CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022535Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	October 15, 2014
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:	*Approval*

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 my previous review from the first cycle of this application, and the other 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 for a two-week titration to three of the 267 mg capsules three times a day (total daily dose 2403 mg). Pirfenidone has been approved in foreign markets (Japan 2008, Europe 2011 and Canada 2012) for the treatment of IPF.

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 (130,000 to 200,000 people in the United States), with 50,000 new cases diagnosed each year, and has a median survival of 3 to 5 years (40,000 deaths each year). Progression can however vary widely between individuals. There presently are not any proven effective non-surgical treatments (lung transplant is an option), although corticosteroids and immunosuppressive agents are used. 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 discussed in my original review during the first cycle, there were two clinical efficacy trials (PIPF-004, PIPF-006). The results of those trials on the surrogate endpoint of Forced Vital Capacity (FVC) indicated statistical evidence of efficacy in one trial (004) but not the other (006). Although statistically significant, the magnitude of effect on mean FVC demonstrated in 004 was small and it was unclear if clinically relevant. Furthermore, secondary endpoints weren't clearly supportive. In sum, a surrogate primary endpoint which yielded inconsistent

results in two trials and limited evidence of clinical benefit were not sufficient to fulfill our regulatory standard of substantial evidence of efficacy to support approval.

With this resubmission, the sponsor has conducted a third trial (016) that is very similar to the original two, although the primary endpoint evaluation was at 52 weeks instead of the 72 weeks that we recommended, as this was the duration in the first two trials.[1] This trial in conjunction with the data submitted in the original cycle has provided substantial evidence of efficacy and resolved the deficiency leading to the original CR action.

Efficacy

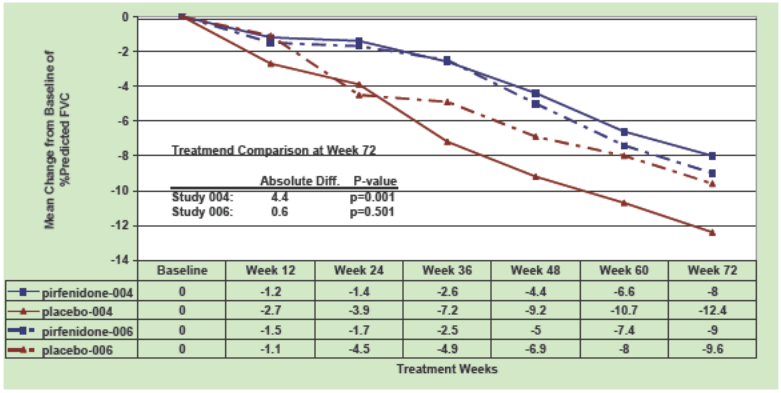
This has been thoroughly covered in Drs. Karimi-Shah, Seymour, Chowdhury, Zhou and Kim's reviews. Please see my original review for a discussion of trials 004 and 006. Efficacy for this application originally was evaluated in two trials, 004 and 006. The CR letter of May 04, 2010 identified lack of substantial evidence of efficacy and recommended conducting a placebo-controlled clinical trial demonstrating a statistically significant benefit in all-cause mortality with the use of pirfenidone, or, a reduction in decline in FVC that replicated the findings of trial 004. The sponsor was informed that the findings must be robust and provide evidence of a clinically meaningful response. Below are the efficacy results from all three trials including trial 016 (From Dr. Chowdhury's review, page 6).

Table 1. Mean change from baseline in percent predicted FVC from baseline to week 72 for studies 004 and 006 and week 52 for study 016 in all randomized patients (rank ANCOVA with imputation*)

	Pirfenidone 2403 mg/day	Pirfenidone 1197 mg/day	Placebo	Difference from Placebo	
				Absolute	p-value
Study 004	-8.0	-9.9	-12.4	4.4	0.001
Study 006	-9.0		-9.6	0.6	0.501
Study 016	-3.7		-6.6	2.9	<0.001
*Missing data imputation: 0 if patient died; sum of squared mean difference method if patient alive					

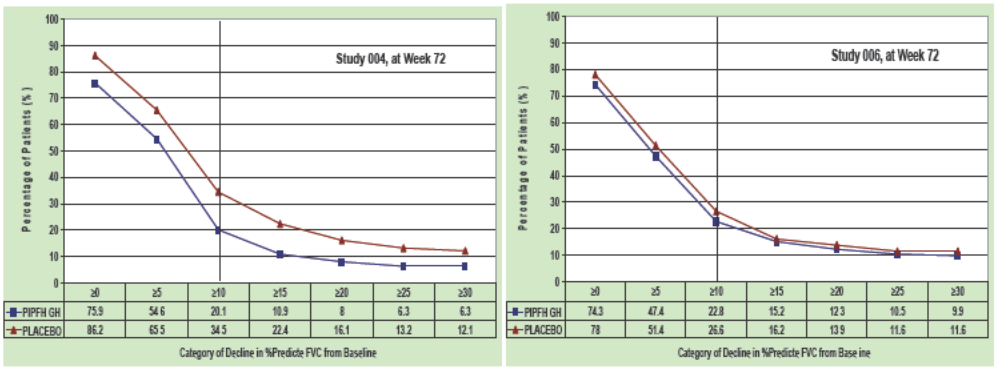
As noted above, the absolute difference in change from baseline percent FVC demonstrated in Study 016 is 2.9%. It is not known what change in FVC would be expected to predict a clinically important difference, but at the March 9, 2010 advisory committee meeting held for pirfenidone, a value of 10% was discussed as that used in a clinical context. The figures below include he mean change in percent predicted FVC from baseline and cumulative responder analyses demonstrating the percentages of patients in each group that have a decline of 10% for all three trials (Dr. Chowdhury's review, page 7-8).

[1] Exploratory analysis of study 006 demonstrated statistical significance at 48 weeks that did not persist to 72 weeks. The sponsor was informed that conducting a third trial of less than 72 weeks would likely need to be supported by mortality findings that trended in the correct direction to resolve the deficiency identified in the action letter.



	Baseline	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72
pirfenidone-004	0	-1.2	-1.4	-2.6	-4.4	-6.6	-8
placebo-004	0	-2.7	-3.9	-7.2	-9.2	-10.7	-12.4
pirfenidone-006	0	-1.5	-1.7	-2.5	-5	-7.4	-9
placebo-006	0	-1.1	-4.5	-4.9	-6.9	-8	-9.6

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



	≥0	≥5	≥10	≥15	≥20	≥25	≥30
PIPFH GH	75.9	54.6	20.1	10.9	8	6.3	6.3
PLACEBO	86.2	65.5	34.5	22.4	16.1	13.2	12.1

	≥0	≥5	≥10	≥15	≥20	≥25	≥30
PIPFH GH	74.3	47.4	22.8	15.2	12.3	10.5	9.9
PLACEBO	78	51.4	26.6	16.2	13.9	11.6	11.6

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

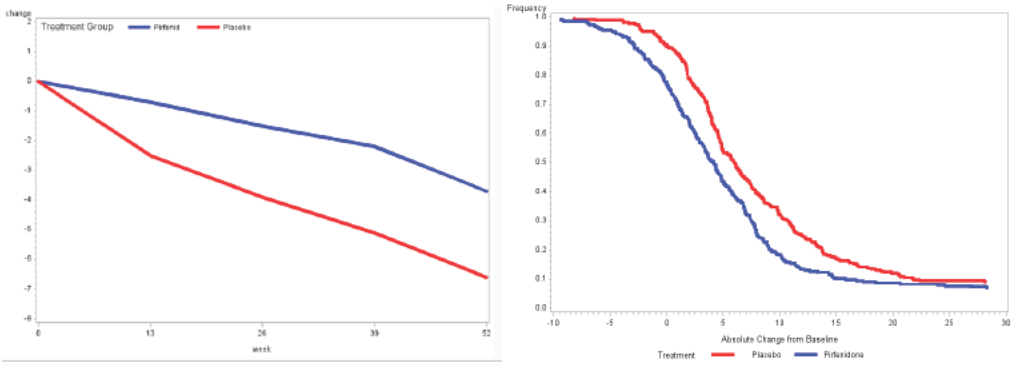


Figure 3. Mean change in percent predicted FVC from baseline (Left Panel), and Cumulative % of patients of change from baseline in % predicted FVC (Right Panel), Study 016

Using an absolute decline in % predicted FVC of 10% or greater to define a responder for trial 016, 17% of patients treated with pirfenidone had a decline greater than 10% compared to 32% of patients in the placebo group.

Other secondary endpoints were examined (6-minute walk distance, progression free survival) and were generally supportive.

Mortality is the most relevant endpoint and was also examined for each trial and for pooling of the trials.[2] Mortality data were analyzed in various ways. Results of studies 004, 006 and study 016 are shown in Table 3 and Table 4 (From Dr. Chowdhury's review, page 10). Mortality results are shown as vital status which is all deaths that occurred during the total study period and defined study follow-up period regardless of whether patients continued study treatment, and as on-treatment defined as deaths that occurred after the first dose and within 28 days after the last dose. Vital status mortality is likely more informative for a demonstration of efficacy.

In studies 004 and 006 the causes of deaths were not adjudicated and a vital status mortality benefit was not demonstrated for the two studies individually or pooled although a numerical trend favoring pirfenidone was demonstrated (Dr. Chowdhury's review, page 9).

Table 2. Mortality analysis from studies 004 and 006

	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				
Study 004	14 (8.0)	10 (11.5)	20 (11.5)	0.68 (0.34, 1.34), p=0.268
Study 006	18 (10.5)		17 (9.8)	1.06 (0.55, 2.07), p=0.856
Study 004+006	32 (9.3)		37 (10.7)	0.85 (0.53, 1.37), p=0.509
All cause death, on-treatment				
Study 004	11 (6.3)	8 (9.2)	15 (8.6)	0.68 (0.31, 1.49), p=0.336
Study 006	10 (5.9)		15 (8.7)	0.66 (0.30, 1.48), p=0.314
Study 004+006	21 (6.1)		30 (8.7)	0.68 (0.39, 1.18), p=0.167
IPF related death†, vital status at end of study				
Study 004	8 (4.6)	7 (8.0)	15 (8.6)	0.51 (0.22, 1.21), p=0.127
Study 006	14 (8.2)		15 (8.7)	0.94 (0.45, 1.95), p=0.863
Study 004+006	22 (6.4)		30 (8.6)	0.72 (0.42, 1.25), p=0.246
IPF related death†, on-treatment				
Study 004	5 (2.9)	6 (6.9)	11 (6.3)	0.45 (0.16, 1.31), p=0.143
Study 006	7 (4.1)		14 (8.1)	0.49 (0.20, 1.23), p=0.129
Study 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)				

Statistically significant benefit was seen in the pooled analysis of IPF-related on-treatment mortality, but this analysis must be viewed with caution due to assessment while on treatment, post-hoc nature of analysis, lack of adjudication of events, and analysis of case narratives that raises questions regarding the consistency of the determination of the cause of death.

[2] Although for Study 004 and 006 examination of mortality was exploratory in nature without formal pre-specified statistical consideration.

In Study 016 the causes of deaths were adjudicated, patients were followed for vital status through 52 weeks regardless of continuation of study medication. As demonstrated in the table below, a mortality benefit was not demonstrated for study 016 individually or when pooled with studies 004 and 006 (Table 4, Dr Chowdhury's review, page 10), when the analysis of all-cause mortality was based on at vital status at end of study.

Table3. Mortality analysis from studies 004, 006, and 016

	Number of events (%)		Hazard Ratio (95% CI), p-value*
	Pirfenidone 2403 mg/day	Placebo	
All cause death, vital status at end of study (72 weeks for 004 and 006, 52 weeks for 016)			
Study 004	14 (8.0)	20 (11.5)	0.65 (0.33, 1.29), p=0.217
Study 006	18 (10.5)	17 (9.8)	1.07 (0.55, 2.08), p=0.833
Study 016	12 (4.3)	21 (7.6)	0.55 (0.26, 1.15), p=0.105
Study 004+006+016	44 (7.1)	58 (9.3)	0.75 (0.50, 1.11) p=0.142
All cause death, 52 weeks for all studies			
Study 004	5 (2.9)	13 (7.5)	0.37 (0.13, 1.04), p=0.049
Study 006	6 (3.5)	9 (5.2)	0.66 (0.24, 1.87), p=0.435
Study 016	11 (4.0)	20 (7.2)	0.55 (0.26, 1.15), p=0.105
Study 004+006+016	22 (3.5)	42 (6.7)	0.52 (0.31, 0.87), p=0.011
*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)			

The numerical trend generally favored pirfenidone but the point estimates are fragile. As an example, the point estimate for study 004 and 006 at 52 weeks and 72 weeks are 0.37, 0.66 and 0.68, 1.06 respectively. This nearly doubling of each point estimate in 20 weeks demonstrates the fragility of these estimates.

Statistically significant benefit was seen in the pooled analysis truncated to 52 weeks.[3] While the 52 week time point was used to make the treatment duration the same for all three studies (Table 4), it is flawed in that a priori it was known that study 006 had a positive trend at this time point compared to pre-specified endpoint of 72 weeks. Such an analysis was specified in the protocol for study 016, which was intended as a support for the FVC endpoint. (b) (4)

(b) (4)

Results of clinical program show a positive benefit of pirfenidone in the treatment of IPF when measured by FVC. Statistically significant improvement of FVC was seen in studies 004 and 016 and this benefit was supported by favorable numerical trends in supportive secondary end points including mortality.

[3] This was originally done so that the pooling would be of similar timepoints. It is important to note however that the 52-week HR for 004 and 006 were of quite different magnitude than at 72 weeks. This calls into question the stability of these estimates, which were based on few events and limited chronicity of exposure, or the persistence of effect if one were to think of the estimate as truth.

Safety

With the original application, the main AEs were gastrointestinal, rash, and photosensitivity reactions, serious AEs were balanced between groups, and there were more study medication discontinuations due to AEs in the pirfenidone group compared to placebo. This remains the same with the addition of data from Trial 016 and I will refer the reader to other reviews for further details. I will however further examine liver-related adverse events as this had been discussed in my previous review.

As previously noted, there were transaminase elevation shifts for those receiving drug compared to those receiving placebo (ALT elevations 3-5 times of normal were reported in 1.9% and 0.3% in pirfenidone and placebo-treated patients, respectively). During the original review cycle, there was noted to be two potential Hy's Law case. However, 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.

The second case is also confounded. This case a 75 year-old male with IPF, diabetes, hypercholesterolemia who was concomitantly taking multiple medications including atorvastatin, naproxen, and metformin. At baseline the patient had normal liver transaminases and total bilirubin elevated to about 1.5 time the upper limit of normal. During the course of treatment his liver transaminases and bilirubin increased (5x ALT, 4x AST, 2.5 x total bilirubin), however his alkaline phosphatase was also noted to be elevated (3x). The patient later underwent genetic testing that confirmed the diagnosis of Gilbert's disease and pirfenidone was not re-started. Liver enzyme abnormalities resolved, and the patient later expired due his underlying IPF.

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

Fifteen pirfenidone-treated patients had a maximum post-baseline ALT or AST elevation of 3 to 5x ULN with 12 remaining on pirfenidone until study completion, 7 on a full dose and 5 on a reduced dose.

I think it is clear that pirfenidone has some effect on the liver, but it is unclear what the potential is to cause severe injury. The cases cited above are all confounded and may not represent Hy's law cases. As such, the applicant has proposed that ALT, AST, and bilirubin should be measured prior to initiation of therapy and then monthly for the first 6 months and every 3 months thereafter. The recommendation seems reasonable, given the current state of knowledge.

Advisory Committee Meeting

A Pulmonary Allergy Drugs Advisory Committee (PADAC) meeting was held March 9, 2010 during the original review cycle. 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 (two committee members voted there was not sufficient data of efficacy but voted for approval) but panelists discussed that they had weighted the severity of the disease, desperation of clinicians and patients including very moving testimonials made during the open public session, and ultimately felt that the drug had some activity.[4]

There was not a repeat Advisory Committee meeting during this review cycle.

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.

With this submission, the sponsor of pirfenidone have demonstrated substantial evidence of efficacy. There is a safety signal of potential liver toxicity, with unclear ramifications regarding severity. Elevations of transaminases occurred in a small number of patients, with most adapting such that therapy could be continued. As such, the potential for severe injury is probably rare, but may exist. The clear efficacy of this drug and severity of IPF and lack of effective drugs establishes a clear risk-benefit assessment that allows approval. However, frequent monitoring of liver function as outlined above is necessary.

There has been a lot of internal discussion regarding whether, or how, mortality findings should be presented in the label. There were not clear pre-specifications for statistical analyses of mortality, and the trend that was demonstrated was not statistically significant. Also, no conclusions can be made as the studies were not powered for mortality and as a result there are a limited number of events and limited duration of exposure such that any point estimate is likely to be fragile. On the other hand, clinicians would likely find this information useful, and it is an important 'hard' endpoint compared to FVC which has never been correlated to mortality findings. As such, we will present the mortality findings in labeling in such a way as to show their relevance but also the limitations of conclusions.

[4] As noted in Dr. Chowdhury's review, it is interesting that after the first AC we received correspondence from both academic physicians and patient advocacy groups questioning whether efficacy had been met. In my experience it is an unusual occurrence that patients with a desperate illness would write advocating the need for more proof of drug effect. This application was also discussed at a Regulatory Briefing on April 16, 2010 with a general consensus that efficacy standards had not been met.

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

/s/

CURTIS J ROSEBRAUGH
10/15/2014