary of Efficacy). The Applicant's analysis also demonstrated a statistically significant result in trial 006.

Reviewer's comment: The statistical significance of a secondary endpoint should be interpreted with caution since the primary endpoint was not met and this is one of many secondary endpoints evaluated. In addition, the MCID for the 6MWT distance in patients with IPF is not known.

6.1.6 Analysis of Clinical Information Relevant to Dosing Recommendations

A lower dose of pirfenidone, 1197 mg/day, was included in trial 004 to explore a dose-response relationship of pirfenidone in the treatment of patients with IPF. There was a numerical reduction in the mean decline from baseline in percent predicted FVC in patients receiving pirfenidone 1197 mg/d compared with those receiving placebo at week 72 ($p=0.172$, rank ANCOVA) (Table 26). This represents an absolute difference of 2.3 and a relative difference of 23.4% between the

pirfenidone 1197 mg/day and placebo. The treatment effect (without any imputation) of pirfenidone 1197 mg/d (1.2) appeared to be intermediate to that of pirfenidone 2403 mg/d (2.1 blue) and placebo in the primary efficacy analysis (Figure 9).

Table 26: Mean Change from Baseline in Percent Predicted FVC, Low Dose Pirfenidone (rank ANCOVA with imputation)							
Week	Pirfenidone 1197 mg/d		Placebo		Treatment Comparison		
	N Observed (Death)	Mean ^a (STD)	N Observed (Death)	Mean ^a (STD)	Absolute Diff. ^c	Relative Diff. ^d	p-value ^b
PIPF-004							
Baseline	87 (0)	76.4 (14.5)	174 (0)	76.2 (15.5)	0.2	--	--
Week 12	87 (0)	-1.2 (3.9)	174 (3)	-2.7 (9.5)	1.4	120	0.524
Week 24	87 (1)	-2.5 (8.6)	174 (5)	-3.9 (12.1)	1.4	56.4	0.498
Week 36	87 (2)	-3.8 (10.4)	174 (10)	-7.2 (15.6)	3.5	92.0	0.081
Week 48	87 (4)	-6.4 (14.2)	174 (13)	-9.2 (17.2)	2.8	43.8	0.205
Week 60	87 (5)	-8.6 (15.3)	174 (14)	-10.7 (17.6)	2.0	23.4	0.387
Week 72	87 (6)	-10.0 (16.7)	174 (16)	-12.4 (18.5)	2.3	23.4	0.172

[a] Mean change from baseline is calculated as post minus baseline.

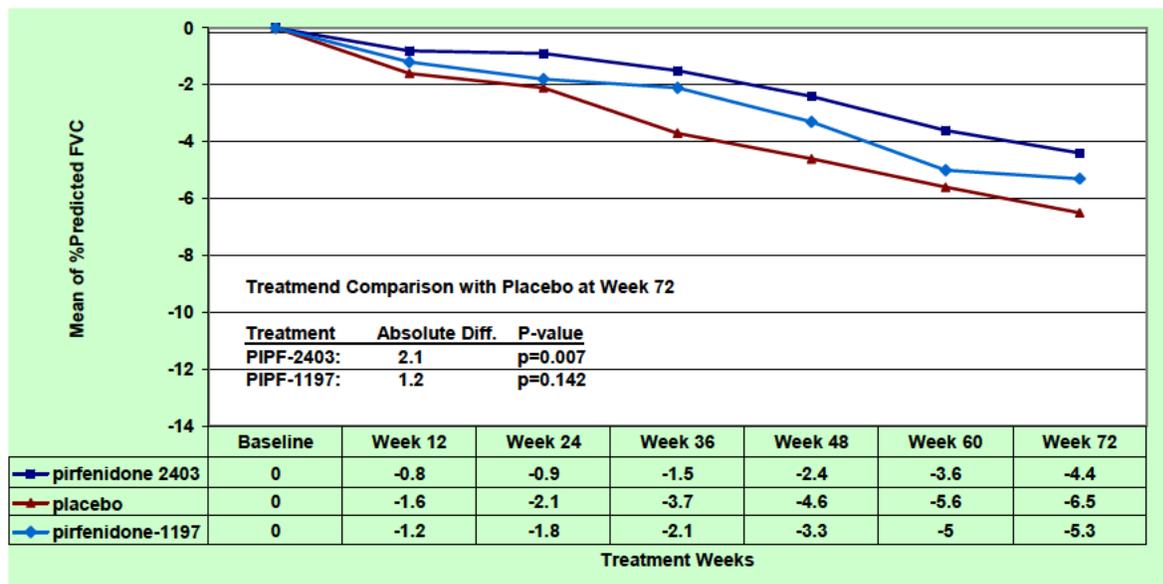
[b] Ranked Analysis of Covariance (ANCOVA), with standardized ranked change from baseline as the outcome variable, treatment and geographic region (USA and ROW) as fixed effects, and standardized ranked baseline as a covariate. Deaths are ranked worst.

[c] Absolute difference in mean change from baseline, pirfenidone - placebo.

[d] Relative difference in mean change from baseline, 100*(pirfenidone-placebo)/absolute (placebo).

[e] The LOCF imputation method will be applied if the patient was alive on week 72 visit. Zero was imputed if the patient died on or prior to the protocol specified date.

Figure 9: Dose Response in Mean Change from Baseline in Percent Predicted FVC (rank ANCOVA, no imputation)



6.1.7 Subpopulations

Dr. Feng Zhou, the Division’s Statistical Reviewer, performed subgroup analyses for trials 004 and 006. A detailed description of this analysis can be found in her review. To summarize, in trial 004, even though there was a treatment interaction for a few variables ($p < 0.1$), the results in the subgroups were in the same direction as the total population. For trial 006, the results of the subgroups were inconsistent, as expected, because this trial showed no treatment effect.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The question of persistence of efficacy is raised by the results demonstrated in trial 006. Initially, the pirfenidone group appeared to do better than placebo, but this separation waned between Weeks 48 and 60. Because the primary endpoint was measured at Week 72 as pre-specified, the treatment effect was not shown to be statistically significant.

Reviewer’s comment: This raises the difficult question of what constitutes an appropriate duration for an IPF clinical trial. As there is no regulatory precedent, if the Applicant had pre-specified 48 weeks or 60 weeks as their endpoint, the interpretation of the results may be different. If this application is to receive a complete response action, we will need to consider the duration of the trials, and the timepoint at which endpoints are statistically analyzed. In the opinion on this reviewer, since we now know that waning at Week 72 is a possibility, the measurement of the endpoint in potential future pirfenidone trials should be measured out until this timepoint.

6.1.10 Additional Efficacy Issues/Analyses

Based upon the review of this NDA, the Applicant does not have replication of efficacy for pirfenidone for the treatment of IPF to reduce decline in lung function. Of the two pivotal trials, only PIPF-004 achieved the primary endpoint. The clinical significance of the findings in trial 004 are uncertain, given the choice of lung function decline as an endpoint, and the magnitude of the treatment effect.

Given the severity of IPF, unmet need in this population, and the fact that only one study met its primary endpoint, mortality was examined in detail, to determine whether either study individually or pooled showed a significant mortality benefit. The Agency typically requires two studies to provide independent substantiation and replication of results; however, there are situations where one study may be adequate. The Agency's Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products describes the situations in which FDA relies upon a single adequate and well-controlled efficacy study to support approval e.g. a multicenter study of excellent design with highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival. A robust statistically significant finding of improved survival might be one instance in which a single study might be relied upon to provide substantial evidence of efficacy. However, neither trial showed a statistically significant mortality benefit. Although the pooled analysis did demonstrate a statistically significant reduction in IPF mortality in the pirfenidone group, this analysis should be interpreted with caution, as it was done post-hoc, and the deaths were not adjudicated.

7 Review of Safety

Safety Summary

The safety information for pirfenidone comes primarily from trials 004 and 006. Pooling of data across trials 004 and 006 to examine the emergence of any safety signals was deemed acceptable as these trials were identically designed and the patient population was comparable in terms of demographics, baseline characteristics, and dose of pirfenidone. Safety assessments in these two trials includes adverse events, physical examinations, vital signs, ECGs, and clinical laboratory testing.

There were a total of 343 patients treated with pirfenidone (87 in the 1197 mg/day group and 345 in the 2403 mg/day group) and 347 patients treated with placebo. The mean treatment duration was similar between the treatment groups. Duration of study treatment was similar between patients treated with pirfenidone 2403 mg/day and patients treated with placebo, respectively (median, 73.4 weeks and 72.7 weeks). The duration of treatment in the pirfenidone 1197 mg/day group (median, 72.7 weeks) was similar to the other treatment groups.

Deaths are discussed in detail in the efficacy section. Overall, there were numerically fewer treatment-emergent deaths in the pirfenidone 2403 mg/day - treated patients (5.5%) vs. placebo-treated patients (8.4%). There were a total of 56-treatment emergent deaths in both trials, and the percentage of deaths was lowest in the pirfenidone 2403 mg/day group compared with the placebo and pirfenidone 1197 mg/day groups (19 patients, 5.5%; 29 patients, 8.4%; and 8 patients, 9.2%, respectively). However, in PIPF-004, where two doses of pirfenidone were explored, no numerical dose response was demonstrated. IPF was the most common cause of death overall. Of the 19 treatment-emergent deaths in the pirfenidone 2403 mg/day group, the largest number were due to IPF (n = 6, 1.7%). Other cases were also classified as IPF-related deaths. These are discussed in detail in Section 6.1.5 Analysis of Secondary Endpoints and Survival.

The overall occurrence of treatment-emergent serious adverse events (SAEs) was equally distributed across treatment groups (31.4%-32.8%). SAEs that were reported more frequently in the pirfenidone 2403 mg/day group as compared with placebo were: coronary artery disease, chest pain, pneumothorax, bladder cancer, fall, and syncope. No dose repose was noted in the pirfenidone 1197 mg/day group with respect to SAEs.

Overall, 14.8% , 10.3%, and 8.6% of patients discontinued study treatment secondary to an AE in the pirfenidone 2403 mg/day, pirfenidone 1197 mg/day, and placebo groups, respectively. Idiopathic pulmonary fibrosis was the most frequently reported AE leading to discontinuation of study treatment (2.9% pirfenidone-treated; 2.6% placebo). The greatest differences in number of patients that discontinued secondary to an adverse event between the pirfenidone and placebo groups, respectively, were due to the AEs of rash, nausea, and bladder cancer.

The overall rates of patients having their dose reduced or treatment interrupted were higher in the two pirfenidone treatment groups than in the placebo group; 46.4% in the pirfenidone 2403 mg/day group, 18.4% in the placebo group and 42.5% in the pirfenidone 1197 mg/day group. The rates were highest in patients with adverse events in the SOCs of Skin and Subcutaneous Tissue Disorders and GI Disorders, which include events that were identified in the dose-modification guidelines for the Phase 3 protocols (see 5.3 Discussion of Individual Studies/Clinical Trials). The common TEAEs ($\geq 4\%$ of patients) that led to dose interruption or reduction that were reported more frequently by patients treated with pirfenidone than placebo included rash, nausea, diarrhea, photosensitivity reaction, vomiting, and fatigue.

Before unblinding trials 004 and 006, the Applicant identified a number of clinically important events AEs of interest. These events of interest were identified based upon relevant non-clinical findings as well as human experience in previously conducted pirfenidone IPF clinical trials. After unblinding the safety data from trials 004 and 006, the Applicant refined the AEs of interest to include only those AEs that occurred with an increased frequency in patients receiving pirfenidone. These AEs of interest can be divided into five major categories: 1) General Disorders: anorexia, decreased appetite, fatigue, 2) Cardiac Disorders: primarily arrhythmias, syncope, 3) GI events: diarrhea, nausea, vomiting, 4) Hepatic laboratory abnormalities: increase in transaminases, and 5) Skin events: photosensitivity reaction and rash. Most of these adverse

events of interest were without significant clinical sequelae, although they did lead to dose reduction or discontinuation of study treatment in a minority of cases. In the case of hepatic laboratory abnormalities, there were no Hy's law cases in the InterMune clinical development program, but potentially one case identified as drug-induced hepatotoxicity in the Shionogi program.

Safety data showed that pirfenidone is most commonly associated with nausea, diarrhea, dyspepsia, vomiting, fatigue, anorexia, dizziness, rash, and photosensitivity reaction, consistent with what had been described as adverse events of interest based upon previous clinical experience with pirfenidone. Pirfenidone does not appear to be associated with an increase risk in infections.

The two phase 3 trials were adequate to assess the safety of pirfenidone. The safety results of these two studies should be factored into the risk-benefit assessment of pirfenidone treatment in patients with IPF.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The Integrated Summary of Safety (ISS) is a review of all safety information from both controlled and uncontrolled clinical trials of pirfenidone conducted by the Applicant, the safety information provided by Shionogi in their two controlled studies of pirfenidone, and the safety results from early clinical trials of pirfenidone initiated by Marnac, the original developer of pirfenidone. Nine clinical studies conducted by the Applicant are presented in the application to provide safety information for pirfenidone. These studies are listed in Table 27.

Table 27: Summary of InterMune Clinical Studies Included in Safety Evaluation					
Study/ Objective	Phase	Study Design/ Duration	Study Treatment/ Dosing Regimen	Population	# Exposed Pirf/Control
PIPF-005 PK	1	SD/MD, CO, food effect study 3 days	Pirf 801 to 4005 mg/day (1 to 5 x 267 mg capsules)	Healthy	41/-
PIPF-007 Thorough QT	1	RDBPC/AC 10 days	Pirf 2403 to 4005 mg/day (3 to 5 x 267 mg capsules)	Healthy	81/81
PIPF-008 MTD/Safety	1	RDBPC 12 days	Pirf 801 to 4806 mg/day (1 to 6 x 267 mg capsules)	Healthy	16/4
PIPF-009 Renal	1	OL, SD	Pirf 801 mg (3 x 267 mg capsules)	Renal or Healthy	26/-
PIPF-010 PK	1	OL, PK effects of CYP1A2 inhibitor 11 days	Pirf 801 mg (3 x 267 mg capsules)	Healthy	54/-
PIPF-011 Hepatic	1	OL, SD	Pirf 801 mg (3 x 267 mg capsules)	Hepatic or healthy	24/-
Pirfenidone Patient Subset: Trial 002, 004, and 006 Pooled					
PIPF-002 Safety/Efficacy	2	OL, Long-term Open-ended	40 mg/kg/day divided TID to max of 3600 mg/day (using 400 mg capsules)	IPF/PF	83/-
Randomized Patient Subset: Trials 004 and 006 Pooled					
PIPF-004 Safety/Efficacy	3	RDBPC 72 Weeks	Pirf 2403 mg/d (3 x 267 mg capsules TID) Pirf 1197 mg/d (3 x 133 mg capsules TID)	IPF	261/174
PIPF-006 Safety/Efficacy	3	RDBPC 72 Weeks	Pirf 2403 mg/d (3 x 267 mg capsules TID)	IPF	171/173
<small>OL: open label; AC: active control; DDI: drug-drug interaction; MTD: maximum tolerated dose; PF: pulmonary fibrosis; PK: pharmacokinetics; CO: crossover; RDBPC: randomized, double blind, placebo controlled; *: this dosing regimen was transitioned to approximately equivalent doses using the 267 mg capsules, PO TID Source: Table 2-1, p. 30, Integrated Summary of Safety, Module 5.</small>					

The Applicant has pooled the safety data into 2 different subsets: the randomized subset and the pirfenidone subset. The randomized subset was comprised of all patients from the two randomized, double-blind, placebo-controlled trials who received at least one dose of study drug. The randomized subset consisted of 432 pirfenidone-treated patients (345 in the high dose group, 87 in the low dose group) and 347 placebo-treated patients. The pirfenidone subset was comprised of all patients who received pirfenidone during any of three IPF studies. The

pirfenidone subset included the pirfenidone-treated patients from trials 004 and 006, and an additional 83 patients from an ongoing phase 2 trial, PIPF-002.

The Applicant has also provided descriptive analyses of safety findings in studies conducted by Shionogi and Marnac. The results of InterMune-sponsored phase 1 studies are also summarized descriptively and integrated as appropriate to evaluate pirfenidone in special populations and settings (Table 27); a number of these studies have been reviewed in detail by other disciplines (e.g. biopharmaceutics). The descriptive safety data from Shionogi- and Marnac-conducted studies have been reviewed, and will be mentioned if relevant.

This clinical review focuses on and emphasizes the safety data as presented in the randomized patient subset (trials 004 and 006). Given the open-label and uncontrolled nature of trial 002, as well as the different dosing regimen that was used, this reviewer felt that patients from 002 should not be pooled with the patients from trials 004 and 006. Pooling of data across trials 004 and 006 to examine the emergence of any safety signals was deemed acceptable as these trials were identically designed and the patient population was comparable in terms of demographics, baseline characteristics, and dose of pirfenidone.

7.1.2 Categorization of Adverse Events

All adverse events were to be collected using medical terminology, and then mapped to system organ classes (SOC) and preferred terms using MedDRA version 11.0 (Medical Dictionary for Regulatory Activities) for the ISS. The focus of the safety analyses are those adverse events which were considered to occur on-treatment. On-treatment was defined as those adverse events that occurred anytime after the 1st day of randomization up until 28 days after study treatment discontinuation. Patients who discontinued study treatment but remained on study were followed for AEs until they withdrew from study; patients who withdrew prematurely from the study were followed for AEs for 28 days after last dose of study treatment. Deaths, serious adverse events, AEs of interest, common AEs, and less common AEs were all analyzed.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Table 28 summarizes the overall exposure to pirfenidone in trials 004 and 006.

Table 28: Overall Duration of Exposure to Pirfenidone (Trials 004 and 006)			
Duration of Study Treatment	Pirfenidone 1197 mg/d N = 87	Randomized Patient Subset	
		Pirfenidone 2403 mg/d N = 345	Placebo N = 347
Duration of Study Treatment (weeks)			
n	87	345	347
Mean	73.0	73.0	73.2
Standard Deviation	19.69	22.56	21.48
Median	72.7	73.4	72.7
Min, Max	13, 109	2, 118	>0, 120
Number of Patients on Study Treatment, n (%)			
>0 to <2 weeks	0	2 (0.6)	2 (0.6)
2 to <6 weeks	0	3 (0.9)	2 (0.6)
6 to <18 weeks	1 (1.1)	11 (3.2)	8 (2.3)
18 to <30 weeks	4 (4.6)	16 (4.6)	12 (3.5)
30 to <42 weeks	4 (4.6)	6 (1.7)	14 (4.0)
42 to <54 weeks	2 (2.3)	7 (2.0)	5 (1.4)
54 to <66 weeks	2 (2.3)	11 (3.2)	7 (2.0)
66 to <78 weeks	41 (47.1)	148 (42.9)	167 (48.1)
78 to <114 weeks	33 (37.9)	139 (40.3)	127 (36.6)
≥ 114 weeks	0	2 (0.6)	3 (0.9)

Source: Table 5-8, p. 118, Integrated Summary of Safety.

In the randomized patient subset, the majority of patients in all treatment groups remained on treatment for the planned treatment period. The number of patients who were on study treatment beyond 66 weeks was slightly less in the pirfenidone 2403 mg/day group, but overall comparable to placebo. Duration of study treatment was similar between patients treated with pirfenidone 2403 mg/day and patients treated with placebo, respectively (median, 73.4 weeks and 72.7 weeks). The duration of treatment in the pirfenidone 1197 mg/day group (median, 72.7 weeks) was similar to the other treatment groups.

Although the total exposure in this clinical development program does not meet ICH guidelines completely (for chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year), given that IPF is an orphan disease, this exposure is adequate for pre-marketing safety assessment.

Demographics

A total of 779 patients were randomized in the two phase 3 trials, 435 patients in trial 004, and 344 patients in trial 006. Within each study, demographic characteristics were comparable between treatment groups with respect to geographic region, age, gender, and race. Specifically, demographic characteristics in the pirfenidone LD group were similar to those reported for the pirfenidone HD group. In both trials, most patients were male (>67%), white (>96%), and of similar age (mean age, 65.7-67 years, range 40-80 years). Demographics between the two trials were also well-balanced, with the exception of geographic region, for which fewer patients were enrolled at US sites in trial 004 than 006. When demographics were compared by geographic region, sex, race, age, and ethnicity were well-balanced between the US and the ROW. A slight imbalance was observed in weight, in that both men and women in the US were generally heavier than patients outside the US (Table 7.5, Integrated Summary of Efficacy, Module 5, NDA 22-535) [See Table 7]. Baseline characteristics were also comparable across the treatment groups and trials (See Table 8).

7.2.2 Explorations for Dose Response

As shown by the analysis of pirfenidone exposure according to total duration and mean daily dose in Table 29, the majority of patients remained on their assigned dose. Of the patients in the pirfenidone 2403 mg/d group, 56% remained on full dose for the planned treatment period and 70% received >1800 mg/d for the planned treatment period (see bold/italicized text in Table 29). Of the patients in the pirfenidone 1197 mg/d group, 70% remained on full dose for the planned treatment period (see bolt text, Table 29).

Table 29: Exposure to Pirfenidone by Total Duration (weeks) & Mean Daily Dose (trials 004 and 006)					
	Mean Daily Dose (mg/day)				
	<0 to ≤1000	> 1000 to ≤1400	>1400 to ≤1800	> 1800 to ≤ 2200	>2200 to ≤ 2600
	Number of Patients, n (%)				
Pirfenidone 1197 mg/d (N = 87)					
>0 to <2 weeks	0	0	0	0	0
2 to <6 weeks	0	0	0	0	0
6 to <18 weeks	1 (1.1)	0	0	0	0
18 to <30 weeks	1 (1.1)	3 (3.4)	0	0	0
30 to <42 weeks	1 (1.1)	3 (3.4)	0	0	0
42 to <54 weeks	1 (1.1)	1 (1.1)	0	0	0
54 to <66 weeks	1 (1.1)	1 (1.1)	0	0	0
66 to <78 weeks	9 (10.3)	32 (36.8)	0	0	0
78 to <114 weeks	4 (4.6)	29 (33.3)	0	0	0
≥ 114 weeks	0	0	0	0	0
Total (Any Duration)	18 (20.7)	69 (79.3)	0	0	0
Pirfenidone 2403 mg/d (N = 345)					
>0 to <2	0	0	0	0	0
2 to <6 weeks	1 (0.3)	0	0	0	2 (0.6)
6 to <18 weeks	1 (0.3)	1 (0.3)	2 (0.6)	3 (0.9)	4 (1.2)
18 to <30 weeks	1 (0.3)	3 (0.9)	2 (0.6)	4 (1.2)	6 (1.7)
30 to <42 weeks	0	1 (0.3)	2 (0.6)	1 (0.3)	2 (0.6)
42 to <54 weeks	1 (0.3)	0	1 (0.3)	0	5 (1.5)
54 to <66 weeks	2 (0.6)	2 (0.6)	1 (0.3)	1 (0.3)	5 (1.5)
66 to <78 weeks	5 (1.5)	4 (1.2)	14 (4.1)	27 (7.9)	98 (28.6)
78 to <114 weeks	4 (1.2)	6 (1.7)	14 (4.1)	21 (6.1)	94 (27.4)
≥114 weeks	0	0	0	0	2 (0.6)
Total (Any Duration)	15 (4.4)	17 (5.0)	36 (10.5)	57 (16.6)	218 (63.6)

Source: Table 5-10, p. 120, Integrated Summary of Safety.

7.2.4 Routine Clinical Testing

The routine clinical testing in the development program for pirfenidone included: serum chemistry, hematology, urinalysis with microscopy, pregnancy testing, and 12 lead ECGs. The routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workshop

7.3 Major Safety Results

7.3.1 Deaths

Deaths were classified in a number of different 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 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.

For the safety analysis, this reviewer will focus on treatment-emergent deaths and vital status-end of study deaths. Death will briefly be discussed in the safety section, but is more extensively covered in the efficacy section, as an important exploratory endpoint. Table 30 displays the number (%) of deaths in each treatment group by trial.

Table 30: Treatment Emergent and Vital Status Deaths: Trials 004 and 006			
	Pirfenidone 1197 mg/day	Pirfenidone 2403 mg/day	Placebo
	# events^a (%)	# events^a (%)	# events^a (%)
PIPF-004			
N randomized	87	174	174
Treatment Emergent	8 (9.2)	10 (5.7)	14 (8.0)
Vital Status – End of Study	10 (11.5)	14 (8.0)	20 (11.5)
PIPF- 006			
N Randomized		171	173
Treatment Emergent		9 (5.3)	15 (8.7)
Vital Status – End of Study		18 (10.5)	17 (9.8)
Trials 004 and 006 Combined			
N randomized	87	345	347
Treatment Emergent	8 (9.2)	19 (5.5)	29 (8.4)
Vital Status – End of Study	10 (11.5)	32 (9.3)	37 (10.7)
Treatment emergent: Death occurring after 1 st dose and within 28 days after last dose of study treatment (on-treatment)			
Vital Status: All deaths that occurred at any time during the study period irrespective of whether study treatment was continued			
Note: The number of deaths summarized in this table differs from the deaths described in Table 10: Disposition, because the disposition analysis includes only those patients who were ON study when they died. This safety table includes patients who had withdrawn from study but were being followed for vital status only.			
Source: Table 12-2, p. 171 and 12-8, p. 190, PIPF-004 CSR; Table 12-2, p. 156 and Table 12-8, p. 170, PIPF-006 CSR; Table 5-34, p. 190, ISS.			

Overall, there were numerically fewer treatment-emergent deaths in the pirfenidone HD treated patients (5.5%) vs. placebo treated patients (8.4%). There were a total of 56 treatment emergent deaths in both trials, and the percentage of deaths was lowest in the pirfenidone 2403 mg/day group compared with the placebo and pirfenidone 1197 mg/day groups (19 patients, 5.5%; 29 patients, 8.4%; and 8 patients, 9.2%, respectively). However, in PIPF-004, where two doses of pirfenidone were explored, no numerical dose response was demonstrated.

Table 31 summarizes the cause of treatment-emergent death in trials 004 and 006. Death was not adjudicated, but rather was based upon investigator judgment. As a result, the data with respect to cause of death should be interpreted carefully, due to the lack of adjudication and the possibility that treatment could have been unblinded by the side effects of pirfenidone.

Table 31: Summary of Cause of Treatment-Emergent Deaths in All Randomized Patients (Trials 004 and 006)

Cause of Death	Number of Patients , n (%)		
	Pirfenidone 1197 mg/d N = 87	Pirfenidone 2403 mg/d N = 345	Placebo N = 347
System Organ Class Preferred Term			
Number of Patients Who Died	8 (9.2)	19 (5.5)	29 (8.4)
Cardiac Disorders	0	1 (0.3)	4 (1.2)
Acute Myocardial Infarction	0	0	1 (0.3)
Arteriosclerosis Coronary Artery	0	0	1 (0.3)
Cor Pulmonale, Acute	0	0	1 (0.3)
Myocardial Infarction	0	1 (0.3)	1 (0.3)
Infections and Infestations	1 (1.1)	3 (0.9)	2 (0.6)
Pneumonia	0	2 (0.6)	2 (0.6)
Septic Shock	1 (1.1)	1 (0.3)	0
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	1 (1.1)	2 (0.6)	1 (0.3)
Bladder Cancer	0	1 (0.3)	0
Rectal Cancer	1 (1.1)	0	0
Small Cell Lung Cancer Metastatic	0	1 (0.3)	0
Small Cell Lung Cancer Stage Unspecified	0	0	1 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	6 (6.9)	13 (3.8)	22 (6.3)
Acute Respiratory Distress Syndrome	0	0	1 (0.3)
Acute Respiratory Failure	0	0	1 (0.3)
Hypoxia	0	1 (0.3)	1 (0.3)
Idiopathic Pulmonary Fibrosis	3 (3.4)	6 (1.7)	14 (4.0)
Pulmonary Hemorrhage	0	1 (0.3)	0
Respiratory Arrest	0	0	1 (0.3)
Respiratory Failure	3 (3.4)	5 (1.4)	4 (1.2)

Source: Table 5-35, p. 191, Integrated Summary of Safety, Module 5.

As shown in Table 31, IPF was the most common cause of death overall. Of the 19 treatment-emergent deaths in the pirfenidone 2403 mg/day group, the largest number were due to IPF (n = 6, 1.7%). Other cases were also classified as IPF-related deaths. These are discussed in detail in Section 6.1.5 Analysis of Secondary Endpoints and Survival.

7.3.2 Nonfatal Serious Adverse Events

Table 32 lists the treatment emergent serious adverse events (TE SAEs) which occurred in > 2 pirfenidone 2403 mg/day-treated patients and more frequently than in the placebo group in trials 004 and 006.

Table 32: Treatment Emergent Serious Adverse Events (TE SAEs) Occurring in > 2 patients in the Pirfenidone 2403 mg/day group and at a Greater Incidence than in the Placebo Group – All Randomized Patients (Trials 004 and 006)

System Organ Class Preferred Term	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 345)	Placebo (N = 347)
	n (%)		
Patients with Any TE SAE	28 (32.2)	113 (32.8)	109 (31.4)
Cardiac Disorders	11 (12.6)	21 (6.1)	17 (4.9)
Coronary Artery Disease	3 (3.4)	6 (1.7)	2 (0.6)
Atrial Fibrillation	3 (3.4)	3 (0.9)	2 (0.6)
Angina Pectoris	2 (2.3)	3 (0.9)	2 (0.6)
General Disorders	3 (3.4)	8 (2.3)	5 (1.4)
Chest Pain	0	4 (1.2)	0
Injury, Poisoning and Procedural Comp.	1 (1.1)	10 (2.9)	2 (0.6)
Fall	0	3 (0.9)	1 (0.3)
Neoplasms Benign, Malignant	5 (5.7)	12 (3.5)	17 (4.9)
Bladder Cancer	0	3 (0.9)	1 (0.3)
Nervous System Disorders	3 (3.4)	8 (2.3)	10 (2.9)
Syncope	1 (1.1)	3 (0.9)	1 (0.3)
Renal and Urinary Disorders	2 (2.3)	8 (2.3)	5 (1.4)
Renal Failure Acute	2 (2.3)	3 (0.9)	2 (0.6)
Respiratory, Thoracic& Mediastinal D/O	11 (12.6)	40 (11.6)	46 (13.3)
Pneumothorax	2 (2.3)	4 (1.2)	1 (0.3)

Source: Table 5-38, p. 200, ISS, Module 5.

The overall occurrence of treatment-emergent SAEs was equally distributed across treatment groups (31.4%-32.8%). In general, the numbers of patients experiencing individual TE SAEs were small, without striking imbalances noted, with the exception of those adverse events noted as follows. The greatest differences in number of patients in TE SAEs that occurred more often in the pirfenidone 2403 mg/day group than in the placebo group, respectively, are as follows:

- 1.7% (6 patients) vs. 0.6% (2 patients): coronary artery disease
- 1.2% (4 patients) vs. 0 patients: chest pain
- 1.2% (4 patients) vs. 0.3% (1 patient): pneumothorax
- 0.9% (3 patients) vs. 0.3% (1 patient): bladder cancer, fall, syncope

It is of note that there were 3 cases of bladder cancer reported as TE SAEs in the pirfenidone 2403 mg/day group. However, there were also 2 cases of transitional cell carcinoma identified in the placebo group, which alleviated the imbalance. Although the number of cases of bladder cancer is small (n=4 total) to comment definitively regarding causality, it is of interest to note that pre-clinical studies did identify the bladder as a target organ of toxicity. In a 6-month oral toxicology study in rats, bladder findings included inflammatory cell infiltration in the lamina propria, transitional cell hyperplasia, and crystals in the urine.

7.3.3 Dropouts and/or Discontinuations

Table 33 summarizes those adverse events that led to early discontinuation of study treatment in all randomized patients in trials 004 and 006. Of note, no AEs leading to discontinuation occurred in more than 1 subject in the pirfenidone 1197 mg/day group.

Table 33: Adverse Events Leading to Discontinuation of Study Treatment in ≥ 2 patients and at a Greater Incidence in the Either Pirfenidone Group than in the Placebo Group – All Randomized Patients (Trials 004 and 006)

TEAE Leading to Treatment Discontinuation	Number of Patients, n (%)	
	Pirfenidone 2403 mg/d (N = 345)	Placebo (N = 347)
Patients with any AE Leading to D/C	51 (14.8)	30 (8.6)
Idiopathic Pulmonary Fibrosis	10 (2.9)	9 (2.6)
Rash	5 (1.4)	0
Nausea	5 (1.4)	0
Bladder Cancer	3 (0.9)	0
Photosensitivity Reaction	3 (0.9)	1 (0.3)
Respiratory Failure	3 (0.9)	1 (0.3)
Weight Decreased	2 (0.6)	0

Source: Table 5-43, p. 217, Integrated Summary of Safety, Module 5.
 Note: There were no AEs leading to discontinuation in the pirfenidone 1197 mg/day group that occurred in more than 1 subject. Hence, this group is not depicted in this summary table.

Overall, 14.8% , 10.3%, and 8.6% of patients discontinued study treatment secondary to an AE in the pirfenidone 2403 mg/day, pirfenidone 1197 mg/day, and placebo groups, respectively. In general, the numbers of patients discontinuing secondary to any particular AE were small. Idiopathic pulmonary fibrosis was the most frequently reported AE leading to discontinuation of study treatment (2.9% pirfenidone-treated; 2.6% placebo). The greatest differences in number of patients that discontinued secondary to an adverse event between the pirfenidone and placebo groups, respectively, are as follows:

- 1.4% (5 patients) vs. 0 patients: rash
- 1.4% (5 patients) vs. 0 patients: nausea
- 0.9% (3 patients) vs. 0 patients: bladder cancer

Rash and nausea occur quite frequently with pirfenidone treatment and will be discussed further in the discussion of adverse events of interest. The imbalance in deaths from bladder cancer is corrected by 2 cases of transitional cell carcinoma and 1 case of bladder cancer that were also reported in the placebo group, that did not lead to discontinuation.

7.3.4 Significant Adverse Events

Treatment-emergent adverse events leading to dose reduction or interruption are summarized in Table 34.

Table 34: Treatment Emergent Adverse Events (TE AEs) Leading to Dose Reduction or Treatment Interruption Occurring in $\geq 2\%$ of patients and at a Greater Incidence in Either Pirfenidone Group than in the Placebo Group – (Trials 004 and 006)

System Organ Class Preferred Term	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 345)	Placebo (N = 347)
	n (%)		
Patients with Any TE SAE Leading to Dose Interruption or Reduction	37 (42.5)	160 (46.4)	64 (18.4)
Gastrointestinal Disorders	9 (10.3)	65 (18.8)	22 (6.3)
Nausea	3 (3.4)	27 (7.8)	7 (2.0)
Diarrhea	3 (3.4)	18 (5.2)	4 (1.2)
Vomiting	4 (4.6)	14 (4.1)	3 (0.9)
Dyspepsia	1 (1.1)	8 (2.3)	0
General Disorders	7 (8.0)	21 (6.1)	6 (1.7)
Fatigue	2 (2.3)	15 (4.3)	3 (0.9)
Asthenia	3 (3.4)	3 (0.9)	0
Investigations	4 (4.6)	24 (7.0)	10 (2.9)
ALT Increased	0	7 (2.0)	1 (0.3)
AST Increased	0	7 (2.0)	1 (0.3)
GGT Increased	3 (3.4)	5 (1.4)	2 (0.6)
Nervous System Disorders	6 (6.9)	16 (4.6)	6 (1.7)
Headache	2 (2.3)	6 (1.7)	0
Dizziness	2 (2.3)	2 (0.6)	2 (0.6)
Skin and Subcutaneous Tissue D/O	16 (18.4)	69 (20.0)	9 (2.6)
Rash	9 (10.3)	40 (11.6)	5 (1.4)
Photosensitivity Reaction	4 (4.6)	17 (4.9)	1 (0.3)
Pruritus	2 (2.3)	5 (1.4)	1 (0.3)

Source: Table 5-44, p. 223, Integrated Summary of Safety, Module 5.

The overall rates of patients having their dose reduced or treatment interrupted were higher in the two pirfenidone treatment groups than in the placebo group; 46.4% in the pirfenidone 2403 mg/day group, 18.4% in the placebo group and 42.5% in the pirfenidone 1197 mg/day group. The rates were highest in patients with adverse events in the SOCs of Skin and Subcutaneous Tissue Disorders and GI Disorders, which include events that were identified in the dose-modification guidelines for the Phase 3 protocols (see 5.3 Discussion of Individual Studies/Clinical Trials). The common TEAEs ($\geq 4\%$ of patients) that led to dose interruption or reduction that were reported more frequently by patients treated with pirfenidone than placebo included rash, nausea, diarrhea, photosensitivity reaction, vomiting, and fatigue.

7.3.5 Submission Specific Primary Safety Concerns

Before unblinding trials 004 and 006, the Applicant identified a number of clinically important events AEs of interest. These events of interest were identified based upon relevant non-clinical findings as well as human experience in previously conducted pirfenidone IPF clinical trials. After unblinding the safety data from trials 004 and 006, the Applicant refined the AEs of

interest to include only those AEs that occurred with an increased frequency in patients receiving pirfenidone. These adverse of interest are summarized in Table 35. Each category will be discussed following the table, with an emphasis on Hepatic and Skin Events.

Table 35: Treatment Emergent Adverse Events (TE AEs) of Interest Occurring in ≥ 2 patients in Any Treatment Group – All Randomized Patients (Trials 004 and 006)			
Adverse Event of Interest	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 345)	Placebo (N = 347)
	n (%)		
General Disorders			
Anorexia	9 (10.3)	37 (10.7)	13 (3.7)
Decreased Appetite	3 (3.4)	30 (8.7)	10 (2.9)
Dizziness	14 (16.1)	63 (18.3)	35 (10.1)
Fatigue	25 (28.7)	104 (30.1)	71 (20.5)
Weight Decreased	8 (9.2)	28 (8.1)	12 (3.5)
Cardiac Disorders			
Supraventricular Tachyarrhythmia	7 (8.0)	11 (3.2)	4 (1.2)
Ventricular Arrhythmia	2 (2.3)	4 (1.2)	2 (0.6)
Unspecified Arrhythmia	0	5 (1.4)	0
AV Block	2 (2.3)	6 (1.7)	0
Valvular incompetence	1 (1.1)	4 (1.2)	0
Bundle Branch Block	1 (1.1)	5 (1.4)	1 (0.3)
Syncope	1 (1.1)	8 (2.3)	10 (2.9)
Gastrointestinal Events			
Diarrhea	22 (25.3)	99 (28.7)	67 (19.3)
Nausea	22 (25.3)	125 (36.2)	60 (17.3)
Dyspepsia	12 (13.8)	66 (19.1)	26 (7.5)
Gastroesophageal Reflux Disease	11 (12.6)	36 (10.4)	26 (7.5)
Stomach Discomfort	4 (4.6)	29 (8.4)	6 (1.7)
Vomiting	11 (12.6)	47 (13.6)	15 (4.3)
Hepatic Events			
ALT Increased	0	12 (3.5)	9 (2.6)
AST Increased	0	11 (3.2)	9 (2.6)
Blood Alkaline Phosphatase Increased	0	3 (0.9)	2 (0.6)
Blood Bilirubin Increased	0	2 (0.6)	1 (0.3)
Cryptogenic Cirrhosis	0	1 (0.3)	0
Gamma-Glutamyltransferase Increased	5 (5.7)	17 (4.9)	8 (2.3)
Hepatic Enzyme Increased	0	0	3 (0.9)
Hepatic Steatosis	0	1 (0.3)	2 (0.6)
Hepatitis	0	2 (0.6)	0
Hepatomegaly	0	0	1 (0.3)
Liver Function Test Abnormal	2 (2.3)	7 (2.0)	1 (0.3)
Transaminases Increased	0	3 (0.9)	0
Yellow Skin	0	1 (0.3)	0
Skin Events			
Photosensitivity Reaction	6 (6.9)	42 (12.2)	6 (1.7)
Rash	15 (17.2)	111 (32.2)	40 (11.5)

Source: Section 5.3.4, p. 224-313, Integrated Summary of Safety, Module 5.

- **General disorders**

Anorexia, decreased appetite, fatigue, dizziness, and decreased weight were frequently reported adverse events of interest. Although reported by a moderate percentage of patients in the pirfenidone groups versus the placebo group, no patients treated with pirfenidone were hospitalized, however, 2 patients did discontinue study treatment due to weight loss (see Table 33). Most of the adverse events listed in this section reflect tolerability issues that were not associated with significant sequelae, however, these types of events did lead to dose interruption in 6% of patients

- **Cardiac disorders (arrhythmias)**

After the review of the integrated safety data from trials 004 and 006, the Applicant noted an imbalance in the cardiac arrhythmia SMQ (standard MedDRA query). Additionally, there were non-clinical findings in the rat toxicology studies that indicated that the heart may be a target organ of toxicity. In order to investigate this signal, composite categories of selected cardiac treatment-emergent adverse events (as outline in Table 35) were generated post-hoc. In general, supraventricular tachyarrhythmia was the most frequently reported cardiac disorder in the pirfenidone 2403 mg/day group (11 patients, 3.2%). Overall, the numbers of cardiac disorders, both conduction and structural abnormalities, were small. It is difficult to identify whether or not these events could be related to pirfenidone, because the elderly population under study is prone to such events at baseline. Of those patients with reported arrhythmias, there were no deaths, and study treatment was discontinued in only one patient experiencing a ventricular arrhythmia.

Reviewer's comment: Although the Applicant provides rationale as to the unrelatedness of cardiac events to study treatment, the relationship is still unclear. If pirfenidone is to be approved for marketing, physicians will need to be instructed in the proper monitoring for cardiac events in their patients.

- **Gastrointestinal Events**

Gastrointestinal events of diarrhea, nausea, dyspepsia, reflux, stomach discomfort, and vomiting were frequently reported by more patients in the pirfenidone treatment groups than in those taking placebo. The events were generally mild-to-moderate in severity. Dose adjustment for GI events was required in about 20% of patients, and 2.3% of patients in the pirfenidone 2403 mg/day group discontinued treatment due to a GI event. The GI events that led to dose modification included nausea, diarrhea, and vomiting. Of the GI events discussed in this section, two patients treated with pirfenidone 2403 mg/day experience GERD categorized as an SAE.

Reviewer's comment: The Applicant recommends that emphasis be placed on taking pirfenidone with food and following the dose escalation guidelines over 2 weeks to minimize these GI adverse events.

• **Hepatic Events:**

Liver-related laboratory outcomes are summarized in Table 36.

Table 36: Liver-Related Laboratory Abnormalities (trials 004 and 006)			
Laboratory Test Result	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 345)	Placebo (N = 347)
AST or ALT			
>3 x ULN	0	14 (4.1%)	2 (0.6%)
>5 x ULN	0	3 (0.9%)	2 (0.6%)
≥10 x ULN	0	1 (0.3%)	1 (0.3%)
≥20 x ULN	0	0	1 (0.3%)

Source: Table 5-67, p. 277, Integrated Summary of Safety, Module 5.
 AST: aspartate aminotransferase; ALT: alanine aminotransferase; ULN: upper limit of normal

Fourteen (4.1%) patients treated with pirfenidone 2403 mg/day developed AST or ALT levels that were >3 times ULN, compared with 2 (0.6%) placebo-treated patients and 0 patients treated with pirfenidone 1197 mg/day. Three (0.9%) patients in the pirfenidone 2403 mg/d group and 2 (0.6%) in the placebo group developed transaminase elevations that were >5 times ULN. Of these, 1 patient each in the pirfenidone 2403 mg/day and placebo groups, respectively, had AST or ALT levels ≥ 10 times ULN. Only one patient in the placebo group developed transaminase elevations that ≥ 20 times ULN. However, there were two notable cases in both the InterMune and Shionogi development programs that are noteworthy, as they may have met criteria for Hy’s Law.

Reviewer’s comment: Hy’s Law describes severe liver injury defined as instances of transaminase elevation accompanied by elevated bilirubin (even if obvious jaundice was not present). These cases have been associated with, and have often predicted, post-marketing serious liver injuries (fatal or requiring transplant). The estimated mortality of such cases is 10%. The rationale here is that hepatocellular injury great enough to interfere with bilirubin excretion involves a large fraction of the liver cell mass (7). Per the Guidance for Industry: Drug Induced Liver Injury: Premarketing Clinical Evaluation, July 2009, the criteria for Hy’s Law are: 1) ALT or AST >3 x ULN in concert with a serum bilirubin >2 x ULN, without initial findings of cholestasis (i.e. elevated alkaline phosphatase) and, 2) no other reason for these elevations, such as viral hepatitis, pre-existing or acute liver disease, or another drug.

Although per central laboratory findings, no patients in the InterMune phase 3 trials met the criteria for Hy’s Law, in one case, a local laboratory reported results that showed elevations in transaminases and total bilirubin that did meet the criteria, but another drug could also have been the culprit. In addition, there was one case in the phase 2 Shionogi trial that also met the criteria for Hy’s Law. These two cases are described below:

InterMune

Patient PIPF-006-30017027, a 69-year-old Caucasian female, was randomized to receive pirfenidone 2403 mg/d. The patient had mild elevations of AST, ALT, and GGT at Baseline, but had no history of prior liver disease. She began a reduced dose of study drug (1 capsule TID) on Day 83 due to fatigue and developed worsening fatigue and yellow skin on Day 313. Laboratory results on Day 316 showed Grade 3 elevations in serum ALT ($7 \times$ ULN), AST ($6 \times$ ULN), total bilirubin ($4 \times$ ULN) and alkaline phosphatase ($10 \times$ ULN). Symptoms of hepatitis occurred 20 days after completion of 10-day course of amoxicillin-clavulanate for a respiratory tract infection (Days 284–293). Pirfenidone therapy was interrupted from Day 322 until Day 406 and then resumed at a dose of 1 capsule TID. Although the investigator attributed the liver injury to amoxicillin-clavulanate, pirfenidone was discontinued on Day 450 due to decision by the sponsor (following the protocol); however, there was no recurrence of transaminitis or hyperbilirubinemia during rechallenge. It was felt by the investigator that the likely etiology of this patient's abnormal LFTs was a drug-induced hepatitis due to amoxicillin-clavulanate rather than pirfenidone, based on the cholestatic presentation, the lack of liver function abnormality during the first 10 months of pirfenidone therapy, the onset of injury approximately 3 weeks after exposure to amoxicillin-clavulanate and the lack of recurrence on rechallenge with pirfenidone.

Shionogi

Patient SP2-02-04 was a 47-year-old male randomized to receive placebo during the blinded phase of the SP2 trial, with no past medical history of liver disease. LFTs were within normal limits at the time of study entry into the blinded phase of the trial and on the first day of pirfenidone 1800 mg/d therapy in the open-label phase of the study. On Day 49, he developed general malaise and anorexia and became jaundiced. On Day 56, laboratory test results showed marked elevations of AST (671 IU/L) and ALT (1590 IU/L), as well as hyperbilirubinemia (197 μ mol/L), elevated alkaline phosphatase (696 IU/L, approximately $2 \times$ ULN), and moderate prolongation of prothrombin and activated partial thromboplastin times. Also on Day 56, pirfenidone was discontinued and abdominal ultrasound was negative for biliary obstruction. Laboratory tests were negative for hepatitis A, B, or C infection. A mild eosinophilia (12%) was present on Day 57. By Day 72, LFT abnormalities were improved; however, the patient developed fever with concomitant pneumonia that led to respiratory decompensation and death on Day 88. Pathological autopsy results showed the cause of death to be respiratory failure and pulmonary fibrosis, with macroscopically discernible causes to be pulmonary congestion and pronounced fibrosis. Shionogi does not have an autopsy report of the liver and does not know whether the liver was sampled.

Based upon the two cases described above, hepatocellular injury due to pirfenidone cannot be ruled out. Of note, there were no liver-related deaths reported in any treatment group in trials 004 or 006. It is also noteworthy that liver findings tended to occur within the first 6-7 months of exposure. Of the 14 patients in the pirfenidone group who developed AST or ALT levels > 3 times ULN, 10 developed the elevations within the first 30 week of exposure to pirfenidone.

- **Skin Events:**

Non-clinical findings as well as previous experience from earlier clinical trials identified both photosensitivity reactions and rash as adverse events of interest. As shown in Table 35, 42 (12.2%) patients treated with pirfenidone 2403 mg/d reported a photosensitivity reaction, compared with 6 (6.9%) patients treated with pirfenidone 1197 mg/day, and 6 (1.7%) patients treated with placebo. Across the three treatment groups, the majority of patients had a single event, most events resolved, and the median duration of the photosensitivity reactions was approximately 3 months in the pirfenidone 2403 mg/d group, compared with 2 months in the placebo group. Nearly half of the patients in the pirfenidone 2403 mg/d group who reported photosensitivity reaction first did so between Weeks 0 and 18.

As shown in Table 35, 111 (32.2%) patients treated with pirfenidone 2403 mg/d reported rash, compared with 40 (11.5%) patients treated with placebo, and 15 (17.2%) patients treated with pirfenidone 1197 mg/d. Across the three treatment groups, most patients had a single event and the majority of events resolved. The median duration of rash was approximately 1 month (38 days, 31 days, and 24 days in the pirfenidone 2403 mg/d, placebo, and pirfenidone 1197 mg/d groups, respectively). Most patients in the pirfenidone 2403 mg/day group who reported a rash first did so between Weeks 0 and 30.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 37 lists the common adverse events that occurred in $\geq 8\%$ of pirfenidone 2403 mg/day treated patients and more frequently than in placebo.

Table 37: Treatment Emergent Adverse Events Occurring in ≥ 8% of Patients In The Pirfenidone 2403 mg/day Treatment Group and More Frequently Than Placebo – All Randomized Patients (Trials 004 and 006)

System Organ Class Preferred Term	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 345)	Placebo (N = 347)
	n (%)		
Patients with Any Common TEAE	85 (97.7)	336 (97.4)	326 (93.9)
Gastrointestinal Disorders	53 (60.9)	254 (73.6)	173 (49.9)
Nausea	22 (25.3)	125 (36.2)	60 (17.3)
Diarrhea	22 (25.3)	99 (28.7)	67 (19.3)
Dyspepsia	12 (13.8)	66 (19.1)	26 (7.5)
Vomiting	11 (12.6)	47 (13.6)	15 (4.3)
Gastroesophageal Reflux Disease	11 (12.6)	36 (10.4)	26 (7.5)
Constipation	9 (10.3)	34 (9.9)	33 (9.5)
Abdominal Distension	3 (3.4)	33 (9.6)	20 (5.8)
Stomach Discomfort	4 (4.6)	29 (8.4)	6 (1.7)
General Disorders	39 (44.8)	147 (42.6)	112 (32.3)
Fatigue	25 (28.7)	104 (30.1)	71 (20.5)
Infections and Infestations	59 (67.8)	232 (67.2)	231 (66.6)
Sinusitis	7 (8.0)	48 (13.9)	40 (11.5)
Urinary Tract Infection	6 (6.9)	35 (10.1)	29 (8.4)
Investigations	12 (13.8)	43 (12.5)	20 (5.8)
Weight Decreased	8 (9.2)	28 (8.1)	12 (3.5)
Metabolism and Nutrition Disorders	12 (13.8)	65 (18.8)	22 (6.3)
Anorexia	9 (10.3)	37 (10.7)	13 (3.7)
Decreased Appetite	3 (3.4)	30 (8.7)	10 (2.9)
Musculoskeletal & Conn. Tissue D/O	33 (37.9)	92 (26.7)	84 (24.2)
Arthralgia	9 (10.3)	36 (10.4)	24 (6.9)
Back Pain	15 (17.2)	35 (10.1)	28 (8.1)
Nervous System Disorders	23 (26.4)	107 (31.0)	79 (22.8)
Headache	14 (16.1)	65 (18.8)	56 (16.1)
Dizziness	14 (16.1)	63 (18.3)	35 (10.1)
Psychiatric Disorders	21 (24.1)	64 (18.6)	52 (15.0)
Insomnia	13 (14.9)	34 (9.9)	23 (6.6)
Respiratory, Thoracic , Mediastinal D/O	55 (63.2)	196 (56.8)	207 (59.7)
Cough	32 (36.8)	103 (29.9)	100 (28.8)
Skin and Subcutaneous Tissue Disorders	28 (32.2)	152 (44.1)	62 (17.9)
Rash	15 (17.2)	111 (32.2)	40 (11.5)
Photosensitivity Reaction	6 (6.9)	42 (12.2)	6 (1.7)

Source: Table 5-24, p. 159, Integrated Summary of Safety, Module 5.
 Note: Patients could be counted more than once for different TEAEs.

Nearly all patients in the pirfenidone 2403 mg/day group, the placebo group, and the pirfenidone 1197 mg/day group, respectively, experienced a common treatment emergent adverse event (TEAE): 97.4%, 93.9%, and 97.7%. The most frequently occurring TEAEs occurred in the following system organ classes (SOCs), in order of decreasing frequency: gastrointestinal,

infections and infestations, respiratory, skin, general, musculoskeletal, nervous system, metabolism/nutrition, psychiatric, and investigations. The most frequently occurring gastrointestinal TEAEs were nausea, diarrhea, dyspepsia, and vomiting. Each of these gastrointestinal adverse effects demonstrated a dose response, occurring most frequently in pirfenidone 2403 mg/day, followed by pirfenidone 1167 mg/day, and lastly, placebo. Similarly, other AEs that demonstrated a dose response were: fatigue, sinusitis, anorexia, decreased appetite, dizziness, rash, and photosensitivity reaction. Of note, IPF was reported as an AE in 10.3%, 15.9%, and 21.3% of patients in the pirfenidone 1197 mg/day, pirfenidone 2403 mg/day, and placebo groups, respectively (not shown in Table 37). This analysis of common adverse events is consistent with the pre-specified “adverse events of interest”, based upon the prior experience with pirfenidone in earlier studies.

Reviewer’s Comment: Given the proposed mechanism of action (inhibition of TNF), the PADAC raised the issue as to whether there was an imbalance in the number of infections in the patients treated with pirfenidone. As can be seen in the table above, although numerically, there were slightly more cases of sinusitis and urinary tract infection in the pirfenidone 2403 mg/day group, there was no suggestion of a dose response.

7.4.2 Laboratory Findings

Overall, the mean changes in hematology, chemistry, and urinalysis parameters did not demonstrate any clinically significant change and were similar across treatment groups. When laboratory tests were examined by shifts, in which a patient shifted from either Grade 0, 1, or 2 to Grade 3 or 4, the following parameters were found to have an imbalance:

Reviewer’s comment: Grading system used is the modified NCI Common Toxicity Criteria.

- ALT/AST: a detailed discussion of this laboratory parameter is located in Section 7.3.5 Submission Specific Primary Safety Concerns.
- Hyponatremia: 8 patients in the pirfenidone group, 1 patient in the placebo group.
- Hypophosphatemia: 9 patients in the pirfenidone group, 3 patients in the placebo group.
- Lymphopenia: 6 patients in the pirfenidone group, 0 patients in the placebo group.

A marked laboratory abnormality on study treatment was defined as any Grade 4 laboratory test result, or any change in toxicity from Baseline of at least 3 grades, using the modified CTCAE toxicity grading scale. Laboratory tests in which 3 or more patients met the criteria for having a marked abnormality are presented in Table 38.

Table 38: Marked laboratory abnormalities that occurred in ≥ 3 patients with Normal Values at Baseline (Trials 004 and 006)

Laboratory Abnormality	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 345)	Placebo (N = 347)
	n		
Hyperglycemia	1	4	3
Hyponatremia	2	5	0
Hypophosphatemia	1	6	3
GGT	0	3	3
Lymphopenia	1	5	0
Hyperuricemia	3	3	7

Source: Table 5-88, p. 335, Integrated Summary of Safety, Module 5.

7.4.3 Vital Signs

No clinically significant mean changes in systolic or diastolic blood pressure, heart or respiratory rate, or body temperature were observed during treatment in patients in trials 004 and 006. A gradual decrease in mean weight was observed with pirfenidone 2403 mg/day compared with placebo at Week 12 through Week 72. Between the sexes, weight loss with pirfenidone 2403 mg/d was generally less in males than in females at Week 24 through Week 72. At Week 72, the change in mean weight with pirfenidone 2403 mg/d in males and females, respectively, was -3.2 and -3.9 kg compared with -0.7 and -0.5 kg in the placebo group. In the pirfenidone 1197 mg/d group, the magnitude of weight loss was less than that in the pirfenidone 2403 mg/d group and greater than that in the placebo group, thereby suggesting a dose-response relationship with pirfenidone and patient weight loss (-1.3 kg and -1.9 kg, males and females, respectively).

Reviewer's comment: The weight loss seen with pirfenidone treatment is likely due to the tolerability effects as already mentioned in the review of adverse events (i.e. anorexia, decreased appetite, etc).

7.4.4 Electrocardiograms (ECGs)

A total of 5 patients (3 in the pirfenidone 2403 mg/d group, 0 in the pirfenidone 1197 mg/d group, 2 in the placebo group) had a TEAE reported of prolonged QT interval. In 3 of the 5 patients, an ECG with QTcB >500 ms was documented at the time of the event; in only 1 (placebo) patient was the dose modified. Two of the 5 patients had no available ECG that documented QT interval prolongation. Four events were considered mild and 1 was moderate. In no pirfenidone-treated patient were cardiac TEAEs reported concurrently with the TEAE of prolonged QT interval.

The clinical findings with respect to QT prolongation in the phase 3 program are of particular relevance, because although a thorough QT study found that pirfenidone did not prolong the QTc

interval, there were several limitations. The assay sensitivity could not be established because the QTc-time profile of moxifloxacin (the positive control) was highly variable and did not follow the expected time course. Also, the supra-therapeutic dose (1335 mg TID), did not cover the maximum pirfenidone exposure increase with co-administration of fluvoxamine, a strong CYP1A2 inhibitor. All ECGs performed during trials 004 and 006 were sent for assessment to a central laboratory after completion of the trials. Based on the analysis of the ECGs, no clear evidence of a pirfenidone-related effect on heart rate, cardiac depolarization, or QT prolongation was found.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Based upon the evaluation of AEs by mean daily dose for those AEs that occurred in $\geq 5\%$ of patients in any dose category, a suggestion of dose response is observed for the following events: nasopharyngitis, urinary tract infection, upper respiratory tract infection, dizziness, cough, bronchitis, dyspnea, IPF, photosensitivity reaction, and rash.

7.5.3 Drug-Demographic Interactions

Based on sub-group analysis of adverse events by sex, race, and age, no meaningful difference were detected between patients in the pirfenidone groups and the placebo groups.

7.5.4 Drug-Disease Interactions

Renal Impairment

Clearance of the major metabolite (5-carboxy-pirfenidone) is highly correlated with creatinine clearance (CrCl), such that clearance of the metabolite decreased in a linear fashion with decreasing creatinine clearance. Following a single oral dose of 801 mg pirfenidone, the systemic exposure ($AUC_{0-\infty}$) to pirfenidone increased ~ 1.4 , 1.5 , and 1.2 -fold in subjects with mild, moderate, and severe renal impairment, respectively. The corresponding AUC of 5-carboxy-pirfenidone increased ~ 1.7 , 3.4 , and 5.5 -fold, respectively. The renal clearance of 5-carboxy-pirfenidone decreased significantly. Per the Applicant and our own review, the major metabolite is not biologically active, and the increased exposure is covered by non-clinical data in animals. Pirfenidone has not been studied in patients with chronic renal failure requiring dialysis because of the expected low incidence of end stage renal disease in IPF patients

Reviewer's Comment: Approximately 75% of patients in the clinical trials had some mild-moderate renal impairment and review of the AE data does not suggest an increase in AEs in this population. Because of the increased exposure in patients with renal impairment, caution should be used in this patient population.

Hepatic Impairment

Results of study PIPF-011 demonstrated that subjects with moderate hepatic impairment have, on average, exposure ~60% higher than normal subjects. Following a single oral dose of 801 mg pirfenidone, the geometric mean of AUC_{0-inf} and C_{max} of pirfenidone increased ~1.6 and ~1.4-fold in subjects with moderate hepatic impairment, respectively. The geometric mean of AUC_{0-inf} of 5-carboxy-pirfenidone increased ~1.02 fold.

Reviewer's Comment: Patients with hepatic impairment were excluded from the clinical trials. Because of the increased exposure in patients with hepatic impairment, caution should be used in this patient population.

7.5.5 Drug-Drug Interactions

The results of study PIPF-005 indicated that co-administration of an antacid (Mylanta Maximum Strength Liquid) did not substantially affect the PK of pirfenidone in either fed or fasted subjects.

Results of study PIPF-010 indicate that co-administration of a strong CYP1A2 inhibitor resulted in 4.0-fold increase in AUC_{0-inf} and 1.7-fold increase in C_{max} of pirfenidone. No change in AUC_{0-inf} of 5-carboxy-pirfenidone was observed. Smoking reduced the systemic exposure (AUC_{0-inf}) to pirfenidone and 5-carboxy-pirfenidone by ~54% and 32%, respectively. Smokers appeared to have a more pronounced increase in systemic exposure to pirfenidone with co-administration of fluvoxamine. This was evident that AUC_{0-inf} of pirfenidone increased ~7-fold in smokers versus ~4-fold in non-smokers.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

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, thyroid follicular adenomas and carcinomas, and uterine adenocarcinomas. The relevance of tumor findings to humans is not clear.

Because the animal carcinogenicity studies were positive, a discussion of neoplasms in the clinical trials is warranted, although the studies were not powered or designed to specifically evaluate neoplasms. Overall, neoplasms occurred in 9-11% of patients. The most common neoplasm was basal cell carcinoma. The numbers of specific neoplasms were generally small and well-balanced across treatment groups. The phase 3 clinical program did not reveal neoplasm to be a safety signal with pirfenidone treatment.

7.7 Additional Submissions/Safety Issues

The Applicant submitted a safety update on January 26, 2010. The safety update includes all safety information in the Integrated Summary of Safety with additional safety data collected since the original ISS data cutoff. The median duration of pirfenidone treatment in the Safety Update Pirfenidone Patient Subset was 84 weeks, compared with 74 weeks in the ISS Pirfenidone Patient Subset and 73 weeks in the Randomized Patient Subset. Analysis of the Safety Update Pirfenidone Patient Subset included 789 patients with 1136 person-years of exposure to pirfenidone (compared with 345 patients with 483 person-years of exposure in the 2403 mg/d treatment group in the Randomized Patient Subset). Thus, the Safety Update Pirfenidone Patient Subset represents the most prolonged exposure to pirfenidone 2403 mg/d in all of the analyzed subsets. Despite the larger patient cohort and longer exposure to pirfenidone, however, the overall incidence and type of adverse events were similar to those reported during the phase 3 clinical trials.

The safety update was reviewed and revealed no new events in any clinical category that resulted in death, were irreversible, or carried serious morbidity. Specifically, no new hepatic events met criteria for Hy's law, and there were no reports of anaphylaxis, Stevens-Johnson syndrome, or toxic epidermal necrolysis. Events in the gastrointestinal and cardiac areas, as well as dizziness and fatigue, were similar to those described in the Randomized Patient Subset in the phase 3 trials. In summary, no new safety findings of concern were identified.

8 Post-market Experience

On October 16, 2008, the Pharmaceutical and Medical Devices Agency (PMDA) in Japan granted Shionogi marketing authorization for pirfenidone tablets (Pirespa 200 mg Tablet) for the treatment of patients with IPF. This represents the first marketing approval of pirfenidone anywhere in the world for any indication. Because this drug was designated as an orphan drug and there had been few subjects in domestic clinical trials at the time of its approval, the PMDA requested that Shionogi conduct a post-marketing surveillance program to further identify the safety and efficacy of treatment with pirfenidone in patients with IPF, including its long-term use.

As of June 11, 2009, InterMune received 31 safety reports of 44 SAEs in 31 patients. These included 10 deaths. Causes of death included cardio-respiratory arrest, IPF, cardiac failure, respiratory failure, interstitial lung disease, and pneumonia. The SAEs were distributed among multiple MedDRA system organ classes. No new safety signal is suggested based on these reports.

As of June 11, 2009, a total of 348 non-serious AEs in 213 patients were reported to InterMune. Consistent with the current understanding of the safety profile of pirfenidone, the most commonly reported AEs were similar to those seen in the InterMune phase 3 program, belonging

to the system organ classes of Gastrointestinal Disorders; Metabolic and Nutritional Disorders; and Skin and Subcutaneous Tissue Disorders.

Due to the limited number of events and their diverse distribution among different MedDRA System Organ Classes, review of these post-marketing SAEs and AEs does not provide evidence for the emergence of any new safety signal.

9 Appendices

9.1 Literature Review/References

1. Collard HR et al. Changes in Clinical and Physiologic Variables Predict Survival in Idiopathic Pulmonary Fibrosis. *Am J. Respir Crit Care Med* 2003; 168: 538-42.
2. Flaherty KR et al. Prognostic Implications of Physiologic and Radiographic Changes in Idiopathic Interstitial Pneumonia. *Am J. Respir Crit Care Med* 2003; 168: 543-48.
3. King TE et al. Analyses of Efficacy End Points in a Controlled Trial of interferon- γ 1b for Idiopathic Pulmonary Fibrosis. *Chest* 2005; 127: 171-77.
4. American Thoracic Society Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. *Am J. Respir Crit Care Med* 2000; 161: 646-664.
5. Hirano A, Kanehiro A, Ono K, Ito W, Yoshida A, et al. 2006. Pirfenidone modulates airway responsiveness, inflammation, and remodeling after repeated challenge. *Am J Respir Cell Mol Biol* 35(3):366–377.
6. InterMune, Inc. 2004. PCLN-PIRF-010. Pirfenidone report. Investigations on the mechanisms of action of pirfenidone. Ono RS1083-T40. On file at InterMune, Inc., Brisbane, CA.
7. Zimmerman HJ. Drug-induced liver disease. In: *Hepatotoxicity The Adverse Effects of Drugs and Other Chemicals on the Liver*. Appleton-Century-Crofts, New York, 1978, 1999.

9.2 Labeling Recommendations

A line-by-line labeling review is ongoing and will not be complete by the time this review is finalized. High level labeling issues from a clinical standpoint include:

- Indication: The propose indication includes a statement about reducing the decline in lung function. If this product is to be approved, this indication may need to be modified to something more general because only one trial was positive for the lung function endpoint.
- Warnings and Precautions: The two precautions included (hepatic events and photosensitivity) are reasonable, but more data needs to be provided in these sections with respect to what events occurred during the clinical trials. An additional section regarding GI effects should also be added.
- Clinical Studies: This section will need to reflect all the data, including the failed Trial 006. A discussion about whether the responder analysis should be included is also necessary.
- Patient Counseling Information: This section likely needs to contain some information for the patient about seeking dose modification in the likely event that they experience an adverse reaction.

9.3 Advisory Committee Meeting

On March 9, 2010, the Division and InterMune discussed the findings from the pirfenidone NDA at a Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting. The open public hearing was filled with patients desperate for a treatment for IPF. Questions were asked about 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 (9 yes, 3 no) that the safety data were adequate for patients with IPF. Regarding the approval question, the results were in favor of approval (9 yes, 3 no). Two individuals who voted that there was not sufficient efficacy data voted for approval of pirfenidone.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	Esbriet (pirfenidone capsules)

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
04/01/2010

SALLY M SEYMOUR
04/01/2010

MEDICAL OFFICER REVIEW
Division Of Pulmonary and Allergy Products (HFD-570)

APPLICATION: NDA # 22-535	TRADE NAME: Esbriet
APPLICANT: InterMune	USAN NAME: Pirfenidone
MEDICAL OFFICER: Banu Karimi-Shah, MD	
TEAM LEADER: Sally Seymour, MD	CATEGORY: Anti-fibrotic/Anti-inflammatory
REVIEW DATE: January 8, 2010	ROUTE: Oral

SUBMISSIONS REVIEWED IN THIS DOCUMENT

<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
November 4, 2009		Original NDA	Electronic Submission

REVIEW SUMMARY:

This is a medical officer 45-day Filing Review of NDA 22-535 for Pirfenidone. InterMune, Inc. has developed pirfenidone as an oral capsule for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is a new molecular entity (NME) in a new pharmacologic class. FDA has granted pirfenidone orphan drug status and fast track designation. Pirfenidone is formulated as a hard gelatin capsule for oral administration. The dosage strength is 267 mg per capsule. The proposed dose/dosing interval follows a pre-specified dose escalation schema, with a final targeted dose proposed to be 2403 mg/day divided into three doses. Pirfenidone (Pirespa®, Shinogi & Co., Ltd.) formulated as a 200 mg tablet, was approved for the treatment of IPF in Japan in October 2008.

This NDA includes 14 controlled and uncontrolled clinical studies of pirfenidone in healthy subjects and patient with IPF conducted by InterMune, Shinogi, and Marnac. An additional long-term open label safety study is ongoing and will be included in the 120-day safety update. Of the 14 studies in the development program, PIPF-004 and PIPF-006 (subsequently referred to as 004 and 006) are the two pivotal studies submitted to provide substantial evidence of efficacy and safety for pirfenidone in IPF patients. The submission is provided in eCTD format.

The Applicant has included the necessary elements (21 CFR 314.50) in this NDA, and therefore the submission is fileable. Given that this is a new molecular entity, in a new pharmacologic class, for an indication which has no FDA-approved therapies, a DSI consult has been requested. The most substantial approvability issue that has been identified thus far is the failure of the program to replicate the efficacy results in two trials. Comments will be communicated to the Applicant in the 74-day letter.

OUTSTANDING ISSUES: None

RECOMMENDED REGULATORY ACTION

IND/NEW STUDIES:	<input type="checkbox"/> SAFE TO PROCEED	<input type="checkbox"/> CLINICAL HOLD
NDA/SUPPLEMENTS:	<input checked="" type="checkbox"/> FILEABLE	<input type="checkbox"/> NOT FILEABLE
	<input type="checkbox"/> APPROVAL	<input type="checkbox"/> APPROVABLE
OTHER ACTION:		<input type="checkbox"/> NOT APPROVABLE

I. General Information

InterMune, Inc. has developed pirfenidone as an oral capsule for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is a new molecular entity (NME) in a new pharmacologic class. FDA has granted pirfenidone orphan drug status and fast track designation. The mechanism of action is not fully established, but based on *in vitro* and animal data, pirfenidone has been shown to have both anti-fibrotic and anti-inflammatory properties. Pirfenidone is formulated as a hard gelatin capsule for oral administration. The dosage strength is 267 mg per capsule. The proposed dose/dosing interval follows the following dose escalation schema (per the proposed product label), with a final targeted dose proposed to be 2403 mg/day divided into three doses.

Treatment days	Total dose (mg/day)	Number of capsules
1-7	801	(1) 267 mg capsule three times a day with food
8-14	1602	(2) 267 mg capsules three times a day with food
15 +	2403	(3) 267 mg capsules three times a day with food

This NDA includes 14 controlled and uncontrolled clinical studies of pirfenidone in healthy subjects and patient with IPF conducted by InterMune, Shinogi, and Marnac. An additional long-term open label safety study is ongoing and will be included in the 120-day safety update. Of the 14 studies in the development program, PIPF-004 and PIPF-006 (subsequently referred to as 004 and 006) are the two pivotal studies submitted to provide substantial evidence of efficacy and safety for pirfenidone in IPF patients. The submission is provided in eCTD format.

II. Regulatory and Foreign Marketing History

A. Regulatory History

The regulatory history of pirfenidone dates back to the 1970s when its development was first begun by Marnac, Inc. The regulatory history is briefly outlined below.

- Mid 1970's: Marnac, Inc. initiated development of pirfenidone
 - Marnac conducted several small uncontrolled studies
 - In the 1990s, Marnac initiated compassionate use and Phase 2 controlled trials in IPF and pulmonary fibrosis patients
 - The formulation was a 400 mg capsule with dosing based on body weight.
- 1997: Shinogi acquires rights to develop pirfenidone in Japan, S. Korea, and Taiwan
 - Shinogi completed 2 randomized, double-blind, placebo-controlled trials of 1800 mg/day (Trials SP2 and SP3)
 - October 2008: Pirespa (pirfenidone 200 mg tablet) was approved for marketing by the Japanese Ministry of Health
- March 2002: InterMune acquired the worldwide rights from Marnac (with the exception of Japan, S. Korea, and Taiwan, which were owned by Shinogi)
- April 2003: IND 67,284 for pirfenidone became active
 - InterMune terminated the compassionate use protocols and limited Phase 2 IPF trials conducted by Marnac due to poor patient enrollment and lack of compliance with good clinical practices.
- March 2005: End of Phase 2 Meeting (EOP2)

The following key issues/comments were discussed:

 - The Agency cautioned that dose/dosing interval were not thoroughly explored in Phase 2. To circumvent this issue, the Agency suggested that an additional dose arm be added to Phase 3.
 - The Agency noted that a single study would not be adequate unless results were “highly clinically and statistically persuasive” and that all available data would be examined to either support or weaken reliance on a single trial
 - The Agency noted the lack of knowledge regarding mechanism of action as a limitation.
 - The proposed primary endpoint (EP) was time to death or to disease progression (relative decline in the % predicted FVC of $\geq 10\%$ on 2 consecutive visits). The applicant also proposed to use FVC $\geq 10\%$ as a surrogate for mortality.
 - Agency voiced concerns regarding surrogate endpoint and stated that mortality would be the ideal endpoint
 - Agency said that if the sponsor proceeded with the proposed primary EP, the efficacy of pirfenidone would not be based solely on winning

on the primary EP, but what drives the EP. If the EP was driven mostly be the decrease in FVC, this would be less compelling.

- May 2005: Special Protocol Assessments for PIPF-004 and PIPF-006
The protocols were powered to detect a difference of 3.5% in predicted FVC between treatment groups. The Agency commented that although this number could be used to aid in the adequate powering of their studies, the Agency did not necessarily agree that this was the minimally important difference.
- September 2008: pre-NDA meeting
 - The Agency reiterated its concern with the primary endpoint
 - The Agency re-emphasized that decline in FVC was not an established surrogate for mortality and further, that the clinically meaningful difference in FVC is unknown.
 - The Agency stated that since the applicant had chosen to use FVC as the primary endpoint, the totality of the data would be examined to determine what was driving the primary endpoint. It would also be important for the secondary endpoints (many of which are clinically meaningful to patients) to support the primary endpoint
 - Because of the difference in trial design, dosing regimens, etc, the Marnac studies should not be incorporated into the Integrated Summary of Efficacy, but a safety summary from these trials should be included in the Integrated Summary of Safety.
 - PIPF-004 and PIPF-006 were to be the pivotal clinical trials.

B. Foreign Marketing History

Pirfenidone (Pirespa®, Shinogi & Co., Ltd.) formulated as a 200 mg tablet, was approved for the treatment of IPF in Japan in October 2008.

III. Items Required for Filing

A. Necessary Elements (21 CFR 314.50)

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin	X			

	Content Parameter	Yes	No	NA	Comment
	(<i>e.g.</i> , are the bookmarks adequate)?				
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (<i>i.e.</i> , Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (<i>i.e.</i> , appropriately designed dose-ranging studies)?	X			
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			

	Content Parameter	Yes	No	NA	Comment
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i> , QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?		X		Given that this is an orphan disease, the exposure is acceptable.
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	X			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?			X	new pharmacologic class
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed;

	Content Parameter	Yes	No	NA	Comment
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

B. Decision

The submission appears adequate from a clinical standpoint to allow for further review, and is therefore fileable.

Reviewer's comment: Based on preliminary review of the product label, it appeared that the Applicant was using a Shinogi-sponsored study (SP3) as a pivotal trial to support the efficacy of pirfenidone, along with the 2 pivotal trials initiated by the applicant (PIPF-004 and PIPF-006). Review of the NDA submission revealed that only an English translation of the

Japanese clinical study report was included. The patient-level data, narratives, and case report forms were absent. If the Applicant had planned to use trial SP3 as a pivotal efficacy trial, the NDA submission would have been incomplete (21 CFR 314.101(d)(3) and 21 CFR 314.50) and this may have been a refuse-to-file issue. On December 11, 2009, the missing information was requested from the Applicant. The Applicant responded on December 14, 2009 that they did not have this Shinogi-owned data, and that the study report for SP3 was submitted only to serve as supportive information in this NDA. As a result, the application was deemed complete upon submission, and therefore FILEABLE.

An additional issue raised during the filing meeting was the lack of result replication, given that only 004 met the primary endpoint. Although traditionally, this might pose a refuse-to-file issue, given that IPF is an orphan disease, with no FDA-approved therapies, it was decided that the lack of replication of efficacy results would be a review issue, and not grounds upon which we would RTF.

IV. Clinical Studies

The NDA submission consists of 14 controlled and uncontrolled studies as outlined in the table below.

Study Number	Phase	Study Design	Study Objective	Subject Status/ Patient Diagnosis	Number Exposed Pirfenidone/ Control
Subjects					
InterMune-Sponsored					
PIPF-005	1	Uncontrolled	PK	Healthy	41/–
PIPF-007	1	RDBPC/AC	Thorough QTc	Healthy	81/81
PIPF-008	1	RDBPC	MTD/Safety	Healthy	16/4
PIPF-009	1	Uncontrolled	Renal Impairment	Renal or healthy	26/–
PIPF-010	1	Uncontrolled	DDI/PK	Healthy	54/–
PIPF-011	1	Uncontrolled	Hepatic Impairment	Hepatic or healthy	24/–
Patients					
InterMune-Sponsored					
PIPF-002	2	Uncontrolled	Safety and Efficacy	IPF/PF	83/–
PIPF-004	3	RDBPC	Safety and Efficacy	IPF	261/174
PIPF-006	3	RDBPC	Safety and Efficacy	IPF	171/173
PIPF-012 ^a	3	Uncontrolled	Safety	IPF	603/–
Marnac-Sponsored					
PIPF-001	2	RDBAC	Safety and Efficacy	IPF/PF	26/26
PIPF-003	2	RDBPC	Safety and Efficacy	IPF/PF	27/25
IPP/Exception	2	Uncontrolled	Safety	IPF/PF	34/–
Shionogi-Sponsored					
SP2	2	RDBPC	Safety and Efficacy	IPF	73/36
SP3	3	RDBPC	Safety and Efficacy	IPF	164/107

AC = active control; DDI = Drug-drug interaction; MTD = Maximum tolerated dose; PF = Pulmonary fibrosis; PK = Pharmacokinetics; RDBPC = randomized, double-blind, placebo-controlled

^a PIPF-012 treated 603 patients (dose of 2403 mg/d) from the Phase 3 studies PIPF-004 and PIPF-006, of whom 274 had received placebo and 329 had received pirfenidone. Data from this study will be included in the Safety Update.

The InterMune-sponsored clinical trials adhered to the International Conference on Harmonization (ICH) guidelines for Good Clinical Practice (GCP) and the relevant regulatory requirements. Subjects were accorded all rights granted by the Declaration of Helsinki. All protocols received approval by the appropriate governing investigational review board, ethics committee, or similar authority.

A. Pivotal Studies

Table 1: Pivotal Studies				
Study #	Study Type/ Design Total N	Age (yrs)	Treatment Groups (N)	Duration Centers/Sites
004	Efficacy/Safety R, DB, PC, PG N=435	45-81	Pirf 2403 mg/d [3 x 267 mg TID] (174) Pirf 1197 mg/d [3 x 133 mg TID] (87) Placebo (174)	72 weeks 64 sites in US, Europe, Australia
006	Efficacy/Safety R, DB, PC, PG N = 344	45-80	Pirf 2403 mg/d (3 x 267 mg TID) (171) Placebo (173)	72 weeks 46 sites in US, Europe, Australia

Legend: R: Randomized; DB: Double blind; PC: placebo-controlled; PG: parallel group; TID: three times daily

Trials 004 and 006 were two nearly identical multinational, randomized, double-blind, placebo-controlled Phase 3 trials of pirfenidone 2403 mg/day (given as three 267 mg capsules TID). Trial 004 also included a lower dose of 1197 mg/d (given as three 133 mg capsules TID). Duration of treatment was until 72 weeks after the last patient was randomized and patients who discontinued were required to continue with study assessments. Enrollment required a confident diagnosis of IPF (definite usual interstitial pneumonia, UIP, on HRCT); surgical lung biopsy was required only for diagnostic uncertainty. Patients were required to have an FVC \geq 50% predicted and a DLco \geq 35% predicted, while those with obstructive airways disease and those receiving concomitant medications for IPF were excluded. Additionally, in order to be included, patients could show no evidence of improvement in their disease over the year preceding enrollment.

The primary efficacy outcome in both clinical trials was change from Baseline in percent predicted FVC at Week 72, analyzed by a rank ANCOVA model.

Reviewer's comment: In such a model, patients with missing data due to death were ranked the worst, and missing data due to reasons other than death were imputed based on data from patients with similar FVC profiles. Dr. Feng Zhou, the Agency's biometrics' reviewer, has analyzed the data using varying models, in order to investigate if a change in the type of analysis would lead to markedly different results. This will be discussed further in the NDA review.

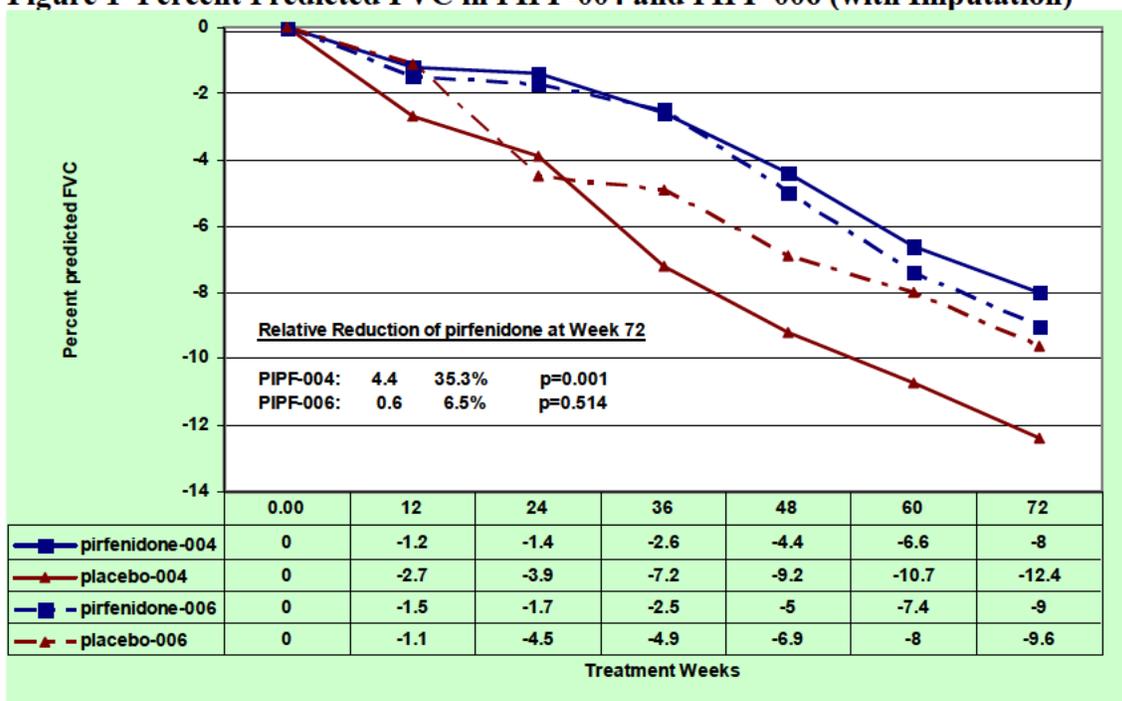
A total of 435 and 344 patients were enrolled at 64 and 46 sites in North America, Europe, and Australia, in PIPF-004 and PIPF-006, respectively. Baseline characteristics were generally balanced across treatment groups. Baseline characteristics across the two studies were also generally similar, except for a larger proportion of PIPF-006 patients 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 clinical trials, over 80% of patients completed study treatment and over 90% completed the study, when deaths and lung transplant patients are classified as completers. Less than 6% of patients in each study had missing data due to reasons other than death at the Week 72 primary endpoint assessment. The median duration of treatment in both PIPF-004 and PIPF-006 was greater than 72 weeks.

Primary Efficacy Analyses

In trial 004, the mean decline from Baseline at Week 72 in percent predicted FVC was significantly reduced in patients receiving pirfenidone 2403 mg/d compared to placebo (-8.0% vs. -12.4%, a 35% relative difference; p = 0.001, rank ANCOVA). Trial 006 showed no difference in the mean decline from Baseline in percent predicted FVC at Week 72 in patients receiving pirfenidone 2403 mg/d compared to placebo (-9.0% vs. -9.6%; p = 0.514, rank ANCOVA). These results are presented graphically in Figure 1.

Figure 1 Percent Predicted FVC in PIPF-004 and PIPF-006 (with Imputation)



Source: Dr. Feng Zhou, Biometric Reviewer

Reviewer’s comment: Although the pirfenidone groups declined similarly in both 004 and 006, the placebo group in 006 (dashed red line/red triangles) did not decline as much as the placebo group in 004 (solid red line), and hence the treatment difference was not statistically significant in this trial. Differences in the two placebo groups will require further investigation during the review process.

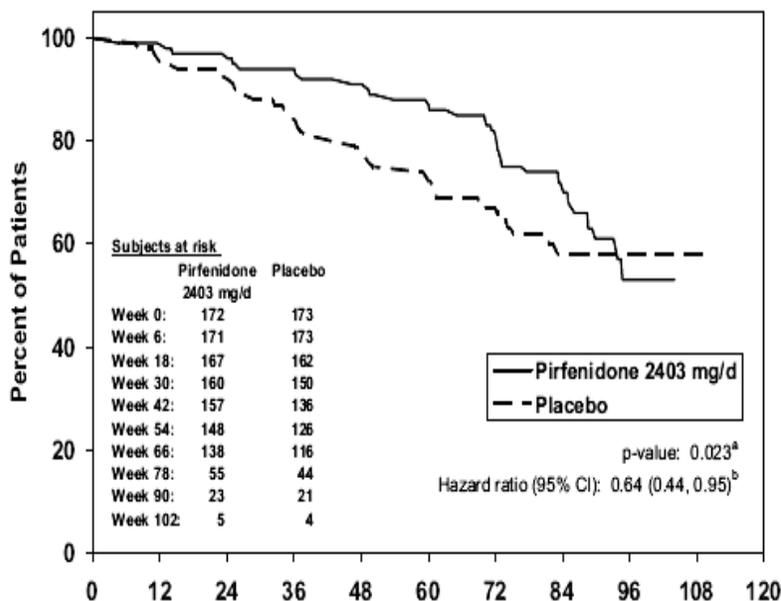
Reviewer’s comment: Given that the Applicant has chosen a lung function endpoint as their primary efficacy variable, the Division had stated during multiple interactions that replication of results would be required to provide substantial evidence of efficacy. However, in this submission, we have one study which meets the primary endpoint (004), and one that does not (006). The robustness and clinical significance of the results provided in 004 to provide substantial evidence of efficacy for pirfenidone in IPF patients will be a review issue.

Secondary Efficacy Analyses

Secondary efficacy endpoints included survival, change in FVC(L), 6MWT distance, change in percent predicted DLco, UCSD SOBQ, progression free survival, and worsening of IPF. Progression free survival was defined as the time to first occurrence of either a 10% absolute decline in percent predicted FVC, a 15% absolute decline in percent predicted DLco, or death. Time to worsening of IPF as defined as time to an acute IPF exacerbation, IPF-related death, lung transplantation, or respiratory hospitalization. The primary time point for all secondary efficacy analyses was at 72 weeks.

In trial 004, the only secondary endpoint that was statistically improved with pirfenidone treatment was progression free survival (PFS). In the Applicant’s PFS analysis, pirfenidone 2403 mg/day reduced the risk of death or disease progression by 36% compared with placebo (HR 0.64; 95% CI 0.44, 0.95; p=0.023, log rank). See Figure 2.

Figure 2 Time to Progression Free Survival (PIPF-004)



Reviewer’s comment: Although there is separation of the two treatment groups at Week 72, it is notable that the curves converge at Week 108.

Reviewer’s comment: 6MWT distance was the only secondary endpoint in favor of pirfenidone with a nominal p-value < 0.05 in PIPF-006, however, given that the study did not

meet its primary endpoint, discussion of secondary endpoints is not relevant in this preliminary overview of the data, with the exception of mortality, which is discussed below.

Survival

Although trials 004 and 006 had low power to assess survival, this endpoint is the most definitive outcome in IPF clinical trials. The analysis (performed by Dr. Feng Zhou) is summarized in Table 2 below. Of note, lung transplant patients were counted as “deaths” for the Agency’s analysis. In 004, only the results of the high dose (proposed to-be-marketed dose) are presented. The results are presented during the 72 week treatment period, and also at the end of the study period (included a 4 week follow-up).

Reviewer’s comment: Given the priority review timeline of this application, and the fact that only one study met its primary endpoint, mortality was examined in detail, to determine whether either study showed a statistically significant mortality benefit. This would be one instance in which a single study might be relied upon to provide substantial evidence of efficacy. Dr. Zhou’s analysis is presented below.

Table 2: Deaths in Studies 004 and 006			
Any Fatal Adverse Event (including lung transplant)	Placebo	Pirfenidone 2403 mg/day	Hazard Ratio (95% C.I.)
	# events (%)	# events (%)	
Study 004			
Sample size	174	174	
Treatment Period	22 (12.6%)	14 (8.0%)	0.61 (0.31, 1.18)
Treatment Period + F/U	24 (13.8%)	17 (9.8%)	0.66 (0.35, 1.23)
Study 006			
Sample size	171	173	
Treatment Period	20 (11.7%)	22 (12.7%)	0.91 (0.50, 1.67)
Treatment Period + F/U	22 (12.9%)	22 (12.7%)	1.01 (0.56, 1.82)
Studies 004 and 006			
Sample size	345	347	<i>Dr. Zhou’s analysis pending</i>
Treatment Period	42	36	
Treatment Period + F/U	46	39	
Source: Biometrics Reviewer, Dr. Feng Zhou			

As is shown in Table 2, neither trial demonstrated a statistically significant mortality benefit. Trial 004 did numerically favor the pirfenidone group, however, with a HR = 0.61 (NS). Trial 006 showed the fatal adverse events (deaths + lung transplants) to be numerically similar between treatment groups.

B. Supportive Studies

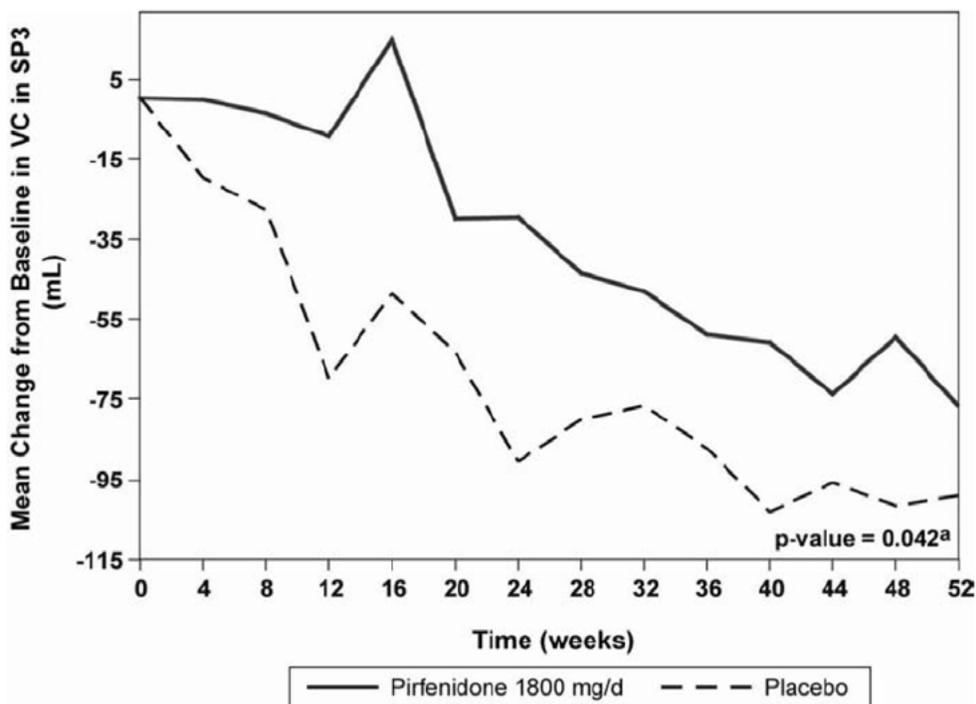
Table 3: Supportive Studies				
Study #	Study Type/ Design Total N	Age (yrs)	Treatment Groups (N)	Duration Centers/Sites
SP3	Efficacy/Safety R, DB, PC, PG N=275	37-74	Pirf 1800 mg/d [3 x 200 mg TID] (110) Pirf 1200 mg/d [2 x 200 mg TID] (56) Placebo (109)	52 weeks 73 sites in Japan

Legend: R: Randomized; DB: Double blind; PC: placebo-controlled; PG: parallel group; TID: three times daily

SP3 was a Shinogi sponsored trial that was the primary basis for approval of pirfenidone in Japan in October 2008. The Applicant has included the results of this study in the NDA submission. SP3 was a randomized, double-blind, placebo-controlled trial of pirfenidone 1800 mg/day, 1200 mg/day, and placebo in Japanese patients with IPF. The treatment duration was 52 weeks with a primary efficacy outcome defined as a change from baseline in vital capacity at week 52.

In the primary efficacy analysis, the mean decline from baseline in VC at week 52 was reported by the Applicant to be significantly reduced in patients receiving pirfenidone 1800 mg/day compared to placebo (-0.09 L vs. -0.16 L, relative difference 44%; p =0.042, ANCOVA). There was also a reduced mean decline in percent predicted VC at week 52 in the pirfenidone 1800 mg/d group compared with placebo (-2.91% vs. -5.13%; p = 0.044, ANCOVA). The results are depicted graphically in Figure 3 below.

Figure 3 Mean Change from Baseline in VC (mL) in trial SP3



Source: Clinical Overview, Module 2.

In an analysis of exacerbation-free survival (subsequently referred to as progression-free survival), pirfenidone 1800 mg/d reduced the risk of death or disease progression by 55% compared with placebo (HR 0.45: 95% CI, 0.11 to 0.79; p = 0.028, log-rank). There was no meaningful treatment effect on the other key secondary endpoint, minimum SpO₂ during the 6MET.

Reviewer's comment: There were many differences between 004/006 and SP3, and thus the ability of SP3 to provide even supportive information will be a review issue. Given that InterMune does not have the data, we cannot perform a substantive review of the results. Even if we could review the data, the differences in patient population, definition of IPF, dose of drug use, drug formulation, choice of endpoint, and treatment duration persist. Therefore the applicability of the results to this clinical development program is circumspect.

V. DSI Review / Audit

A DSI consult has been requested for this application because it is a new molecular entity for an indication which currently has no FDA-approved therapies. This application consists of 2 pivotal studies, PIPF-004 and PIPF-006. Given that only PIPF-004 met the primary endpoint, the sites requested for inspection are all a part of this protocol. Based on the analysis of the Biometrics' reviewer, Dr. Feng Zhou, there were no centers that were driving the results seen in PIPF-004. Therefore, we have chosen the sites in Table 4 below based on those sites with the highest enrollment, and results favoring the active treatment. Site selection was discussed via email with Anthony Orenca, the DSI primary reviewer, who had no additional site recommendations.

Table 4: Sites Selected for DSI Audit			
Site # (Name, Address, Phone number, email, fax#)	Protocol ID	Number of Subjects	Indication
Site #1016 James N. Allen, MD The Ohio State University 201 The Dorothy M. Davis Heart and Lung Research Institute 473 West 12 th Avenue Columbus, OH 43210 – USA Phone: 614-293-4925	PIPF-004	23	IPF
Site # 1001 1001 David Zisman, MD UCLA Division of Pulmonary & Critical Care 10833 Le Conte Avenue Room 37-121 CHS Box 951690 Los Angeles, CA 90095, - USA Phone: 310-825-8689	PIPF-004	18	IPF

VI. Brief Review of Proposed Labeling

Draft labeling in the new structured product label format is included in the electronic submission. A REMS that consists of a Medication Guide and a communication plan has been included. The serious risks have been identified as phototoxicity and hepatotoxicity.

(b) (4)

Reviewer's comment: Although the NDA submission treats SP3 as a "pivotal trial", the sponsor's response to our information request clearly states that it is only supportive data. The patient-level data for study SP3 are proprietary and belong to Shinogi, Inc. As a result, the results of this study cannot be confirmed,

(b) (4)

VII. Timeline for Review

Milestone	Target Date for Completion
Filing Planning Meeting	December 9, 2009
Filing Date	January 3, 2010
74 th Day Letter	January 17, 2010
Mid-Cycle Meeting	February 3, 2010
Full Labeling Meeting	TBD (previously scheduled meeting conflicts with AC)
Advisory Committee Meeting	March 9, 2010
Wrap-up Meeting	March 31, 2010
Primary Reviews	April 5, 2010
Draft CDTL Memo	April 9, 2010
Labeling Tcon with Applicant	April 12, 2010
CDTL Memo	April 12, 2010
Secondary Reviews	April 9, 2010
PDUFA Due Date	May 4, 2010

VIII. Summary

This is a medical officer 45-day Filing Review of NDA 22-535 for Pirfenidone. InterMune, Inc. has developed pirfenidone as an oral capsule for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function. Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is a new molecular entity (NME) in a new pharmacologic class. FDA has granted pirfenidone orphan drug status and fast track designation. Pirfenidone is formulated as a hard gelatin capsule for oral administration. The dosage strength is 267 mg per capsule. The proposed dose/dosing interval follows a pre-specified dose escalation schema, with a final targeted dose proposed to be 2403 mg/day divided into three doses. Pirfenidone (Pirespa®, Shinogi & Co., Ltd.) formulated as a 200 mg tablet, was approved for the treatment of IPF in Japan in October 2008.

This NDA includes 14 controlled and uncontrolled clinical studies of pirfenidone in healthy subjects and patient with IPF conducted by InterMune, Shinogi, and Marnac. An additional long-term open label safety study is ongoing and will be included in the 120-day safety

update. Of the 14 studies in the development program, PIPF-004 and PIPF-006 (subsequently referred to as 004 and 006) are the two pivotal studies submitted to provide substantial evidence of efficacy and safety for pirfenidone in IPF patients. The submission is provided in eCTD format.

The Applicant has included the necessary elements (21 CFR 314.50) in this NDA, and therefore the submission is fileable. Given that this is a new molecular entity, in a new pharmacologic class, for an indication which has no FDA-approved therapies, a DSI consult has been requested. The most substantial approvability issue that has been identified thus far is the failure of the program to replicate the efficacy results in two trials. Comments will be communicated to the Applicant in the 74-day letter.

IX. Comments to the Sponsor

Based upon preliminary review, you do not have replication of efficacy of pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. Of the two pivotal clinical trials, only PIPF-004 met the primary endpoint. The Shinogi clinical trial (SP3) cannot be used to support the efficacy of pirfenidone as the data were not submitted for review. The adequacy of your application to support the efficacy of pirfenidone for the treatment of IPF will be a review issue.

We note that you have [REDACTED] (b) (6) In your response (December 14, 2009) to our request for information, you stated that “SP3 only serves as supportive information in the InterMune NDA 22-535.” Given that you have not provided the information requested, the Agency cannot review the patient level data from trial SP3. [REDACTED] (b) (6)

Reviewed by:
Banu Karimi-Shah, M.D.
Medical Officer, Division of Pulmonary and Allergy Products

Sally Seymour, M.D.
Deputy Director of Safety, Division of Pulmonary and Allergy Products

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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
01/08/2010

SALLY M SEYMOUR
01/08/2010
I concur.