CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022535Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 22,535/0045
Drug Name:	Esbriet® (pirfenidone) capsules
Indication(s):	Treatment of Idiopathic Pulmonary Fibrosis (IPF)
Applicant:	InterMune, Inc.
Date(s):	Submitted: May 23, 2014
	PDUFA: November 23, 2014
Review Priority:	Priority
Biometrics Division:	Division of Biometrics II
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Keywords: NDA, clinical studies, missing data, rank ANCOVA model

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1 EXECUTIVE SUMMARY

InterMune, Inc. has proposed Esbriet® (pirfenidone) capsule for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. The applicant previously submitted two studies, 004 and 006, in 2009 but received Complete Response Letter (CRL) citing lack of replicated evidence for efficacy as only Study 004 demonstrated statistically significant treatment effect with respect to the primary endpoint, absolute change lung function after 72 weeks of treatment. The information for the proposed use of pirfenidone 2403 mg per day (mg/d) in IPF patients consist of the efficacy and safety data collected from Study 016 in the NDA resubmission as response to FDA's CRL of 04 May 2010, in addition to Study 004 and Study 006 in the original NDA.

Based on my collective evaluation of Study 004, Study 006, and Study 016 in patients with IPF, I conclude that Study 004 and Study 016 showed statistically significant evidence in favor of pirfenidone on the primary endpoint of decline in lung function. Also I conclude that Study 004 and Study 016 showed statistically significant evidence on the secondary endpoint of progression free survival and that Study 006 and Study 016 showed statistically significant evidence on the secondary endpoint of 6-minute walk test (6MWT) distance in favor of pirfenidone providing additional support. Therefore, from a statistical perspective, the overall package provided substantial evidence of pirfenidone's efficacy benefit.

2 INTRODUCTION

2.1 Overview

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown etiology characterized by fibrosis of the lung interstitium, decrease in lung volume, and progressive pulmonary insufficiency typically leading to death. There is currently no approved treatment for IPF in the United States (USA). The Applicant, InterMune, Inc. developed pirfenidone for the treatment of patients with IPF. The Applicant claimed that "Pirfenidone is a small, synthetic, non-peptide molecule of low molecular weight (185.2 daltons). The mechanism of action of pirfenidone has not been fully established. However, existing data suggest that pirfenidone exerts both anti-fibrotic and anti-inflammatory properties and may mitigate the lung damage associated with IPF in humans."

The proposed indication for pirfenidone is for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. FDA has granted pirfenidone Orphan Drug and Fast Track designations.

The Applicant submitted this resubmission on May 23, 2014 (NDA 22-535/0045) to address CRL of 04 May 2010. The resubmission included a phase 3, randomized, double-blind, placebo-controlled trial, Study 016. The objective of the study was to evaluate the efficacy and safety of pirfenidone 2403 mg/d (three 267-mg capsules three times a day [TID]) compared with placebo (three placebo capsules TID) in patients with IPF. In the study, patients were to receive study

treatment from randomization until 52 weeks of randomized treatment in the study. The primary efficacy outcome variable was the absolute change in %Predicted forced vital capacity (FVC) (post-bronchodilator) from Baseline to Week 52.

Prior to this resubmission, the Applicant submitted the original NDA on November 4, 2009 (NDA 22-535/0000) in support of the proposed indication for the pirfenidone 2403mg/daily dosage strength for the treatment of patients with IPF to reduce decline in lung function. The submission included two Phase 3, randomized, double-blind, placebo-controlled studies, 004 and 006, that were nearly identical in design. The objective of each study was to evaluate the efficacy and safety of pirfenidone 2403 mg/d (three 267-mg capsules TID) compared with placebo (three placebo capsules TID) in patients with IPF. In each study, patients were to receive study treatment from randomization until the last patient had completed approximately 72 weeks of randomized treatment in the study. The primary efficacy outcome variable was the absolute change in %Predicted FVC (post-bronchodilator) from Baseline to Week 72.

Main focus of my review was on the efficacy data from Study 016, but I also reviewed data from the studies 004 and 006 when needed.

History of Drug Development and Regulatory Interactions

The clinical development plan was introduced to the Division of Pulmonary and Allergy Products by InterMune, Inc. via IND 67,284 (April 21, 2003) and discussed during several meetings. Discussions mainly focused on the adequacy of the proposed primary endpoint. At the pre-NDA meeting (dated October 1, 2008), the division emphasized the important review issues as follow:

- *The Division stated that mortality is the ideal primary endpoint in a study of IPF treatment.*
- *The Division stated that the proposed FVC as the primary outcome is not an established surrogate for mortality.*
- *The Division stated that the efficacy of pirfenidone will not be based solely upon "winning" on the primary endpoint of change in FVC, but also based on the totality of the data and what drives the primary endpoint.*
- *The Division stated that the secondary endpoints, many of which are those that are clinically meaningful to patients, should support the primary endpoint and the efficacy of pirfenidone in IPF patients.*

The Applicant submitted this application on November 4, 2009 (NDA 22-535) in support of the proposed indication for the pirfenidone 2403mg/daily dosage strength for the treatment of patients with IPF to reduce decline in lung function. The submission included two Phase 3, randomized, double-blind, placebo-controlled studies, 004 and 006, that were nearly identical in design.

Complete Response Letter of 04 May 2010 was sent to the Applicant with the following deficiencies and recommendations relevant to statistics:

> "The submitted data do not provide substantial evidence of efficacy of pirfenidone for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce the decline in lung function. The positive

finding of forced vital capacity (FVC) in trial PIPF-004 was not replicated in trial PIPF-006. The clinical program also does not provide substantial replicate evidence on other clinically meaningful efficacy measures. 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.

To support approval of pirfenidone for patients with idiopathic pulmonary fibrosis, 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 idiopathic pulmonary fibrosis to reduce decline in lung function, conduct a clinical trial with FVC as the primary endpoint that 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 trial pooled with the all-cause mortality data from trial PIPF-004 and PIPF-006 should also provide supportive evidence of benefit."

In April 2012, the Applicant received a Type C meeting written response from the Division, where input was received regarding the proposed phase 3 study. The Division provided the following statistical comments on the proposed analysis plan:

- *The Division concurred with the proposed statistical analysis plan for Study 016.*
- *The Division recommended a sensitivity analysis comparing the slopes of the two treatment groups at Week 52 for each study (Study 004, Study 006, and Study 06).*

In May, 2014, the resubmission of NDA was submitted for pirfenidone for the proposed treatment of IPF.

2.1.1 Specific Studies Reviewed

The focus of this review is on the efficacy data from the new phase 3 efficacy study, Study 016. When necessary, I reviewed the results from Study 004 and Study 006 and referred to the statistical review on the original NDA. The design of the three studies, which is also referenced in the label, is described in Table 1. For a detailed review of studies 004 and 006 see the statistical review by Dr. Feng Zhou dated April 5, 2010.

Table 1. Clinical Trials Reviewed

InterMune Trial No.	Phase	Design	Treatment Arms	Number of Patients	Dates
PIPF-016	3	52-week, randomized, double-blind, parallel-group, placebo-controlled	Pirfenidone 2403 mg/d Placebo	278 277	06/2011-02/2014
PIPF-004	3	72-week, randomized, double-blind, parallel-group, placebo-controlled	Pirfenidone 2403 mg/d Pirfenidone 1197 mg/d Placebo	174 87 174	07/2006-11/2008
PIPF-006	3	72-week, randomized, double-blind, parallel-group, placebo-controlled	Pirfenidone 2403 mg/d Placebo	171 173	04/2006-10/2008

Source: Reviewer

2.2 Data Sources

NDA 22-535 can be found in the electronic document room (EDR) of the Center for Drug Evaluation and Research. The study report including protocols, statistical analysis plan, and all referenced literature can be found in the EDR. The program codes used in statistical analyses and the electronic data sets with raw and derived variables and data definitions were provided in the EDR using the following path:

\\CDSESUB5\EVSPROD\NDA22535\0045\m5\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

In general, the submitted efficacy data were acceptable in terms of quality and integrity. I was able to reproduce the primary and secondary efficacy endpoints analyses. No noticeable deviations between the case report forms and analysis datasets relevant to primary and secondary endpoints were identified.

Study 016 seemed to be conducted properly based on the submission when I assessed the history of regulatory interactions, protocol revisions/amendments, study report, study datasets, and internal consistency among those components. The Office of Scientific Investigations had not finalized their inspection of this application at time my review was finalized.

3.2 Evaluation of Efficacy

Study 016 included in the current submission will be discussed in this section. For simplicity, pirfenidone 2403 mg/d will be denoted as pirfenidone.

Study Design, Efficacy Endpoints, and Statistical Methodologies

Study 016 was a phase 3, randomized, double- blind, placebo-controlled multinational study, that was conducted from 2011–2014. All study design features (eligibility criteria, study schedule, primary efficacy outcome variable and analysis, secondary and exploratory efficacy outcome measures and analyses, and all safety outcome measures and analyses) were almost identical to the two previously reviewed phase 3 studies, Study 004 and Study 006, except for treatment duration. The duration of Study 016 was 52 weeks while the duration of Study 004 and Study 006 was 72 weeks.

The objective of the study was to evaluate the efficacy and safety of pirfenidone compared with placebo in patients with IPF. In the study, patients were to receive randomized study treatment during the double blind treatment period of 52 weeks.

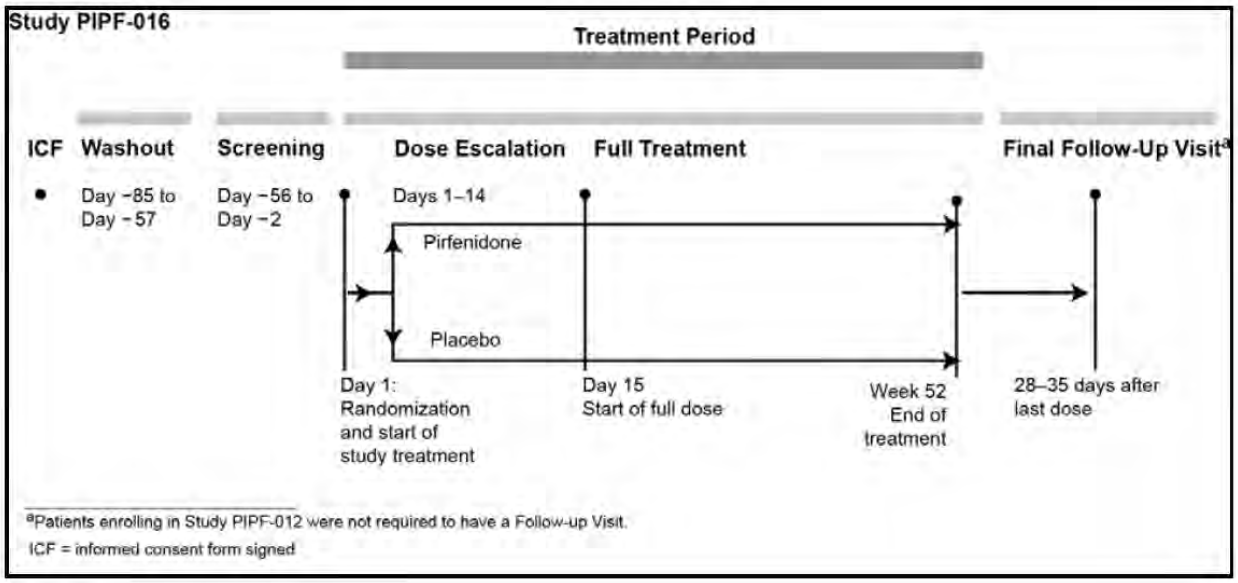
The study consisted of a washout period, a screening period, a study treatment period, and a final follow-up visit (see Figure 1). During the study treatment period, patients were to be monitored at Week 1, via a telephone assessment, and during study visits scheduled at Weeks 2, 4, 8, 13, 16, 20, 26, 39, 52A and 52B. There were 2 Week 52 visits: 52A and 52B, with the Week 52B visit occurring 1–3 days after the Week 52A visit.

During the 4-weeks washout period (at least 28 days before the start of screening), patients were required to discontinue any prohibited medication they were taking, including therapy targeted to treat IPF. Patients who completed the washout period and met the inclusion/ exclusion criteria were randomized by geographic region (USA or the rest of the world [ROW]) to receive study treatment. In the study, patients were randomized at a 1:1 ratio to receive pirfenidone or placebo.

In the study, treatment was escalated to a full maintenance dose of three capsules TID over a 15-day period as follows:

- Days 1–7: 1 capsule TID (3 capsules daily)
- Days 8–14: 2 capsules TID (6 capsules daily)
- Day 15 and continuing: 3 capsules TID (maximum of 9 capsules daily).

Figure 1. Study Schema



Source: Excerpted from the Clinical Study Report (page 22).

Enrollment required a confident clinical and radiographic diagnosis of IPF; surgical lung biopsy was required only for diagnostic uncertainty. Patients were required to have %Predicted FVC ≥50% and ≤90% and %Predicted carbon monoxide diffusing capacity (DL_{CO}) ≥30% and ≤90%, and 6MWT distance ≥150 m.

Spirometry measurements, including FVC and FEV_1 were to be assessed at Screening, Day 1 (before randomization), at Weeks 2, 4, 8, 13, 16, 20, 26, 39, 52A and 52B. At each visit, three FVC values were collected before and after bronchodilator, respectively, until maximum acceptable FVC value was chosen.

The primary analysis population was the intent-to-treat (ITT) patient population (all randomized patients).

The primary efficacy outcome variable was the absolute change in %Predicted FVC (post-bronchodilator) from Baseline to Week 52. Baseline FVC was defined as the mean of the maximum acceptable FVC measurements obtained during the screening and the day 1 visits. The FVC at Week 52 was defined as the mean of the maximum acceptable FVC measurements obtained on two separate days at the Week 52 visit (Week 52A and Week 52B).

> %predicted FVC was calculated as 100 * (Actual FVC value in liters / predicted FVC).
> Predicted FVC for men
> Caucasian-American = $0.00018642 \times \text{height (cm)}^2 + 0.00064 \times \text{Age (yrs)} - 0.000269 \times \text{Age (yrs)}^2 - 0.1933$
> African-American = $0.00016643 \times \text{height (cm)}^2 - 0.01821 \times \text{Age (yrs)} - 0 \times \text{Age (yrs)}^2 - 0.1517$
> Mexican-American = $0.00017823 \times \text{height (cm)}^2 - 0.00891 \times \text{Age (yrs)} - 0.000182 \times \text{Age (yrs)}^2 + 0.2376$
> Predicted FVC for women
> Caucasian-American = $0.00014815 \times \text{height (cm)}^2 + 0.01870 \times \text{Age (yrs)} - 0.000382 \times \text{Age (yrs)}^2 - 0.3560$
> African-American = $0.00013606 \times \text{height (cm)}^2 + 0.00536 \times \text{Age (yrs)} - 0.000265 \times \text{Age (yrs)}^2 - 0.3039$
> Mexican-American = $0.00014246 \times \text{height (cm)}^2 + 0.00307 \times \text{Age (yrs)} - 0.000237 \times \text{Age (yrs)}^2 + 0.1210$

The analysis of the primary endpoint was a rank ANCOVA, with a standardized rank change in FVC as the outcome and standardized rank baseline FVC as a covariate. Ties were assigned the mean of the corresponding ranks. Standardized ranks corresponded to modified ridits in the SAS® system and were obtained as ranks for all patients (regardless of treatment) divided by the sample size plus one. For details, refer to the section 7.7, pages 174-177 of Stokes et al. (2000). The treatment effect was to be tested using the Mantel-Haenszel mean score chi-square test. The test of significance for the primary analysis of the primary efficacy outcome variable was to use a two-sided alpha of 0.0498; adjusting for two anticipated interim mortality analyses.

The magnitude of the treatment effect of pirfenidone was presented as the distribution (number and percentage) of patients across the following categories of change from Baseline:

- Decline of ≥10% or death before the Week 52 visit
- Decline of <10% to >0%
- Stability or improvement of ≥0%.

The primary approach in handling missing data was pre-specified and was detailed in the protocol and the Statistical Analysis Plan. Missing assessments were handled as follows.

> Data that were missing as a result of death were ranked "worse" than data missing for reasons other than death and the ranking will be based on the time-to-death, with the shortest time until death as the worst rank. Missing data due to reasons other than death (e.g. missing visits, early

withdrawal from the study, including missing values due to lung transplantations) were imputed with average measurements for similar patients at the same time point using the sum of squared differences (SSD) method.

The "SSD method" imputation procedure and selection criteria are outlined as follows:
Step 1: For each post-Baseline missing value to be imputed at a visit (Visit X) for a particular patient (Patient A), a set of all patients from the same study without any missing values at the same visits from Baseline up to Visit X as Patient A will be selected. If Patient A is missing all data from Baseline up to Visit X, then that patient's missing value will not be imputed and instead will be left as missing and not included in the analysis.
Step 2: For the patients in this set, the sum of squared differences (SSDs) between each patient selected in Step 1 and Patient A will be calculated across all non-missing values from Baseline up to the visit prior to Visit X.
Step 3: The 3 patients with the smallest SSDs will be identified and the average of their non-missing value at Visit X will be used to impute the missing value for Patient A at that visit. The number of smallest SSDs to calculate the average can be less than 3 due to availability of patients defined in Step 1 or more than 3 based on tied SSDs.

Supportive analyses of the primary efficacy outcome included the following:

1. A repeated measures mixed linear model for rank change from Baseline in %FVC will be presented, using ranks calculated for change to Weeks 13, 26, 39, and 52. The mixed model will include fixed effects for treatment; covariates for Baseline %FVC, and a repeated effect of assessment week, unstructured covariance structure, and patient as the subject factor. Treatment effect will be tested at each visit (with a treatment by visit interaction term) and overall. Patients who die will be ranked worse than all other recorded data at the corresponding 13 week visit following the death and then within this group will be ranked by time until death.

2. Change from Baseline to Weeks 13, 26, 39, and 52 in FVC volume. This analysis will use the same analysis methods as the primary efficacy analysis, ranking the relative change in volume. The relative change is defined for each 13-week visit as (visit FVC volume- Baseline FVC volume)/Baseline FVC volume. The magnitude of the treatment effect of pirfenidone will be presented as the distribution (number and percentage) of patients across the following categories of change from Baseline:
- Relative decline of ≥10% or death before the corresponding 13-week visit
- Relative decline of <10% to >0%
- Stability or improvement of ≥0%

3. Landmark analyses of change from Baseline in %FVC to Weeks 13, 26, and 39. These will use the same analysis methods and summary of treatment effect as the primary efficacy analysis.

The secondary efficacy outcome variables adjusted for multiplicity were as follows:

- Change in distance walked in the 6MWT from Baseline to Week 52
- Progression-free survival (PFS), defined as time from randomization to the first occurrence of any of the following events:
  - Confirmed ≥10% absolute decline in percent predicted FVC, or
  - Confirmed ≥50 meter decline from Baseline in 6MWT distance, or
  - All-cause mortality

  In the case of FVC or DLco, the decline was to be confirmed at 2 consecutive visits at least 6 weeks apart

Of note, the definition of PFS in Study 016 is different from the definition in Study 004 and Study 006: the component of "Confirmed ≥15% absolute decline in percent predicted Hgb-corrected DLco" was replaced with "Confirmed ≥50 meter decline from Baseline in 6MWT distance."

The log-rank test and Kaplan-Meier estimator were used to compare treatment groups for the progression-free survival time. The estimate of hazard ratio between two groups and its 95% confidence interval were obtained by Cox's proportional hazards regression model with only treatment in the model.

The same rank ANCOVA model as in the primary analysis was used for analysis of change from baseline at Week 52 in 6MWT distance comparing two groups.

The Applicant proposed a gatekeeping testing with Hochberg procedure to adjust for multiple endpoints. To test the key secondary endpoints, the primary endpoint must be statistically significant at the 4.98% level. If so, then test the key secondary endpoints. If the largest p-value for two key secondary endpoints is < 0.05, declare statistical significance for both endpoints. If not, see if the remaining p-value is < 0.025. If so, declare the statistical significance of the second endpoint. Otherwise declare no statistical significance on either key secondary endpoint.

Other secondary and exploratory efficacy outcome variables without adjustment for multiplicity were as follows:

- Change in dyspnea from Baseline to Week 52, as measured by UCSD SOBQ score
- All-cause mortality
- Treatment-emergent IPF-related mortality

Similar statistical analyses as in the primary and key secondary endpoints analyses were conducted for other secondary and exploratory endpoints.

Sample Size Calculation

The primary efficacy analysis was adequately powered to detect a significant treatment effect with respect to the primary efficacy endpoint, change in %Predicted FVC from baseline to Week 52 Based on the applicant's sample size calculation, 250 patients in placebo group and 250 patients in pirfenidone group provided 90% power to detect a treatment difference (in normalized ranks of change at Week 52 of 0.08) between Baseline and Week 52, assuming a standard deviation of 0.27 at a significance level of 0.05.

Of note, the study was not powered to show a significant benefit of mortality. Even pooling data from this study with those from Study 004 and Study 006 provided less than 20% power to detect a hazard ratio of 0.77 at a significance level of 0.05.

Changes in the SAP

There were two amendments to the original SAP dated March 12, 2012 and December 23, 2013. The Applicant claimed that these amendments were made prior to unblinding and analyses of the

efficacy data. Most of the changes were updated section references, corrected efficacy analyses procedures, and clarified wording to make the SAP more complete and clear. The applicant modified the analysis model for 6MWT as follows:

> Ranked Baseline DLco was added to the analysis model for testing the treatment effect on the 6MWT distance because publications indicate a strong association between DLco and disease progression and this association was also observed in the PIPF-004 and PIPF-006 studies. Adding DLco to the analysis model for 6MWT should increase the statistical power for detecting a treatment difference for this key secondary endpoint which has relatively low statistical power due to large data variation.

Patient Disposition, Demographic and Baseline Characteristics

A total of 555 patients (278 pirfenidone and 277 placebo) were randomized (Table 2) and the majority (83%) of patients completed the 52 weeks of active treatment. The most common reason for discontinuation was adverse event. Compared to placebo, pirfenidone-treated patients had a higher percentage of dropouts due to adverse event.

The disposition of patients is summarized in two ways. First, I present the disposition for those subjects that discontinued study treatment but completed the study. Second, I present the disposition for those subjects that discontinued study treatment and withdrew from the study. Results are shown in Table 2.

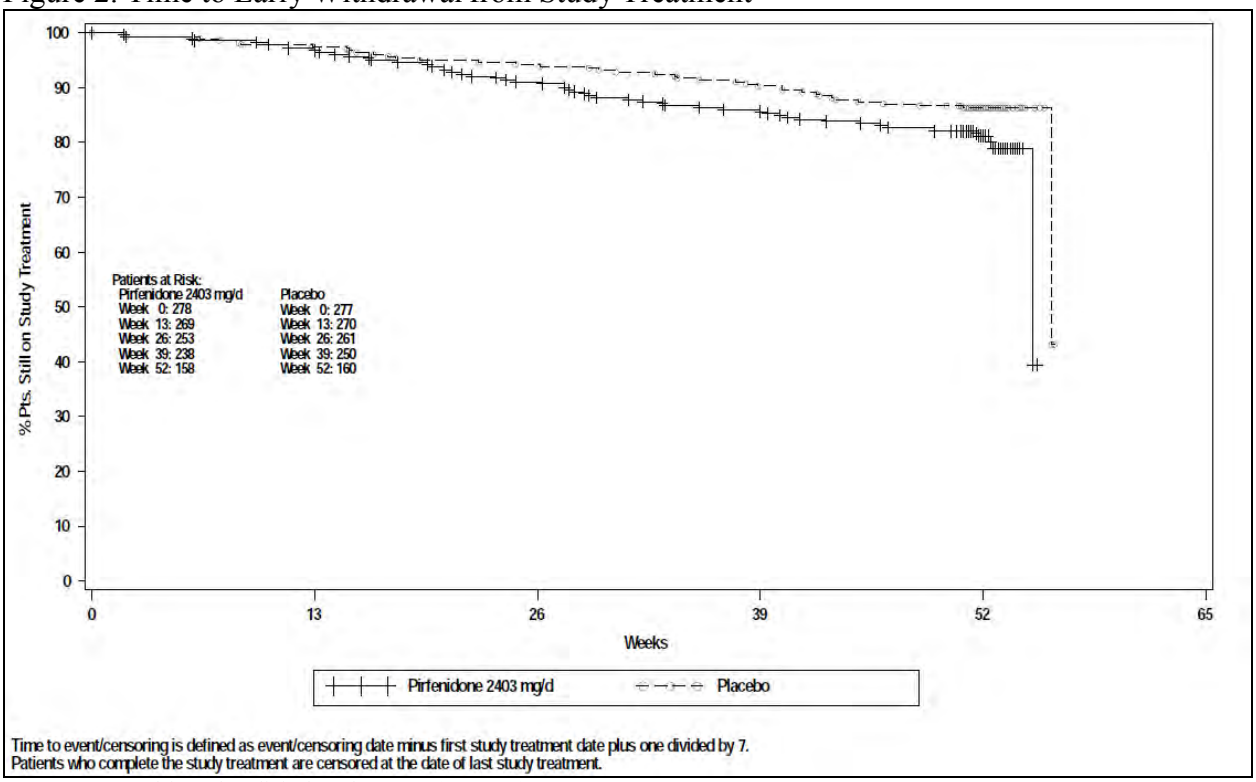
Table 2. Patients' Accountability, N (%) (All Randomized Patients)

	Study 016 (N=555)	
	Pirfenidone (n=278)	Placebo (n=277)
Received study treatment	278	277
Completed study treatment	223 (80)	238 (86)
Discontinued study treatment	55 (20)	39 (14)
Reason of early discontinuation of study treatment		
Adverse event	35 (13)	24 (9)
Withdrawal by patient	9 (3)	7 (3)
Lost to follow-up	0	1 (0)
Death	4 (2)	5 (2)
Lung transplantation	6 (2)	1 (0)
Other	1 (0)	1 (0)
Received treatment	278	277
Completed study	243 (87)	241 (87)
Discontinued study	35 (13)	36 (13)
Reason of withdrawal from the study		
Death	12 (5)	19 (7)
Adverse event	6 (2)	7 (3)
Withdrawal by patient	4 (2)	4 (2)
Lost to follow-up	2 (0)	1 (0)
Consent withdrawal	4 (2)	3 (1)
Lung transplant	6 (2)	1 (0)
Other	1 (0)	1 (0)

Source: Excerpted from the Clinical Study Report (page 56).

The survival curves for premature study drug discontinuations are presented in Figure 2. The dropout rates were slightly higher in the pirfenidone group compared to the placebo group.

Figure 2. Time to Early Withdrawal from Study Treatment



Source: Excerpted from the Clinical Study Report (page 513).

The demographic and baseline disease characteristics were generally well balanced and comparable between the treatment groups (Table 3). Overall, the mean age was 68 years. Majority of patients were Caucasian and approximately 78% of patients were male.

Table 3. Patients' Demographic and Baseline Characteristics by Treatment, N (%)

	Study 016 (N=555)	
Demographic parameter	Pirfenidone (n=278)	Placebo (n=277)
Age at Randomization (yrs)		
Mean (SD)	68 (6.7)	68 (7.3)
Sex		
Male	222 (80)	213 (77)
Female	56 (20)	64 (23)
Race		
White	255 (92)	251 (91)
Black	4 (2)	2 (1)
Asian	2 (1)	7 (3)
Other	17 (5)	17 (5)
Geographic region		
ROW	187 (67)	184 (66)
US	91 (33)	93 (34)
Time since IPF diagnosis (yrs)		
Mean (SD)	1.7 (1.1)	1.7 (1.1)
FVC (%predicted)		
Mean (SD)	68 (11.2)	69 (10.9)
6MWT distance (m)		
Mean (SD)	415 (99)	421 (98)

Source: Excerpted from the Clinical Study Report (pages 61 and 63).

The average percentage of compliance to the study treatment was above 90% in both studies (Table 4). The median duration of treatment was close to 52 weeks while the mean duration was slightly above 48 weeks.

Table 4. Study Treatment Compliance and Duration by Treatment

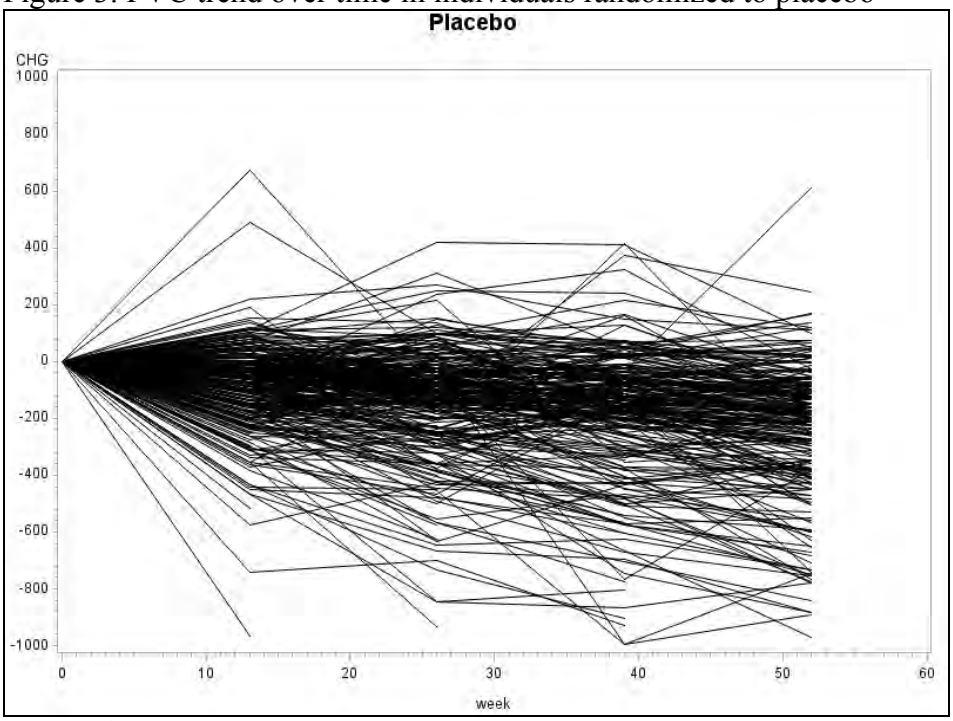
	Study 016 (N=555)	
Treatment compliance	Pirfenidone (n=278)	Placebo (n=277)
Patients who received any amount of study treatment		
N (%)	278 (100)	277 (100)
Percent compliance per patient		
Mean (SD)	90 (20)	94 (16)
Median (Range)	98 (4-100)	99 (2-100)
N (%)		
<40%	16 (6)	7 (3)
40% to 60%	11 (4)	6 (2)
60% to 80%	14 (5)	7 (3)
80% to 100%	237 (85)	256 (92)
Treatment duration in weeks		
Mean (SD)	48 (12)	49 (10)
Median (Range)	52 (2-55)	52 (2-56)

Source: Reviewer

Results and Conclusions

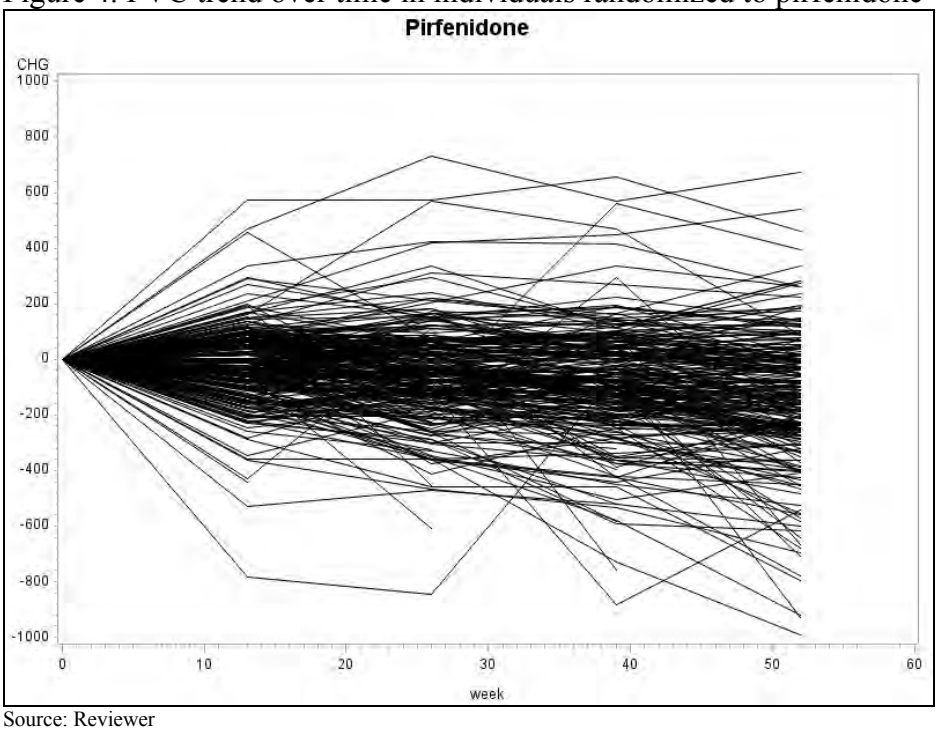
Primary Efficacy Endpoint – Absolute change in %Predicted FVC from Baseline to Week-52
The following graphs describe the FVC (mL) change from baseline over time in each individual patient by treatment group. Majority of patients seem to experience decline in FVC although degree of decline appears slightly smaller in pirfenidone group. In group mean graph, the slope of decline in FVC of pirfenidone group is smaller than the slope of placebo group (Figures 3-5).

Figure 3. FVC trend over time in individuals randomized to placebo



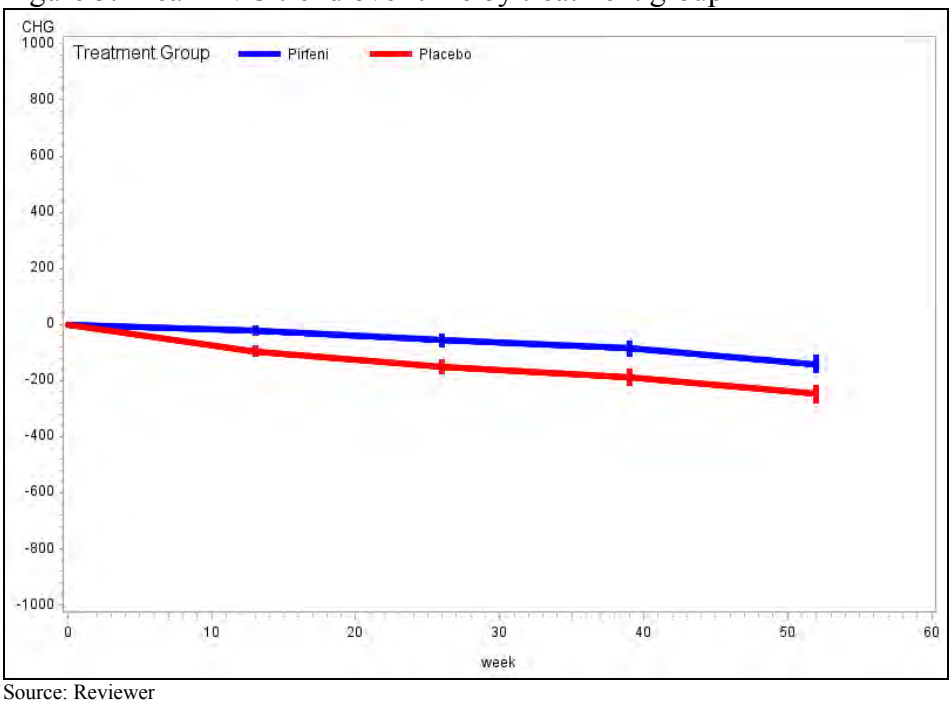
Source: Reviewer

Figure 4. FVC trend over time in individuals randomized to pirfenidone



Source: Reviewer

Figure 5. Mean FVC trend over time by treatment group



Source: Reviewer

The primary analysis of the primary endpoint was a rank ANCOVA using the imputed data. Of

note, imputation was applied to missing data at Week 52 on 24 patients in the pirfenidone group (N=278) and 18 patients in the placebo group (N=277) for reasons other than death. Given the small numbers, and uniform distribution of patient dropouts across treatment groups, missing data did not represent a meaningful source of bias in the interpretation of the efficacy. Therefore, the pre-specified imputation method (SSD) was acceptable. Hereafter, all analyses were conducted using imputed data unless stated otherwise.

Patients receiving pirfenidone had a smaller mean decline from Baseline in %Predicted FVC compared to those receiving placebo at Week 52 ($p < 0.001$, rank ANCOVA) (Table 5). This represents an absolute difference of 2.9% (i.e. -3.7 – -6.6 = 2.9 %Predicted FVC) and a relative difference of 44% (i.e. 2.9/6.6 = 0.44) between the two treatment groups.

Table 5. Mean Change in %Predicted FVC (Imputed)

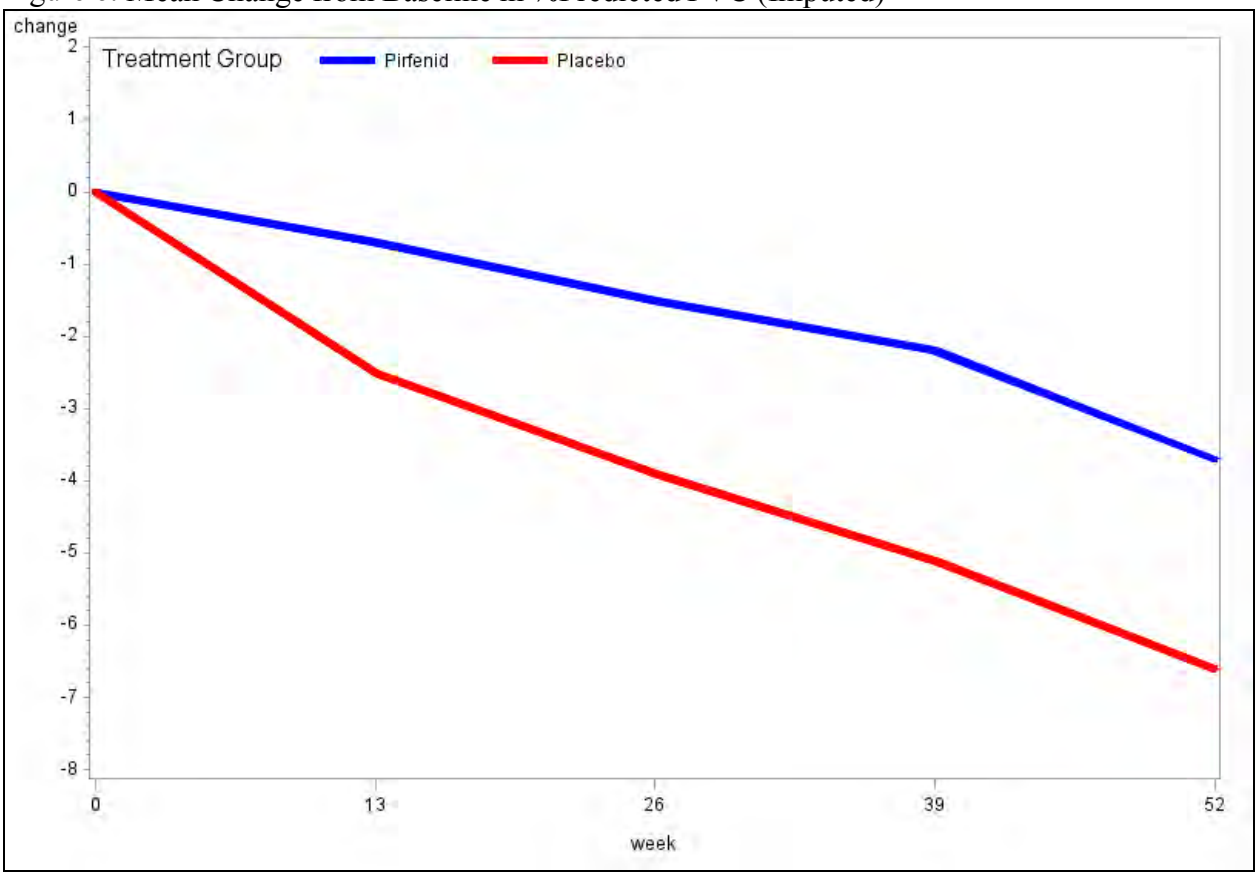
	Pirfenidone		***Placebo***		***Treatment Comparison***		
Week	***N Observed (Death)***	***Mean[a] (STD)***	***N Observed (Death)***	***Mean[a] (STD)***	***Absolute Diff.[c]***	***Absolute Diff.[d]***	***p-value[b]***
Baseline	278 (0)	67.8 (11.2)	277 (0)	68.6 (10.9)	-0.8	--	--
Week 13	273 (1)	-0.7 (4.0)	270 (0)	-2.5 (4.4)	1.8	72.0	<0.001
Week 26	255 (4)	-1.5 (4.5)	262 (6)	-3.9 (5.2)	2.4	61.5	<0.001
Week 39	246 (7)	-2.2 (5.1)	246 (8)	-5.1 (6.4)	2.9	56.9	<0.001
Week 52	**243 (11)**	**-3.7 (6.7)**	**239 (20)**	**-6.6 (6.7)**	**2.9**	**43.9**	**<0.001**

Source: Reviewer

[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 as fixed effect, 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).
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 0 was imputed for the assessment.

In Figure 6, the solid blue line represents the pirfenidone arm and the solid red line represents the placebo arm. The x-axis shows the corresponding weeks the FVC measures were collected and reported, and the y-axis shows the mean change from baseline in %Predicted FVC. There is evidence that the mean change from baseline in %Predicted FVC in the pirfenidone arm is smaller than the mean change in the placebo group.

Figure 6. Mean Change from Baseline in %Predicted FVC (Imputed)



Source: Reviewer

The Applicant's primary approach in handling missing data was reasonable. Different analytic techniques for data imputation by the Applicant and me resulted in similar conclusions (i.e. significant p-value in favor of pirfenidone). Estimates of treatment effect (depending on imputation or estimation methods) ranged from 2.8 to 4.8 (Table 6).

Table 6. Analyses on %Predicted FVC Change from Baseline to Week 52

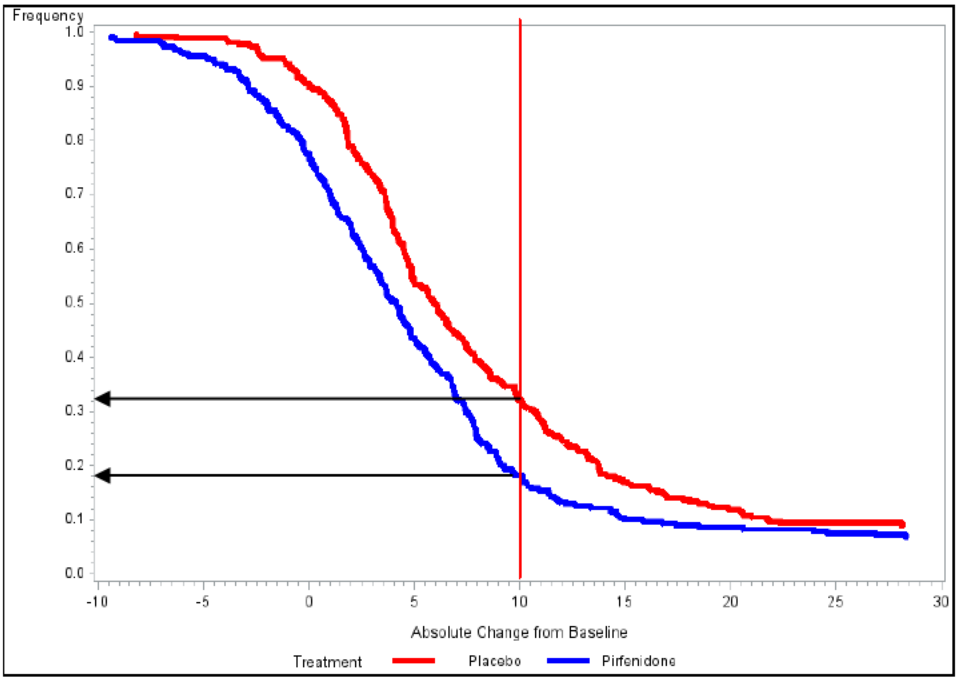
	Pirfenidone	*Placebo*	*Difference*
Applicant's Primary Analysis: Rank ANCOVA Model with SSD Imputation			
Mean (STD)	-3.7 (6.2)	-6.6 (6.7)	2.9
p-value			<0.001
Applicant's Supportive Analysis: Repeated Measure Model with SSD Imputation [a]			
LSMean (SE)	-6.2 (0.9)	-11.0 (0.9)	4.8
p-value			<0.001
My Sensitivity Analysis: ANCOVA with Placebo Mean Imputation [b]			
LSMean (SE)	-3.7 (0.5)	-6.5 (0.5)	2.8
p-value			<0.001
My Sensitivity Analysis: Random Coefficient Regression without Imputation [c]			
LSMean (SE)	-3.0 (0.6)	-6.8 (0.6)	3.8
p-value			<0.001

Source: Reviewer
[a] Mixed Linear model comparing Pirfenidone 2403 mg/d to Placebo, with change from baseline as the outcome variable. Treatment and assessment week as fixed effects; covariates of baseline percent predicted FVC, and a repeated effect of assessment week, unstructured covariance structure and patient as the subject factor.
[b] ANCOVA model comparing Pirfenidone 2403 mg/d to Placebo, with mean change from baseline to week 52 as the outcome variable. Treatment and baseline percent predicted FVC as covariates.
[c] Mixed Linear model comparing Pirfenidone 2403 mg/d to Placebo, with change from baseline as the outcome variable. Treatment and sex as fixed effects; intercept and slope as random effects on assessment week, unstructured covariance structure and patient as the subject factor.

I also performed a continuous responder analysis. Continuous responder curves for each treatment arm were plotted. In these plots, all patients who drop out from treatment due to death or lung transplantation were considered non responders (i.e. highest decline in %Predicted FVC) and other missing values were imputed using SSD method. Note that these figures were created to provide a visual display of the relative benefit of pirfenidone across the entire range of response at Week 52. The x-axis shows the decline in %Predict FVC from baseline (or worsening) at Week 52, and the y-axis show the corresponding percentage of patients achieving that level of %Predicted FVC decline or greater. The positive treatment effect of pirfenidone was demonstrated by consistent separation of the curve across different level of response. As an example, only 17% of pirfenidone-treated patients had at least a 10% decline in %Predicted FVC compared to 32% in placebo (Figure 7).

In consultation with the clinical team, the cut-off point of at least 10% decline in %Predicted FVC was chosen to perform a two category responder analysis. This responder analysis confirmed the primary analysis result, which is pirfenidone shows some benefit in reducing lung function decline.

Figure 7. Cumulative distribution of absolute change from baseline in %Predicted FVC



Source: Reviewer

I conducted the analyses on the FVC (mL) with the same rank ANCOVA model using imputed data with protocol specified imputation method (Table 7). An absolute difference of 193 (mL) between the two treatment groups was statistically significant and the significance was supported by sensitivity analyses by the applicant and me.

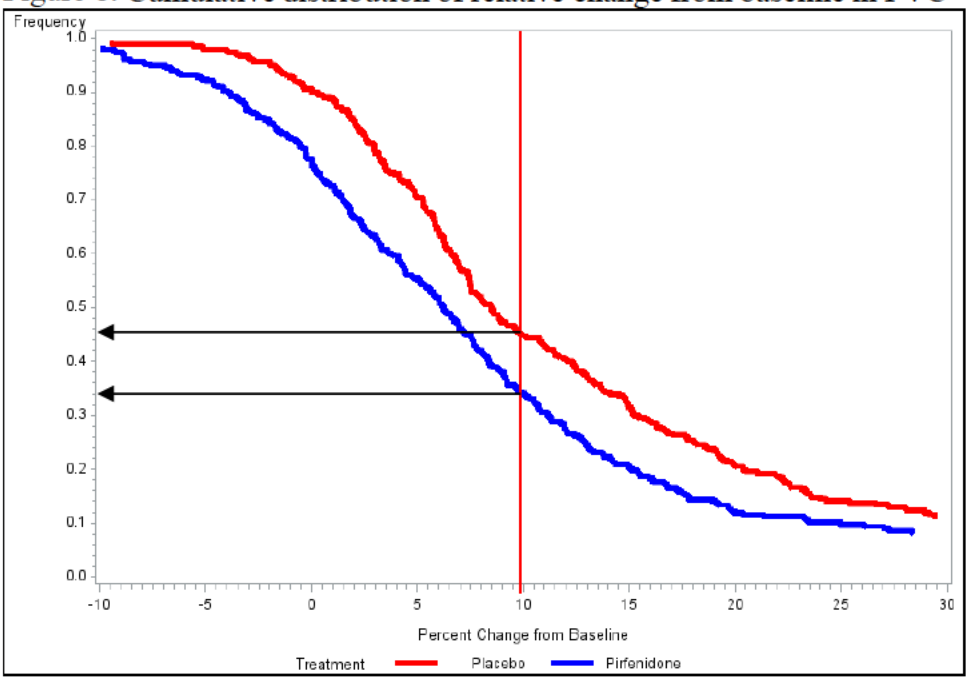
Table 7. Analyses on FVC (mL) Change from Baseline to Week 52

	Pirfenidone	***Placebo***	***Difference***
Applicant's Pre-specified Analysis: Rank ANCOVA Model with SSD Imputation			
Mean (STD)	-235 (457)	-428 (679)	193
p-value			<0.001
Applicant's Supportive Analysis: Linear Slope Mixed Model without Imputation [a]			
LSMean (SE)	-164 (18)	-280 (18)	116
p-value			<0.001
My Sensitivity Analysis: ANCOVA Model with SSD Imputation [b]			
LSMean (SE)	-177 (44)	-378 (44)	201
p-value			<0.001
My Sensitivity Analysis: ANCOVA Model with Placebo Mean Imputation [b]			
LSMean (SE)	-140 (24)	-232 (24)	91
p-value			<0.001
My Sensitivity Analysis: Random Coefficient Regression without Imputation [c]			
LSMean (SE)	-118 (23)	-265 (23)	146
p-value			<0.001

Source: Reviewer
[a] Mixed Linear model comparing Pirfenidone 2403 mg/d to Placebo, with change from baseline as the outcome variable. Treatment and sex as fixed effects; subject and subject by assessment week as random effects, variance component covariance structure.
[b] ANCOVA model comparing Pirfenidone 2403 mg/d to Placebo, with mean change from baseline to week 52 as the outcome variable. Treatment and sex as fixed effects and age, height and baseline percent predicted FVC as covariates.
[c] Mixed Linear model comparing Pirfenidone 2403 mg/d to Placebo, with change from baseline as the outcome variable. Treatment and sex as fixed effects; intercept and slope as random effects on assessment week, unstructured covariance structure and patient as the subject factor.

From the cumulative responder plot, the positive treatment effect of pirfenidone on change was demonstrated by consistent separation of the curve and only 35% of pirfenidone-treated patients have at least 10% decline in FVC (mL) compared to 45% in placebo (Figure 8).

Figure 8. Cumulative distribution of relative change from baseline in FVC



Source: Reviewer

In summary, Study 016 in patients with IPF, showed statistically significant evidence in favor of pirfenidone on the change in lung function (primary efficacy endpoint). Several secondary analyses were conducted on the primary efficacy endpoint to assess the robustness of the primary analysis. Although the magnitude of treatment effects varies depending on the methods of imputation and the statistical approaches used, the conclusions from these analyses were consistent.

Secondary Efficacy Endpoints

I was able to confirm the results of the Applicant's analyses of the secondary endpoints.

A review of the two pre-specified secondary efficacy endpoints is described in the next subsections for each individual study. A gatekeeping strategy with Hochberg method was proposed to adjust for multiple tests. Also a review on all-cause mortality endpoint is presented for individual study data as well as pooled data.

The Time to Progression-Free Survival

The Applicant's results of the progression-free survival analysis are summarized in Table 8 and Figure 8. Kaplan-Meier estimates were used to summarize progression-free survival, and treatment differences were analyzed using the log-rank test. The hazard ratio (HR) was determined based on the Cox proportional hazard model, with only treatment in the model, to estimate the magnitude of the effect. Overall, treatment with pirfenidone resulted in a higher proportion of progression-free survival than treatment with placebo (73%, 204/278 vs. 58%, 160/277 of patients, respectively). Treatment with pirfenidone was associated with a 43%

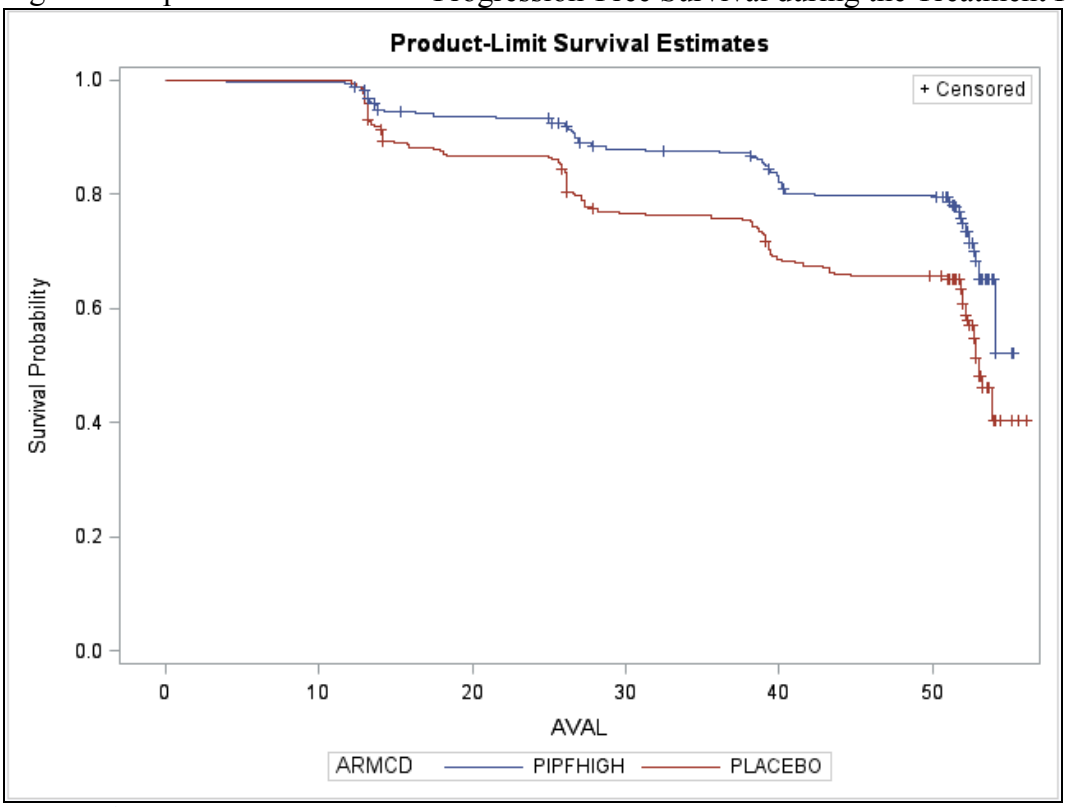
relative reduction of the combined risk of disease progression or death before disease progression compared to placebo (HR [95% CI]: 0.57 [0.43–0.77]). Exploring the individual components of this combined endpoint, the reduction appears to be mainly due to disease progression. In particular, a ≥10% decline in percent predicted FVC occurred in 7% of patients in the pirfenidone group compared to 18% of patients in the placebo group (Table 8). There was also evidence of a treatment effect of pirfenidone that began at approximately Week 13 and extended to Week 52 (Figure 9).

Table 8. Survival Analysis on Progression-Free Survival during the Treatment Period

	Pirfenidone	***Placebo***	***Hazard Ratio (95% CI)*** [b]
	N of Event (%)	***N of Event (%)***	***p-value*** [a]
Study 016			
N of Randomized	278	277	
Death or Disease Progression	74 (26.6)	117 (42.2)	0.57 (0.43, 0.77), <0.001
Decline in %Predicted FVC≥10%	18 (6.5)	49 (17.7)	
Decline in 6MWT≥50m	46 (16.5)	54 (19.5)	
Death	10 (3.6)	14 (5.1)	

Source: Reviewer
[a] p-value was based on the log-rank test.
[b] Hazard ratio was based on the Cox proportional hazard model with only treatment in the model.

Figure 9. Kaplan-Meier Curve of Progression-Free Survival during the Treatment Period



Source: Reviewer

The Change from baseline in 6MWT distance (m)

The results from the analyses of the mean change from baseline in Six-Minute Walk Test are summarized in Table 8. The endpoint was analyzed using the same rank ANCOVA model as in the primary analysis. The mean decline in 6MWT distance in patients treated with pirfenidone is lower compared to patients treated with placebo (-33.6 vs. -60.2 meters, respectively; difference of 26.7 meters). However, the statistical significance was disappeared my sensitivity analysis after imputing missing data with placebo completer group mean although pirfenidone was numerically better than placebo.

Table 9. Change from Baseline in 6MWT at Week 52

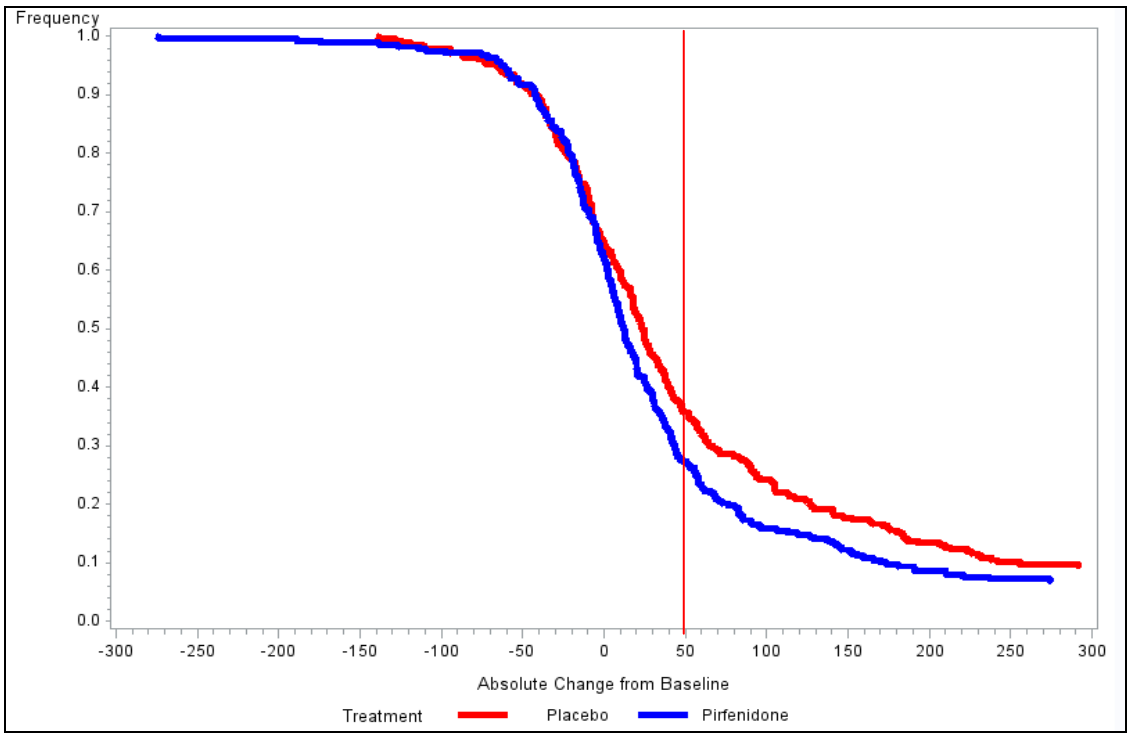
	Study 016 (N=555)	
	Pirfenidone (n=278)	Placebo (n=277)
Applicant's Rank ANCOVA analysis with SSD Imputation		
N	278	277
MEAN (SD)	-33.6 (95.7)	-60.2 (122.6)
vs. Placebo	26.7	
p-value	0.036	
My ANCOVA analysis with Placebo Mean Imputation		
N	278	277
LSMEAN (SE)	-18.0 (6.2)	-25.2 (6.2)
vs. Placebo	7.2 (6.9)	
p-value	0.302	

Source: Reviewer

A continuous responder analysis on the relative change from baseline in 6MWT distance at Week 52 was conducted. Again, all patients who drop out from treatment due to death or lung transplantation were considered non responders (i.e. highest decline in 6MWT distance) and other missing values were imputed using SSD method. From the cumulative responder plot, the positive treatment effect of pirfenidone on change was demonstrated by separation of the curve and approximately 28% of pirfenidone-treated patients have at least 50 m decline in 6MWT distance compared to approximately 36% in placebo (Figure 10).

Two responder curves were separated supporting the rank ANCOVA analysis, but the distance between them was not big, indicating that the difference might not be robust as shown in my sensitivity analysis.

Figure 10. Cumulative distribution of absolute change from baseline in 6MWT distance at Week 52



Source: Reviewer

All-cause mortality

The Applicant conducted an analysis comparing death (includes all death except those occurring after lung transplantation) between the treatment groups. Kaplan-Meier estimates were used to summarize survival time up to the end of the study treatment period. Survival time is measured by time from randomization to death. Treatment differences were analyzed using the log-rank test. The hazard ratio (HR) was determined based on the Cox proportional hazard model, with only treatment in the model. The results are displayed in Table 10 and Figure 11. The study did not demonstrate a mortality benefit, partly because the study was not powered for the survival endpoint.

Table 10. Survival Analysis on All-Cause Mortality during the Treatment Period (All Treated Patients)

	Pirfenidone	***Placebo***	***Hazard Ratio (95% CI)*** [c]
	N of Event (%)	***N of Event (%)***	***p-value*** [b]
Study 016			
N of ITT	278 [a]	277 [a]	
Death	11 (4.0)	20 (7.2)	0.55 (0.26, 1.15), 0.105
Censored	267 (96.0)	257 (92.8)	
Studies 016, 004, and 006 pooled			
N of ITT	623 [a]	624 [a]	
Death	22 (3.5)	42 (6.7)	0.52 (0.31, 0.87), 0.011
Censored	621 (96.5)	582 (93.3)	

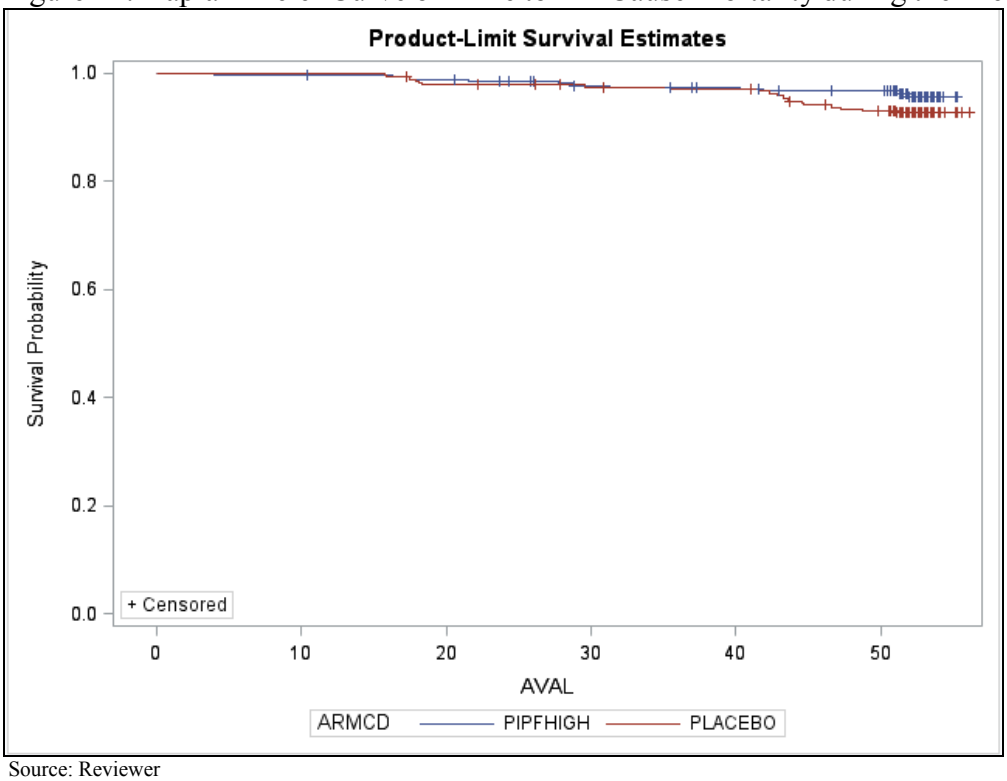
Source: Reviewer

[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 rescue (if one occurred), or the end of the Treatment Period.

[b] p-value was based on the log-rank test comparing pirfenidone with placebo.

[c] Hazard ratio was based on the Cox proportional hazard model with term for treatment.

Figure 11. Kaplan-Meier Curve of Time to All-Cause Mortality during the Treatment Period



Source: Reviewer

Since the study was not powered for the survival endpoint, a post-hoc analysis pooling the mortality data from Study 016, Study 004, and Study 006 was conducted to increase the power to detect difference if any. The pooled analysis showed that there was statistically significant evidence of survival benefit in the pirfenidone group compared to placebo on all-cause mortality over 52 weeks (4%, 22/623 vs. 7%, 42/624) with a 48% relative reduction of the all-cause

mortality compared to placebo (HR [95% CI]: 0.52 [0.31–0.87], p=0.011) (Table 11 and Figure 12).

Table 11. Survival Analysis on All-Cause Mortality during the Treatment Period of 52 Weeks (Study 016, Study 004, and Study 006 pooled)

	Pirfenidone	***Placebo***	***Hazard Ratio (95% CI)*** [c]
	N of Event (%)	***N of Event (%)***	***p-value*** [b]
Studies 016, 004, and 006 pooled			
N of ITT	623 [a]	624 [a]	
Death	22 (3.5)	42 (6.7)	0.52 (0.31, 0.87), 0.011
Censored	621 (96.5)	582 (93.3)	

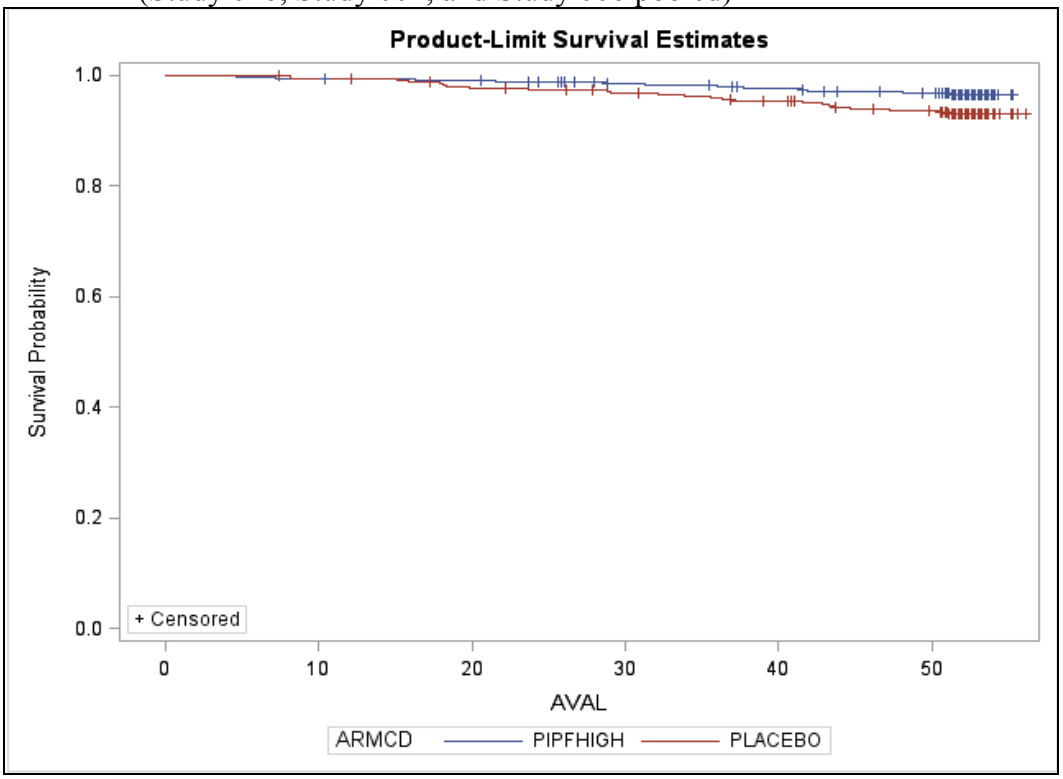
Source: Reviewer

[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 rescue (if one occurred), or the end of the Treatment Period.

[b] p-value was based on the log-rank test comparing pirfenidone with placebo.

[c] Hazard ratio was based on the Cox proportional hazard model with term for treatment.

Figure 12. Kaplan-Meier Curve of Time to All-Cause Mortality during the Treatment Period of 52 Weeks (Study 016, Study 004, and Study 006 pooled)



Source: Reviewer

3.3 Evaluation of Safety

The assessment of the safety of the study drug was mainly conducted by the reviewing medical team. The reader is referred to Dr. Banu Karimi-Shah's review for information regarding the safety profile of the drug.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Gender, Race, Age, and Geographic Region

The following analyses are tabular and graphical presentation of the subgroup analyses by demographics, region, and baseline disease characteristics in terms of %Predicted FVC change from baseline at Week 52 with pooled data from Study 016, study 004, and Study 006. The subgroup analyses were consistent with the results from the overall population in terms of %Predicted FVC change, except for a interaction toward increase in treatment benefit in patients with a longer time since IPF diagnosis at the study entry (Table 12 & Figure 13).

Table 12. Reviewer's Subgroup Analyses on %Predicted FVC– Studies 016, 004, and 006 pooled

	Pirfenidone		Placebo		
	N	Mean	N	Mean	ABS Diff (95% CI)
Overall (p<0.001) [a]					
	623	-7.4	624	-11.0	3.5 (1.6, 5.4)
Sex (p=0.232) [b]					
Males	463	-8.1	465	-10.8	2.7 (0.5, 5.0)
Female	160	-5.5	159	-11.3	5.8 (2.5, 9.1)
Age (p=0.742) [b]					
<65 yrs	218	-7.6	222	-11.0	3.5 (0.4, 6.6)
≥65 yrs	405	-7.4	402	-10.9	3.5 (1.2, 5.9)
Region (p=0.902) [b]					
ROW [c]	174	-8.5	176	-10.3	1.8 (-1.7, 5.4)
USA	449	-7.0	448	-11.2	4.2 (2.0, 6.4)
Race (p=0.696) [b]					
White [d]	592	-7.3	590	-11.0	3.7 (1.8, 5.6)
N-White	31	-9.8	34	-9.8	0 (-6.6, 6.6)
Baseline %Predicted FVC (P=0.609) [b]					
<70%	291	-8.6	308	-12.4	3.8 (1.0, 6.6)
≥70%	332	-6.4	316	-9.5	3.1 (0.6, 5.6)
Smoke History (P=0.851) [b]					
Never S	204	-7.3	221	-9.2	1.9 (-0.8, 4.6)
Smoke	419	-7.5	403	-11.9	4.4 (1.9, 6.9)
Time Since IPF Diagnosis (P=0.034) [b]					
<1 yrs	281	-8.1	282	-10.4	2.3 (-0.6, 5.1)
≥1 yrs	342	-6.9	342	-11.5	4.5 (2.1, 7.0)

Source: Reviewer

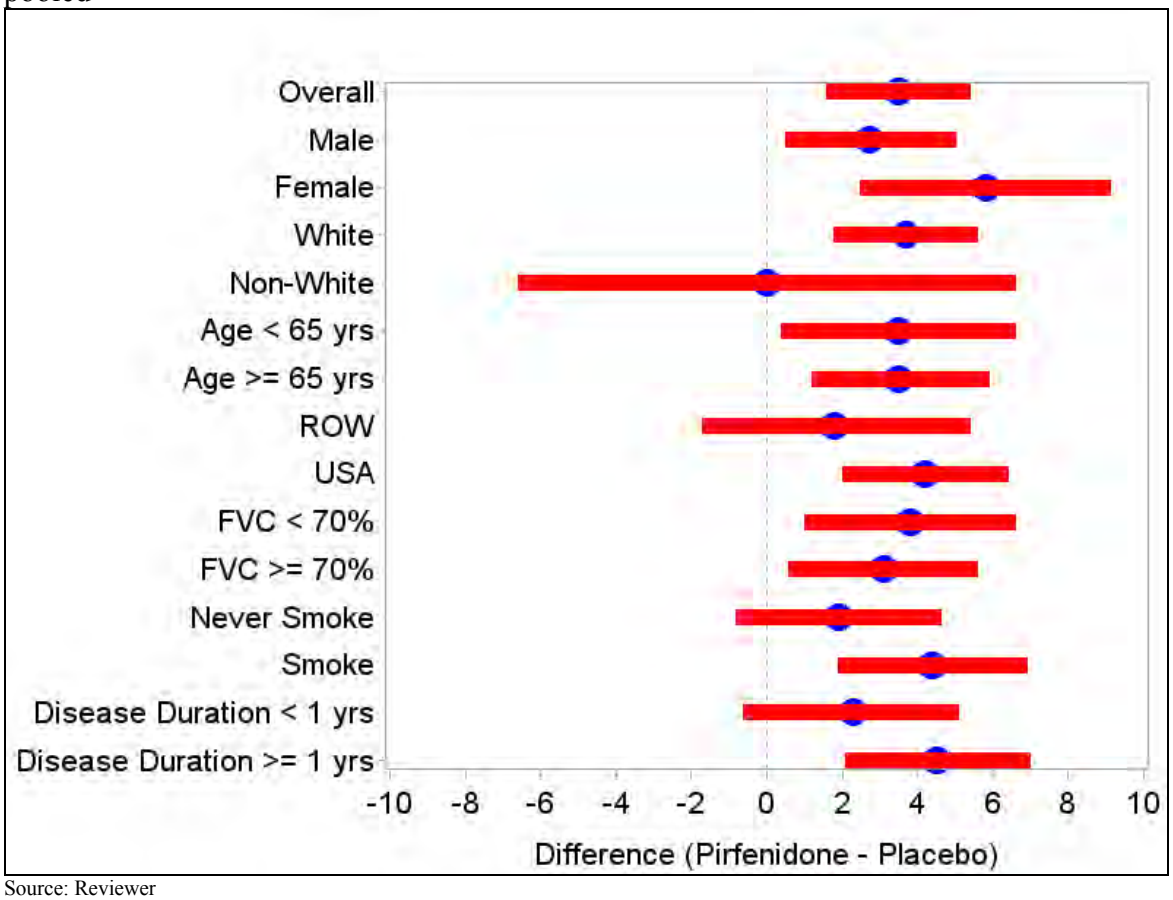
[a] Rank ANCOVA model, comparing pirfenidone to placebo.

[b] Rank ANCOVA model for interaction between treatment arm and subgroup.

[c] ROW includes Australia, Belgium, Brazil, Canada, Croatia, France, Germany, Ireland, Israel, Italy, Mexico, New Zealand, Peru, Poland, Singapore, Spain, Switzerland, and the United Kingdom.

[d] Hispanic/Latino ethnicity grouped with nonwhite for subgroup analyses.

Figure 13. Reviewer's Subgroup Analyses on %Predicted FVC– Studies 016, 004, and 006 pooled



Source: Reviewer

5. SUMMARY AND CONCLUSIONS

Statistical Issues and Collective Evidence

During my review of this application, several potential statistical issues were identified, handling of missing data, multiplicity, substantial evidence of efficacy on key secondary endpoints, and a post hoc pooled analysis on all-cause mortality. Upon review of the Applicant's pre-specified approach for handling missing data in the primary analysis, imputing the worst rank for patients who died, and applying sum of square difference for missing data due to reason other than death, I found this approach is acceptable and not a statistical issue. I also conducted a sensitivity analysis with imputation of missing data using the mean of placebo completers to penalize early dropouts in pirfenidone group with good results before treatment discontinuation.

The Applicant proposed a rank-based analysis of covariance (ANCOVA) model to analyze the primary endpoint, assuming that the data for the change from Baseline outcomes are not normally distributed. Since actual distribution of the data appeared not far from normality, I

conducted a parametric ANCOVA model analysis to assess impact of the assumption on the results. The results were consistent.

In terms of multiplicity, the Applicant did not apply any formal adjustments for the analysis of the secondary endpoints in Studies 004 and 006 in the original NDA submission (mainly due to the nature of exploration for secondary endpoints). However in Study 016, they proposed a gatekeeping strategy with Hochberg method for the key secondary endpoints. To test the secondary endpoints, the primary endpoint must be statistically significant at 0.0498% level, adjusting for the two anticipated interim mortality analyses. Then, they test on the secondary endpoints using Hochberg method on the two key secondary endpoints, i.e., progression-free survival and change from baseline in 6MWT distance at 52 weeks.

The analysis of the primary endpoint, decline in lung function, was shown to be statistically significant in two of the phase 3 studies, Study 016 in the current submission and Study 004 in the original NDA submission . However, two key secondary endpoints, progression-free survival and 6MWT distance, were shown to be statistically significant when pirfenidone was compared to placebo in two different combinations of the three studies, Study 016, Study 004, and Study 006. That is, they won the endpoint of progression-free survival in Study 004 and Study 016, but they won the endpoint of change from baseline in 6-minute walk test at 52 weeks in Study 006 and Study 016. With this evidence from the three studies, overall package seems to provide substantial evidence on both primary and key secondary endpoints.

All-cause mortality was not shown statistically significantly different between pirfenidone and placebo although there was a trend favoring pirfenidone. This was expected since the studies were not powered for the mortality endpoint. In order to increase power, mortality data from the three studies were pooled. Then, the trend favoring pirfenidone in the pooled analysis reached the statistical significance.

Findings from the review of studies, Study 016, Study 004, and Study 006 are summarized below.

Primary Endpoint – Change from Baseline in %Predicted FVC
In Study 016, patients receiving pirfenidone had a smaller mean decline from Baseline in %Predicted FVC compared to those receiving placebo at Week 52 ($p < 0.001$, rank ANCOVA). This represents an absolute difference of 4.8% and a relative difference of 44% between the two treatment groups.

As shown in the statistical review for the original NDA, in Study 004, patients receiving pirfenidone had a smaller mean decline from Baseline in %Predicted FVC compared to those receiving placebo at Week 72 ($p < 0.001$, rank ANCOVA). This represents an absolute difference of 4.4% and a relative difference of 35% between the two treatment groups. However, this finding was not replicated in Study 006.

Key Secondary Endpoints – Time to Progression-Free Survival
In Study 016, treatment with pirfenidone resulted in a higher proportion of progression-free survival than treatment with placebo (73%, 204/278 vs. 58%, 160/277 of patients, respectively). Treatment with pirfenidone was associated with a 43% relative reduction of the combined risk of disease progression or death before disease progression compared to placebo (HR [95% CI]: 0.57 [0.43–0.77]). However, exploring the individual components of this combined endpoint, the reduction appears to be mainly due to disease progression.

As shown in the statistical review for the original NDA, in Study 004, treatment with pirfenidone resulted in a higher proportion of progression-free survival than treatment with placebo (74%, 127/172 vs. 64%, 111/173 of patients, respectively). Treatment with pirfenidone was associated with a 36% relative reduction of the combined risk of disease progression or death before disease progression compared to placebo (HR [95% CI]: 0.64 [0.44–0.95]). However, this finding was not replicated in Study 006.

Key Secondary Endpoints – Change from Baseline in 6MWT Distance
In Study 016, patients receiving pirfenidone had a smaller mean decline from Baseline in 6MWT distance compared to those receiving placebo at Week 52 (p=0.036, rank ANCOVA). This represents an absolute difference of 27 m and a relative difference of 44% between the two treatment groups.

As shown in the statistical review for the original NDA, in Study 006, patients receiving pirfenidone had a smaller mean decline from Baseline in 6MWT distance compared to those receiving placebo at Week 72 (p=0.001, rank ANCOVA). This represents an absolute difference of 32 m and a relative difference of 35% between the two treatment groups. However, this finding was not replicated in Study 004.

Other Endpoint – All-cause Mortality
Difference in all-cause mortality was not shown statistically significant in any of phase 3 studies, Study 016, Study 004, and Study 006 as expected since the studies were not powered for this rare event. However, there was some numerical evidence in favor of pirfenidone in Study 016 (4%, 11/278 vs. 7%, 20/277; HR [95% CI]: 0.55 [0.26, 1.15], p=0.105), in Study 004 (6%, 11/174 vs. 10%, 17/174; HR [95% CI]: 0.61 [0.28, 1.29], p=0.191) , and in Study 006 (9%, 16/171 vs. 10%, 17/173; HR [95% CI]: 0.95 [0.48, 1.87], p=0.872) . Pooled data from all three studies were analyzed by the Applicant showing that there was statistically significant evidence of survival benefit in the pirfenidone group compared to placebo on all-cause mortality over 52 weeks (4%, 22/623 vs. 7%, 42/624) with a 48% relative reduction of the all-cause mortality compared to placebo (HR [95% CI]: 0.52 [0.31–0.87], p=0.011).

Conclusions and Recommendations
Based on my collective evaluation of Study 004, Study 006, and Study 016 in patients with IPF, I conclude that Study 004 and Study 016 showed statistically significant evidence in favor of

pirfenidone on the primary endpoint of decline in lung function. Also I conclude that Study 004 and Study 016 showed statistically significant evidence on the secondary endpoint of progression free survival and that Study 006 and Study 016 showed statistically significant evidence on the secondary endpoint of 6MWT distance in favor of pirfenidone providing additional support.

Positive findings on the primary and key secondary endpoints were replicated in the 3 studies, Study 004, Study 006, and Study 016. Therefore, from a statistical perspective, the overall package provided substantial evidence of pirfenidone's efficacy benefit.

Labeling Recommendations

Following is an excerpt from the relevant clinical studies section in the proposed label. I generally agree with the study description and primary analysis results and their interpretation. (b) (4) the clinical review team did not think these (b) (4) provided useful information and recommended removal (b) (4) from the label. Additionally, even though pre-specified, the clinical review team recommended removing (b) (4) from the label. Instead, the individual results for each study will be presented. This information was considered to be supportive of the primary efficacy endpoint.

(b) (4)

2 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

APPENDICES

Table 13. Proportion of %Predicted FVC Responders at 52 Weeks (Study 016)

Change from Baseline at Week 52[a]	Number of Patients, n (%)		p-value[a]
	Pirfenidone 2403 mg/d (N = 278)	Placebo (N = 277)	
Decline of ≥10% or death	46 (16.5)	88 (31.8)	<0.000001
Decline of <10% to 0%	169 (60.8)	162 (58.5)	
No decline (change in percent predicted FVC >0%)	63 (22.7)	27 (9.7)	

[a] p-value by rank ANCOVA

Source: Excerpted from the Clinical Study Report of Study 016 (page 71).

Table 14. Proportion of %Predicted FVC Responders at 72 Weeks (Study 004)

	Number of Patients, n (%)		p-value[a]
	Pirfenidone 2403 mg/d (N = 174)	Placebo (N = 174)	
Change from Baseline to Week 72[b]			<0.001
Severe decline of ≥20%, death, or lung transplantation	14 (8.0%)	27 (15.5%)	
Moderate decline of <20% but ≥10%	21 (12.1%)	33 (19.0%)	
Mild decline of <10% but ≥0%	97 (55.7%)	90 (51.7%)	
Mild improvement of >0% but <10%	40 (23.0%)	24 (13.8%)	
Moderate improvement of ≥10%	2 (1.1%)	0	

[a] p-value was based on Cochran-Mantel-Haenszel (CMH) row mean scores test stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d with placebo.

Source: Excerpted from the Clinical Study Report of Study 1199.34 (page 123).

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/s/

YONGMAN KIM
09/03/2014

DAVID M PETULLO
09/03/2014
I concur.

THOMAS J PERMUTT
09/03/2014
I concur.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	NDA22-535
Drug Name:	Pirfenidone capsules
Indication(s):	Treatment of patients with idiopathic pulmonary fibrosis to reduce decline in lung function
Applicant:	InterMune, Inc.
Date(s):	Received 11/4/09; User Fee 05/4/10
Review Priority:	6-months
Biometrics Division:	Division of Biometrics II/Office of Biostatistics
Statistical Team:	Zhou, Feng, M.S. (Statistical Reviewer) Buenconsejo, Joan, Ph.D. (Acting Statistical Team Leader) Permutt, Thomas J, Ph.D. (Division Director of Biometrics II)
Medical Division:	Division of Pulmonary and Allergy Products
Clinical Team:	Karimi-Shah, Banu, M.D. (Medical Reviewer) Seymour, Sally, M.D. (Medical Team Leader) Chowdhury, Badrul A, M.D., Ph.D. (Medical Division Director)
Project Manager:	Chung, Eunice

Keywords: Clinical Studies, NDA review, Dropouts

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

InterMune, Inc. has proposed Esbriet® (pirfenidone) capsule for "the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function." The information for the proposed use of pirfenidone 2403 mg/d in IPF patients consists of the efficacy and safety data collected from Study 004 and Study 006.

Based on my collective evaluation of Study 004 and 006, I conclude that only one of the two studies in patients with IPF, Study 004, showed statistically significant evidence in favor of pirfenidone on the primary outcome variable of change in lung function. Most of the secondary endpoints in Study 004 were also numerically in favor of pirfenidone providing additional support.

Positive findings from Study 004 were not replicated in Study 006. Therefore from a statistical perspective, the overall package failed to provide substantial evidence of pirfenidone's efficacy benefit.

1.2 Brief Overview of Clinical Studies

The Applicant submitted this application on November 4, 2009 (NDA 22-535) in support of the proposed indication for the pirfenidone 2403mg/daily dosage strength for the treatment of patients with idiopathic pulmonary fibrosis to reduce decline in lung function. The submission included two Phase 3, randomized, double-blind, placebo-controlled studies, 004 and 006, that were nearly identical in design. The objective of each study was to evaluate the efficacy and safety of pirfenidone 2403 mg/d (three 267-mg capsules three times a day [TID]) compared with placebo (three placebo capsules TID) in patients with IPF. In each study, patients were to receive study treatment from randomization until the last patient had completed approximately 72 weeks of randomized treatment in the study. The primary efficacy outcome variable was the absolute change in %Predicted FVC (post-bronchodilator) from Baseline to Week 72.

The Applicant also submitted the study report of Study SP3, which was sponsored by Shionogi & Co., Inc. and formed the basis for the marketing approval of pirfenidone to treat patients with IPF in Japan on October, 2008. Because the Applicant did not submit the data for SP3, the results cannot be verified. Upon consultation with the clinical team, we have decided to exclude the results of Study SP3 from this review.

1.3 Statistical Issues and Findings

The main issue for this application is that only one of the two Phase 3 studies in patients with IPF, Study 004, showed statistically significant evidence in favor of pirfenidone on the primary outcome variable of change in lung function. In other words, positive findings from Study 004 were not replicated in Study 006. From a statistical perspective, this application failed to provide substantial evidence of pirfenidone's efficacy benefit.

During my review of the application, several potential statistical issues were identified, including the approach to handle missing data, multiplicity, and change in study design (sample size). Upon review of the Applicant's pre-specified approach to handle missing data when analyzing the primary endpoint, that is, to impute the worst rank to patients who died, and applying sum of square difference to missing data due to reason other than death, I find that this approach is acceptable and not a statistical issue.

In terms of multiplicity, the Applicant did not apply any formal adjustments for the secondary and exploratory endpoints. They stated that:

> Because of the limited information in the literature about assessing IPF and the lack of regulatory precedence to guide in the selection of endpoints for IPF, there were no adjustments for multiple comparisons of secondary and exploratory endpoints.

Instead, they analyzed the secondary outcome variables using the pooled data from both studies, when the primary efficacy analyses (absolute change in percent predicted FVC) from PIPF-004 and from PIPF-006 each showed efficacy ($p \leq 0.0498$). They considered the results from the analyses of pooled data to be primary to that of the individual study results.

This is an issue, in particular, when a study failed to show significant treatment difference on the primary endpoint (Study 006). In the strictest sense of alpha spending, the entire alpha has been spent by the primary efficacy analyses. Furthermore, the Applicant stated that they will only analyze secondary outcome variables using the pooled data from both studies, when each study showed efficacy.

Multiplicity is also an issue in Study 004, because the Applicant would like to add the result from the analysis of secondary endpoint (i.e. progression-free survival) in the label. Of note, PFS is one of many secondary endpoints analyzed by the Applicant.

The Applicant also made some changes in the conduct of the study prior to unblinding. Some of these changes are extending the duration of blinded therapy and increasing the total sample size from 325 to 400 patients. Because these changes were made prior to unblinding and no efficacy analyses were conducted, these changes are not an issue.

Findings from the review of Study 004 and Study 006 are summarized below.

Primary Endpoint - %Predicted FVC

Patients receiving pirfenidone had a smaller mean decline from Baseline in %Predicted FVC compared to those receiving placebo at Week 72 ($p < 0.001$, rank ANCOVA) in Study 004. This represents an absolute difference of 4.4% and a relative difference of 35% between the two treatment groups.

In contrast, there was no statistically significant reduction in the mean decline from Baseline in %Predicted FVC in patients receiving pirfenidone compared to those receiving placebo at Week 72 in Study 006.

Secondary endpoint – Time to Progression-Free Survival

Overall, treatment with pirfenidone resulted in a higher proportion of progression-free survival than treatment with placebo (74%, 127/172 vs. 64%, 111/173 of patients, respectively) in Study 004. Treatment with pirfenidone was associated with a 36% relative reduction of the combined risk of disease progression or death before disease progression compared to placebo (HR [95% CI]: 0.64 [0.44–0.95]). However, this finding was not replicated in Study 006. Furthermore, exploring the individual components of this combined endpoint, the reduction appears to be mainly due to disease progression.

Post Hoc Endpoint – IPF-Related Deaths

IPF-related deaths were analyzed post-hoc by the Applicant. When data from both studies were pooled, the Applicant stated there is some evidence of survival benefit in the pirfenidone group compared to placebo on on-treatment IPF-related death. However, because all deaths (including IPF-related deaths) were not adjudicated, it is difficult to make definitive conclusion about this result.

2. INTRODUCTION

2.1 Overview

Idiopathic pulmonary fibrosis (IPF) is a disease of unknown etiology characterized by fibrosis of the lung interstitium, decrease in lung volume, and progressive pulmonary insufficiency typically leading to death. There is currently no approved treatment for IPF in the United States (USA). The Applicant, InterMune, Inc. developed pirfenidone for the treatment of patients with IPF. The Applicant claimed that "Pirfenidone is a small, synthetic, non-peptide molecule of low molecular weight (185.2 daltons). The mechanism of action of pirfenidone has not been fully established. However, existing data suggest that pirfenidone exerts both anti-fibrotic and anti-inflammatory properties and may mitigate the lung damage associated with IPF in humans."

The proposed indication for pirfenidone is for the treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. FDA has granted pirfenidone Orphan Drug and Fast Track designations.

The clinical development plan was introduced to the Division of Pulmonary and Allergy Products by InterMune, Inc. via IND 67,284 (April 21, 2003) and discussed during several meetings. Discussions mainly focused on the adequacy of the proposed primary endpoint. At the pre-NDA meeting (dated October 1, 2008), the division emphasized the important review issues as follow:

> "We remind you of the Division's stance in the End-of-Phase 2 (EOP2) meeting in which we stated that mortality is the ideal primary endpoint in a study of IPF treatment. You have proposed forced vital capacity (FVC) as the primary outcome in your pivotal efficacy studies, which is not an established surrogate for mortality in this patient population. Further, we remain uncertain as to what would constitute a clinically meaningful outcome based on FVC. As you have chosen to proceed with a clinical development program in which mortality is not the primary endpoint, we remind you that the efficacy of pirfenidone will not be based solely upon "winning" on the primary endpoint of change in FVC. We will look at the totality of the data and what drives the primary endpoint. It is imperative that the secondary endpoints, many of which are those that are clinically meaningful to patients, support the primary endpoint and the efficacy of pirfenidone in IPF patients."

The Applicant submitted this application on November 4, 2009 (NDA 22-535) in support of the proposed indication for the pirfenidone 2403mg/daily dosage strength for the treatment of patients with IPF to reduce decline in lung function. The submission included two Phase 3, randomized, double-blind, placebo-controlled studies, 004 and 006, that were nearly identical in design. The Applicant also submitted the study report of Study SP3, which was sponsored by Shionogi & Co., Inc. and formed the basis for the marketing approval of pirfenidone to treat patients with IPF in Japan on October, 2008. The design of the three studies, which is also referenced in the label, is described in Table 1. Of note, only an English translation of the clinical study report for Study SP3 was included. The patient-level data, narratives, and case report forms were not provided. 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 Shionogi-

owned data, and that the study report for SP3 was submitted only to serve as supportive information in this NDA. Because the Applicant did not submit the data for SP3, the results cannot be verified. Upon consultation with the clinical team, we have decided to exclude the results of Study SP3 from this review.

Table 1. Clinical Trials

Study/Center /Study Period	***Study Design***	***Key Inclusion Criteria***	***Patient entered/ completed***	***Primary Endpoint***
004 Phase 3 64 centers in US, Europe, Australia 7/14/06-11/7/08 72 wks DB period with 4-weeks follow up	Efficacy/Safety Randomized Multi-center Double-blind Parallel-group International Placebo-control N=435	Age 40 - 80 yrs patients with a diagnosis IPF. 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 ≥ 50% predicted and a DLco ≥ 35% predicted, while those with obstructive airways disease and those receiving concomitant medications for IPF were excluded.	Pirfenidone 2403 mg/d [3 x 267 mg TID] (174) Pirfenidone 1197 mg/d [3 x 133 mg TID] (87) Placebo (174)	Absolute change from baseline in %Predicted FVC at week 72
006 Phase 3 46 centers in US, Europe, Australia 4/27/06-10/31/08 72 wks DB period with 4-weeks follow up	Efficacy/Safety Randomized Multi-center Double-blind Parallel-group International Placebo-control N=344	Same as study 004	Pirfenidone 2403 mg/d (3 x 267 mg TID) (171) Placebo (173)	Absolute change from baseline in %Predicted FVC at week 72
SP3 Phase 3 73 sites in Japan 7/13/04-8/30/06 52 wks DB period	Efficacy/Safety Randomized Multi-center Double-blind Parallel-group Placebo-control N=275	Age 20-75, criteria based on Ministry of Health, Labor, and Welfare Specific Diffuse Pulmonary Disease Research Group's IPF Clinical Diagnosis Criteria	Pirfenidone 1800 mg/d [3 x 200 mg TID] (110) Pirfenidone 1200 mg/d [2 x 200 mg TID] (56) Placebo (109)	Mean change from baseline in VC at week 52

TID: Three times daily

2.2 Data Sources

Documents reviewed were accessed from the CDER document room at:
\\...\CDSESUB1\EVSPROD\NDA022353\022535.ENX

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Studies 004 and 006

3.1.1.1 Study Design, Efficacy Endpoints, and Statistical Methodologies

During the year of 2006 and 2008, the Applicant conducted two phase 3, randomized, double-blind, placebo-controlled international studies, Study 004 and Study 006.

The objective of each study was to evaluate the efficacy and safety of pirfenidone 2403 mg/d (three 267-mg capsules three times a day [TID]) compared with placebo (three placebo capsules TID) in patients with IPF. In each study, patients were to receive study treatment from randomization until the last patient had completed approximately 72 weeks of randomized treatment in the study. The full maintenance dose of pirfenidone, three capsules TID (total of 9 capsules taken with food), was to be administered after a 14-day dose-escalation period. Study 004 was also designed to obtain descriptive efficacy and safety data for pirfenidone in a lower dose group, 1197 mg/d (three 133-mg capsules TID).

Study 004 included three dose groups (pirfenidone 2403 mg/d, placebo, and pirfenidone 1197 mg/d), whereas 006 included two dose groups (pirfenidone 2403 mg/d and placebo). Study 004 (but not Study 006) also included plasma sampling to allow pharmacokinetic/pharmacodynamic (PK/PD) analyses and Study 006 (but not Study 004) included a high-resolution computed tomography (HRCT) scan at Baseline and Week 72. In all other study design features (eligibility criteria, study schedule, primary efficacy outcome variable and analysis, secondary and exploratory efficacy outcome measures and analyses [except for HRCT], and all safety outcome measures and analyses), the studies were identical.

Each controlled efficacy study consisted of a washout period, a screening period, a study treatment period, and a final follow-up visit (see Figure 1). During the study treatment period, patients were to be 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.

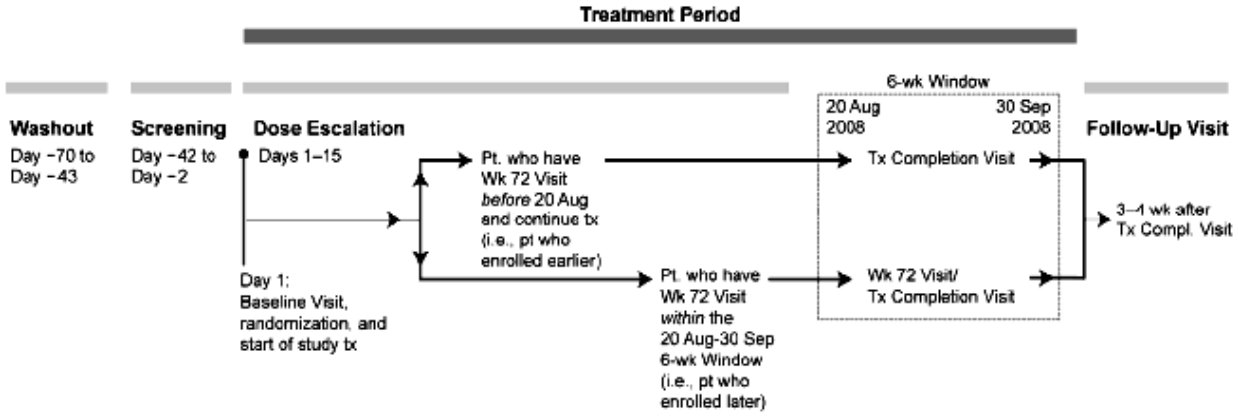
During the 4-weeks washout period (at least 28 days before the start of screening), patients were required to discontinue any prohibited medication they were taking, including therapy targeted to treat IPF. In each study, patients who completed the washout period and met the inclusion/ exclusion criteria were randomized by geographic region (USA or the rest of the world [ROW]) to receive study treatment. In Study 004, patients were randomized at a 2:2:1 ratio to receive pirfenidone 2403 mg/d, placebo, or pirfenidone 1197 mg/d. In Study 006, patients were randomized at a 1:1 ratio to receive pirfenidone 2403 mg/d or placebo. Pirfenidone 2403 mg/d (the to-be-marketed dose) versus placebo was the primary comparison.

In both Study 004 and Study 006, study treatment was escalated to a full maintenance dose of three capsules TID over a 15-day period as follows:

- Days 1–7: 1 capsule TID (3 capsules daily)
- Days 8–14: 2 capsules TID (6 capsules daily)
- Day 15 and continuing: 3 capsules TID (maximum of 9 capsules daily).

Patients were to remain on the full maintenance dose of three capsules TID until approximately 72 weeks after the last patient had been randomized in the study. This implies that patients randomized early in the enrollment period will likely be on blinded therapy for approximately 32 months.

Figure 1. Study Schema



Compl. = Completion; pt = patient(s); tx = treatment; wk = week(s)
Note: Actual Visit windows varied from planned windows as follows: 1st Treatment Completion Visit occurred August 13, 2008; last Treatment Completion Visit occurred October 17, 2008; 1st Final Follow-Up Visit occurred September 4, 2008; last Final Follow-Up occurred November 7, 2008.

Enrollment required a confident clinical and radiographic diagnosis of IPF; surgical lung biopsy was required only for diagnostic uncertainty. Patients were required to have %Predicted forced vital capacity (FVC) ≥50% and %Predicted carbon monoxide diffusing capacity (DLCO) ≥35%, while those with obstructive airways disease and those receiving concomitant medications to treat IPF were excluded.

Spirometry measurements, including FVC and forced expiratory volume 1 (FEV1) were to be assessed at Screening, Day 1 (before randomization), at Week 12, and every 12 weeks thereafter until the Final Follow-up visit. At each visit, three FVC values were collected before and after bronchodilator, respectively, until maximum acceptable FVC value was chosen.

The primary efficacy outcome variable was the absolute change in %Predicted FVC (post-bronchodilator) from Baseline to Week 72. Baseline FVC was defined as the mean of the maximum acceptable FVC measurements obtained during the screening and the 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 Week 72B).

%predicted FVC was calculated as 100 * (Actual FVC value in liters / predicted FVC).

Predicted FVC for men
Caucasian-American = 0.00018642 x height (cm) ^{2} + 0.00064 x Age (yrs) - 0.000269 x Age (yrs) ^{2} – 0.1933
African-American = 0.00016643 x height (cm) ^{2} - 0.01821 x Age (yrs) - 0 x Age (yrs) ^{2} – 0.1517
Mexican-American = 0.00017823 x height (cm) ^{2} - 0.00891 x Age (yrs) – 0.000182 x Age (yrs) ^{2} + 0.2376
Predicted FVC for women
Caucasian-American = 0.00014815 x height (cm) ^{2} + 0.01870 x Age (yrs) - 0.000382 x Age (yrs) ^{2} – 0.3560
African-American = 0.00013606 x height (cm) ^{2} + 0.00536 x Age (yrs) – 0.000265 x Age (yrs) ^{2} – 0.3039
Mexican-American = 0.00014246 x height (cm) ^{2} + 0.00307 x Age (yrs) – 0.000237 x Age (yrs) ^{2} + 0.1210

The primary analysis of the primary endpoint was a rank ANCOVA, with a standardized rank change in FVC as the outcome variable and standardized rank baseline FVC as a covariate. The analysis was to be stratified (fixed effect) by geographic region (USA vs. ROW) within the MITT patient population (all randomized patients who received any amount of study treatment) including only the pirfenidone 2403-mg/d and placebo groups. The treatment effect was to be tested using the Mantel-Haenszel mean score chi-square test. The test of significance for the primary analysis of the primary efficacy outcome variable was to use a two-sided alpha of 0.0498. Of note, all randomized patients were treated with study drug; therefore, the prespecified MITT analysis represents a true ITT analysis.

The primary approach in handling missing data was pre-specified and was detailed in the protocol and the Statistical Analysis Plan. Missing assessments were handled as follows.

Data that were missing as a result of death were ranked "worse" than data missing for reasons other than death and the ranking will be based on the time-to-death, with the shortest time until death as the worst rank. Missing data due to reasons other than death (e.g. missing visits, early withdrawal from the study, including missing values due to lung transplantations) were imputed with average measurements for similar patients at the same time point using the sum of squared differences (SSD) method.

The "SSD method" imputation procedure and selection criteria are outlined as follows:
Step 1: For each post-Baseline missing value to be imputed at a visit (Visit X) for a particular patient (Patient A), a set of all patients from the same study without any missing values at the same visits from Baseline up to Visit X as Patient A will be selected. If Patient A is missing all data from Baseline up to Visit X, then that patient's missing value will not be imputed and instead will be left as missing and not included in the analysis.
Step 2: For the patients in this set, the sum of squared differences (SSDs) between each patient selected in Step 1 and Patient A will be calculated across all non-missing values from Baseline up to the visit prior to Visit X.
Step 3: The 3 patients with the smallest SSDs will be identified and the average of their non-missing value at Visit X will be used to impute the missing value for Patient A at that visit. The number of smallest SSDs to calculate the average can be less than 3 due to availability of patients defined in Step 1 or more than 3 based on tied SSDs.

Three separate supportive analyses were pre-specified to assess robustness and provide estimates of the magnitude of effect:

1. Mean change from Baseline in percent predicted FVC. For this analysis, missing FVC data due to death were assigned a value of 0 and missing FVC data due to reasons other than death were imputed using the "SSD method".
2. Repeated measures analysis of percent predicted FVC across all study time-points for inference and estimation. For this analysis, missing FVC data due to death were assigned a value of 30% and missing FVC data due to reasons other than death were imputed using the SSD method.

3. Ogive plot. The cumulative distribution of change from Baseline in percent predicted FVC based on FVC rank was computed.

The secondary efficacy outcome variables for each study were as follows:

- Time to worsening of IPF, defined as the first to occurrence of one of the following events:
  - Acute IPF Exacerbation
  - IPF-related death (excluding deaths that were not the reason for treatment or study discontinuation and more than 28 days after the last study treatment and more than 98 days after the last study visit for patients who did not complete the study).
  - Lung transplantation
  - Respiratory hospitalization
- Progression-free survival, defined as time from randomization to the first occurrence of any of the following events:
  - 10% absolute decline in percent predicted FVC, or
  - 15% absolute decline in percent predicted Hgb-corrected DLco, or
  - All-cause mortality

  In the case of FVC or DLco, the decline was to be confirmed at 2 consecutive visits at least 6 weeks apart
- Categorical assessment of the absolute change in percent predicted FVC from Baseline to Week 72
- Change in dyspnea from Baseline to Week 72
- Change in percent predicted Hgb-corrected DLco from Baseline to Week 72
- Change in the worst oxygen SpO2 measurement observed during the 6MWT from Baseline to Week 72
- Change in the HRCT assessment of lung fibrosis from Baseline to Week 72 (Study 006 only)
- Change in distance walked in the 6MWT from Baseline to Week 72

The Applicant did not apply any multiple adjustments for the secondary and exploratory endpoints. Their reason is stated as follow:

Because of the limited information in the literature about assessing IPF and the lack of regulatory precedence to guide in the selection of endpoints for IPF, there were no adjustments for multiple comparisons of secondary and exploratory endpoints.

In the protocol, the Applicant also stated:

If the primary efficacy analyses (absolute change in percent predicted FVC) from PIPF-004 and from PIPF-006 each showed efficacy ($p \leq 0.0498$), 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. The pooled analyses were to be stratified by study.

The exploratory efficacy outcome variables for each study were as follows:

- Overall survival time, as measured by time from randomization to death
- Change from Baseline to Week 72 in respiratory status, measured by St. Georges Respiratory Questionnaire (SGRQ)
- Change from Baseline to Week 72 in resting A-a gradient
- Change from Baseline to Week 72 in the absolute percent predicted TLC
- Time from randomization to first requirement for prescribed outpatient oxygen use for patients not on supplemental oxygen at Baseline
- Change from Baseline to Week 72 in quality of life, measured by the World Health Organization Quality-of-Life (WHO QOL) questionnaire

• Change from Baseline to Week 24 in biomarkers (this analysis has not been conducted to date and will not be a part of the NDA)
• Change from Baseline to Week 72 in breathlessness in the Borg scale
• Number of days alive without a respiratory hospitalization through Week 72

Sample Size Calculation

The primary efficacy analysis was adequately powered for evaluating the primary efficacy outcome variable in the pirfenidone 2403-mg/d versus the placebo group in both studies. Based on the Applicant's sample size calculation, 160 patients per group were expected to provide 97% power to detect a treatment difference of 2.75% in the absolute change in %Predicted FVC between Baseline and Week 72, assuming a standard deviation of 6% at a significance level of 0.05. For Study 004, an additional 80 patients randomized to pirfenidone 1197-mg/d would provide descriptive information for the dose-response relationship of pirfenidone's efficacy.

Changes in Conduct of the Study

There were two amendments to the original protocol (January 27, 2006): Amendment 1 (March 19, 2007), and Amendment 2 (December 21, 2007). The Applicant claimed that these amendments were made prior to unblinding and analyses of the efficacy data.

1. Extend duration of blinded therapy and adjust the visit schedule after the first 72 weeks of treatment. Currently, the protocol requires 60 weeks of therapy for all patients. This is extended to 72 weeks to increase the power and broaden the clinical experience. This change will also provide additional blinded safety and efficacy data and likely 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 is randomized. The primary outcome of the study remains unchanged.

2. The study sample size has increased by 75 patients from 325 to 400.
During the enrollment period of Study 004 and Study 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, we have decided to modify the study design of the studies to provide appropriate powering for primary and secondary efficacy outcome measures.

In general terms, at appropriate places throughout the protocol, the text describing this increase is similar to the following: Approximately 400 patients will be randomized by geographic region to receive pirfenidone 2403 mg/d (n = 160 patients), placebo equivalent (n = 160 patients) or pirfenidone 1197 mg/d (n = 80) in a 2:2:1 ratio using an interactive voice-response system (IVRS).

3. Additionally, the DMC requested a stopping rule to guide their recommendations in the event of strongly favorable efficacy results around survival. This stopping rule will be invoked if an analysis of survival time utilizing pooled data from both studies (Study 006 and Study 004) in the 2403 mg group versus the placebo group is 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 percent predicted FVC for each study will be 0.0498 based on an adjustment for the two DMC mortality analyses. This stopping rule is 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 is not based on power calculations or an expectation that the study is likely to stop early.

4. A pooled analysis from both studies is specified because if the primary FVC analysis is significant in both studies all of the specified efficacy endpoints and the safety data will 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 is best estimated with the larger sample size of a combined analysis.

Changes in the Statistical Analysis Plan (SAP)

There were two amendments to the original SAP (August 8, 2007), Amendment 1 (July 14, 2008), and Amendment 2 (January 6, 2009). The Applicant claimed that these amendments were made prior to unblinding and analyses of the efficacy data. Most of the changes were updated section reference, corrected efficacy analyses procedure, clarified wording to make SAP more complete and clear.

> Modifications made in the planned statistical analysis plan in Protocol Amendment 1 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 percent predicted FVC in secondary efficacy outcome variables), the range of individual categories in percent predicted FVC to more evenly distribute patients, and the methods for handling missing data.
>
> Modifications made in the planned statistical analysis in Protocol Amendment 2 consisted of an added pooled analysis of secondary and exploratory efficacy outcome variables using combined data from Study 004 and Study 006; added stopping rules at the request of the DMC in the event of statistically significant improvement in survival time in pirfenidone-treated patients observed using pooled data from Study 004 and Study 006; and a modified alpha level for the final efficacy analysis to account for the stopping rules for the DMC.

Amendment 2 provided additional information about the Study Period (under the Study Design section of the protocol). This information is important to understand how they conducted the time-to-event analyses:

> The Study Period consists of a Treatment Period and a Follow-up Period. The duration of the Treatment Period (duration of intended blinded therapy) for each patient differs depending on when the patient was randomized into the study. Study treatment was to stop during a 6 week window starting on 20 August 2008 and terminating on 30 September 2008, which is 72 weeks after the last patient was randomized. All patients still undergoing study assessments at the start of the 6 week window are 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 is 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 will end at the start of the 6 week window. Following the completion of the Treatment Period, patients enter the Follow-up Period.

Other changes made to the planned analysis, which were not a part of a protocol amendment, are summarized in the Statistical Analysis Plan.

Trial Monitoring and Interim Analysis

As planned, the first DMC meeting for safety assessment occurred on April 1, 2007 after enrollment of approximately 50% of patients in both studies. The DMC reviewed the data from both studies at that time. Additional meetings took place approximately every 6 months until the conclusion of the trials (i.e. September 28, 2007 and April 11, 2008). The DMC reviewed the

unblinded interim analyses and have concluded that the survival boundary was not crossed. The Applicant submitted the three interim analyses datasets on December 29, 2009 upon my request.

3.1.1.2 Patient Disposition, Demographic and Baseline Characteristics

The focus of this review will be on two treatment groups, pirfenidone 2403 mg/d and placebo. For simplicity, when all three treatment arms are presented, pirfenidone 2403 mg/d will be denoted by HD, pirfenidone 1197 will be denoted by LD, and placebo by PL. When only pirfenidone 2403 mg/d and placebo are presented, pirfenidone 2403 mg/d will be denoted by pirfenidone.

A total of 779 patients (345 HD, 87 LD, and 347 PL) were randomized (Table 2) and the majority (80%) of patients completed the 72 weeks of active treatment. The most common reason for discontinuations was adverse event. Compared to placebo, pirfenidone-treated patients had a higher percentage of dropouts due to adverse event.

In both studies, two types of case report forms (CRF) collected information about treatment discontinuation (i.e. the treatment CRF and the AE CRF) and the number of patients who were reported as discontinuing from treatment due to an AE differs between these two forms. The Applicant failed to reconcile the difference. Instead they reported the discontinuation data that was recorded on the Treatment CRF. This discrepancy did not effect the overall efficacy conclusion.

The disposition of patients is summarized in two ways:

- By study treatment (completion of study treatment or permanent discontinuation from study treatment)
- By study (completion of study or premature withdrawal from study)

Table 2. Patients' Accountability, N (%) (All Randomized Patients)

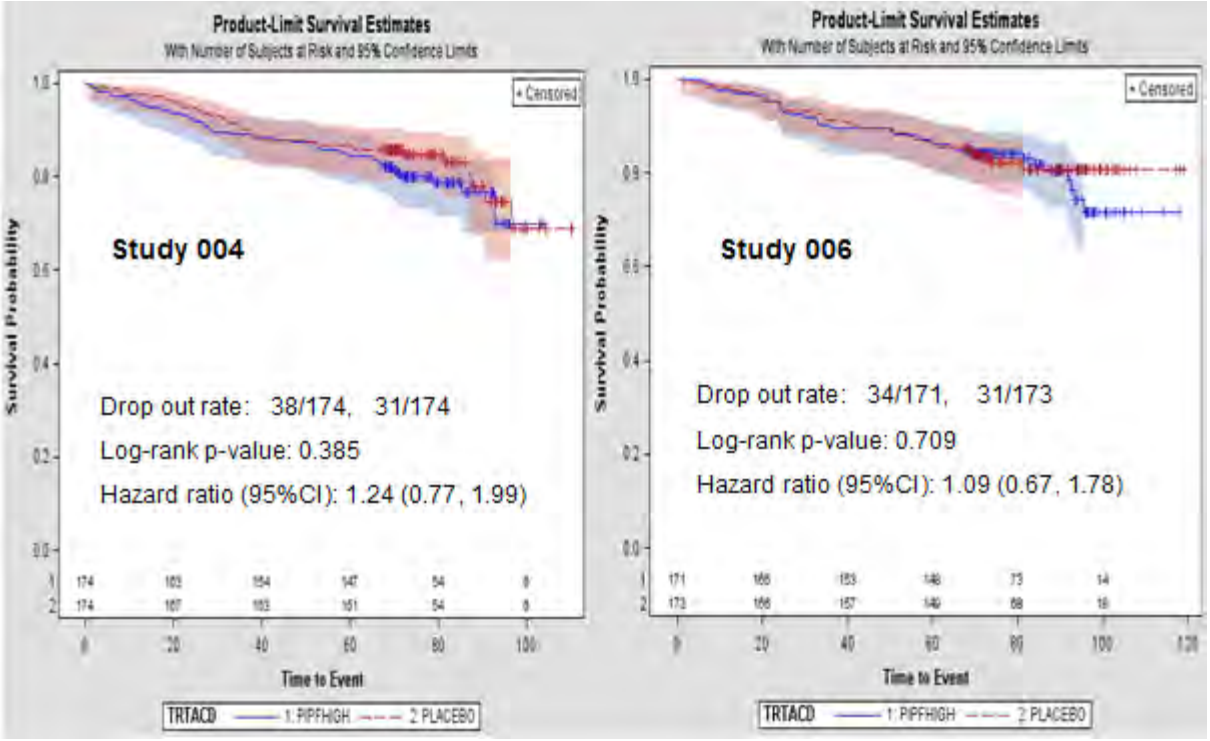
	Study 004 (N=435)			***Study 006 (N=344)***	
	Pirfenidone 1197 mg/d (n=87)	Pirfenidone 2403 mg/d (n=174)	Placebo (n=174)	Pirfenidone 2403 mg/d (n=171)	Placebo (n=173)
Received study Treatment	87	174	174	171	173
Completed study treatment	70 (80.5)	136 (78.2)	143 (82.2)	137 (80.1)	142 (82.1)
Discontinued study treatment	17 (19.5)	38 (21.8)	31 (17.8)	34 (19.9)	31 (17.9)
Reason of early discontinuation of study treatment					
Adverse event	11 (12.6)	21 (12.1)	14 (8.0)	24 (14.0)	14 (8.1)
Death	4 (4.6)	5 (2.9)	9 (5.2)	1 (0.6)	11 (6.4)
Lung transplantation	0	3 (1.7)	4 (2.3)	2 (1.2)	3 (1.7)
Applicant decision	0	0	0	1 (0.6)	0
Patient's decision	2 (2.3)	5 (2.9)	4 (2.3)	3 (1.8)	3 (1.7)
Other	0	4 (2.3)	0	3 (1.8)	0
Received Treatment	87	174	174	171	173
Completed study	73 (83.9)	146 (83.9)	144 (82.8)	139 (81.3)	146 (84.4)
Discontinued study	14 (16.1)	28 (16.1)	30 (1.2)	32 (18.7)	27 (15.6)
Reason of withdrawal from the study					
Adverse event	3 (3.4)	8 (4.6)	3 (1.)	5 (2.9)	4 (2.3)
Death	9 (10.3)	12 (6.9)	18 (10.3)	15 (8.8)	14 (8.1)

Lung transplantation	0	3 (1.7)	4 (2.3)	4 (2.3)	4 (2.3)
Applicant decision	0	0	0	1 (0.6)	0
Patient's decision	2 (2.3)	4 (2.3)	5 (2.9)	6 (3.5)	5 (2.9)
Other	0	1 (0.6)	0	3 (1.8)	0

Note: Results from study report and dataset of ADSL.xpt.

The survival curves for premature study drug discontinuations are presented in Figure 2. The dropout rates were slightly higher in the pirfenidone group compared to the placebo group.

Figure 2. Time to Early Withdrawal from Study Treatment



In both studies, the demographic and baseline disease characteristics were generally well balanced and comparable between the treatment groups (Table 3). Overall, the mean age was 66 years. Majority of patients were Caucasian and approximately two-thirds of patients were male. Of note in Study 004, a slightly higher proportion of female patients in the pirfenidone group compared to the placebo group were enrolled. The overall baseline mean %Predicted FVC for the population was 75%. Approximately 65% of patients in Study 004 and approximately 86% of patients in Study 006 were enrolled at sites in the USA.

With the exception of gender, the demographic and baseline disease characteristics were generally well balanced and comparable between the geographic region (i.e. USA and ROW) in both studies. The proportion of female in ROW was different between studies (67% in Study 004 and 20% in Study 006) (Table 4).

Table 3. Patients' Demographic and Baseline Characteristics by Treatment, N (%)

	Study 004 (N=348)		***Study 006 (N=344)***	
Demographic Parameter	Pirfenidone 2403 mg/d (N=174)	Placebo (N=174)	Pirfenidone 2403 mg/d (N=171)	Placebo (N=173)
Age at Randomization (yrs)				
Mean (SD)	65.7 (8.15)	66.3 (7.53)	66.8 (7.9)	67.0 (7.80)
Range	45 – 80	40 – 79	45 – 80	42 – 80
<65	75 (43.1)	73 (41.9)	70 (40.9)	61 (35.3)
65 – 74	72 (41.4)	69 (39.7)	64 (37.4)	83 (48.0)
≥75	27 (15.5)	32 (18.4)	37 (21.6)	29 (16.8)
Sex				
Male	118 (67.8)	128 (73.6)	123 (71.9)	124 (71.7)
Female	56 (32.2)	46 (26.4)	48 (28.1)	49 (28.3)
Race				
White	168 (96.6)	168 (96.6)	169 (98.8)	171 (98.8)
Black	2 (1.1)	2 (1.1)	1 (0.6)	2 (1.2)
Asian	2 (1.1)	4 (2.3)	1 (0.6)	0
Native American	2 (1.1)	0	0	0
Geographic Region				
ROW	60 (34.5)	60 (34.5)	23 (13.4)	23 (13.3)
USA	114 (65.5)	114 (65.5)	148 (86.5)	150 (86.7)
BMI at baseline (kg/m^2)				
Mean (SD)	30.1 (4.2)	29.9 (4.6)	30.7 (4.9)	30.3 (4.5)
Range	21 – 44	20 - 48	22 – 47	15 - 46
FVC (% predicted)				
Mean (SD)	74.5 (14.5)	76.2 (15.5)	74.9 (13.2)	73.1 (14.2)
Range	52 – 124	48 – 136	50 – 108	52 – 128
DLco (% predicted)				
Mean (SD)	46.4 (9.5)	46.1 (10.2)	47.8 (9.8)	47.4 (9.2)
Range	30 – 81	30 – 90	31 – 81	33 – 78
Supplemental oxygen use				
Yes	29 (16.7)	25 (14.4)	48 (28.1)	49 (28.3)
No	145 (83.3)	149 (85.6)	123 (71.9)	124 (71.7)
Time since IPF diagnosis to randomization (yrs)				
Mean (SD)	1.3 (0.96)	1.4 (1.12)	1.2 (1.09)	1.1 (0.99)
Range	>0 – 4	>0 – 4	>0 – 4	>0 – 4
<1 yr	83 (47.7)	81 (46.6)	100 (58.5)	108 (62.4)
≥1 yrs	91 (52.3)	93 (53.4)	71 (41.5)	65 (37.6)
Smoking status at screening, N (%)				
Never smoked	56 (32.2)	51 (29.3)	59 (34.5)	64 (37.0)
Previously smoked	110 (63.2)	114 (65.5)	112 (65.5)	101 (58.4)
Currently smokes	8 (4.6)	9 (5.2)	0	8 (4.6)

Note: Results from study report and dataset of ADSL.xpt.

Table 4. Patients' Demographic and Baseline Characteristics by Regions, N (%)

	Study 004 (N=348)		***Study 006 (N=344)***	
Demographic Parameter	ROW (N=120)	USA (N=228)	ROW (N=46)	USA (N=298)
Age at Randomization (yrs)				
Mean (SD)	66.7 (8.0)	65.7 (7.8)	65.0 (7.4)	67.2 (7.9)
Range	45 – 80	40 - 80	46 – 79	42 – 80
<65	49 (40.8)	99 (43.3)	22 (47.8)	109 (36.6)
65 – 74	46 (38.3)	95 (41.7)	20 (43.5)	127 (42.6)
≥75	25 (20.8)	34 (14.9)	4 (8.7)	62 (20.8)
Sex				
Male	80 (33.3)	166 (72.8)	37 (80.4)	210 (70.5)
Female	40 (66.7)	62 (27.2)	9 (19.6)	88 (29.5)
Race				
White	118 (98.3)	218 (95.6)	46 (100)	294 (98.7)
Black	0	4 (1.8)	0	3 (1.0)
Asian	0	6 (2.6)	0	1 (0.3)
Native American	2 (1.7)	0	0	0
BMI at baseline (kg/m^2)				
Mean (SD)	29.3 (4.5)	30.3 (4.4)	29.1 (4.0)	30.7 (4.7)
Range	20 – 48	22 - 44	22 – 46	15 – 47
FVC (% predicted)				
Mean (SD)	77.1 (16.6)	74.5 (14.1)	73.2 (12.5)	74.1 (13.9)
Range	51 – 136	48 – 120	54 – 101	50 – 128
DLco (% predicted)				
Mean (SD)	46.1 (10.4)	46.3 (9.6)	45.3 (10.0)	47.9 (9.4)
Range	30 – 81	30 – 90	33 – 73	31 - 81
Supplemental oxygen use				
Yes	5 (4.2)	49 (21.5)	1 (2.2)	96 (32.2)
No	115 (95.8)	179 (78.5)	45 (97.8)	202 (67.8)
Time since IPF diagnosis to randomization (yrs)				
Mean (SD)	1.3 (1.1)	1.4 (1.0)	1.1 (1.1)	1.1 (1.0)
Range	>0 – 4	>0 – 4	>0 – 3.6	>0 – 4
<1 yr	59 (49.2)	105 (46.1)	30 (65.2)	178 (59.7)
≥1 yrs	61 (50.8)	123 (53.9)	16 (34.8)	120 (40.3)
Smoking status at screening, N (%)				
Never smoked	43 (35.8)	64 (28.1)	18 (39.1)	105 (35.2)
Previously smoked	65 (54.2)	159 (69.7)	27 (58.7)	186 (62.4)
Currently smokes	12 (10.0)	5 (2.2)	1 (2.2)	7 (2.4)

Note: Results from study report and dataset of ADSL.xpt.

The average percentage of compliance to the study treatment was above 90% in both studies (Table 5). The proportion of patients with ≥80% compliance was slightly lower in the pirfenidone group compared to the placebo group. The average percentage of compliance to study treatment was similar between USA and ROW (Table 6).

Table 5. Study Treatment Compliance and Duration by Treatment

	Study 004 (N=348)		Study 006 (N=344)	
Treatment Compliance	Pirfenidone 2403 mg/d (N=174)	Placebo (N=174)	Pirfenidone 2403 mg/d (N=171)	Placebo (N=173)
Patients who Received Any Amount of Study Treatment				
N (%)	174 (100)	174 (100)	171 (100)	173 (100)
Percent Compliance per Patient [a]				
Mean (SD)	88.9 (23.1)	93.8 (14.6)	91.4 (17.9)	93.7 (16.2)
Median (Range)	98 (2 – 100)	99 (1 – 100)	98 (10 – 100)	98 (0 – 100)
N (%)				
80% to 100% [b]	151 (86.8)	161 (92.5)	152 (88.9)	162 (93.6)
60% to < 80%	7 (4.0)	5 (2.9)	6 (3.5)	2 (1.2)
40% to <60%	1 (0.6)	4 (2.3)	4 (2.3)	3 (1.7)
<40%	15 (8.6)	4 (2.3)	9 (5.3)	6 (2.5)
Treatment Duration in weeks				
Mean (SD)	70.3 (22.5)	71.1 (20.7)	75.0 (22.4)	74.6 (22.2)
Median (Range)	72 (1 - 104)	72 (0 - 110)	75 (6 – 118)	73 (1 – 120)

Note: Results from study report and dataset of ADSL.xpt.

Table 6. Study Treatment Compliance and Duration by Regions

	Study 004 (N=348)		Study 006 (N=344)	
Treatment Compliance	ROW (N=120)	USA (N=228)	ROW (N=46)	USA (N=298)
Patients who Received Any Amount of Study Treatment				
N (%)	120 (100)	228 (100)	46 (100)	298 (100)
Percent Compliance per Patient [a]				
Mean (SD)	91.9 (20.0)	91.1 (19.2)	96.0 (12.5)	92.0 (17.6)
Median (Range)	99 (1.3 – 100)	98 (1.7 – 100)	99 (23 – 100)	98 (0 – 100)
N (%)				
80% to 100% [b]	108 (90.0)	204 (89.5)	43 (93.5)	271 (90.9)
60% to < 80%	4 (3.3)	8 (3.5)	2 (4.3)	6 (2.0)
40% to <60%	2 (1.7)	3 (1.3)	0	7 (2.4)
<40%	6 (5.0)	13 (5.7)	1 (2.2)	14 (4.7)
Treatment Duration in weeks				
Mean (SD)	70.0 (21.4)	71.0 (21.7)	75.5 (18.5)	74.7 (22.9)
Median (Range)	72 (0 - 110)	72 (1 - 110)	77 (6 – 100)	73 (1 – 120)

Note: Results from study report and dataset of ADSL.xpt.

3.1.1.3 Results and Conclusions

Primary Efficacy Endpoint – Absolute change in %Predicted FVC from Baseline to Week-72

The primary analysis of the primary endpoint was a rank ANCOVA using the imputed data. Of note, in Study 004, imputation was applied to missing data at Week 72 on 12 patients in the pirfenidone group and 8 patients in the placebo group for reasons other than death. Similarly in Study 006, imputation was applied to missing data on 10 patients in the pirfenidone group and 9 patients in the placebo group for reasons other than death. Given the small numbers, and uniform distribution of patient dropouts across treatment groups, missing data did not represent a meaningful source of bias in the interpretation of the efficacy. Therefore, the pre-specified imputation method (SSD) was acceptable. Hereafter, all analyses were conducted using imputed data unless stated otherwise.

Patients receiving pirfenidone had a smaller mean decline from Baseline in %Predicted FVC compared to those receiving placebo at Week 72 ($p < 0.001$, rank ANCOVA) in Study 004 (Table 7). This represents an absolute difference of 4.4% (i.e. -8.0 – -12.4 = 4.4 %Predicted FVC) and a relative difference of 35% (i.e. 4.4/12.4 = 0.35) between the two treatment groups.

In contrast, in Study 006, there was no statistically significant difference in the mean decline from Baseline in %Predicted FVC in patients receiving pirfenidone compared to those receiving placebo at Week 72 (Table 7).

Table 7. Mean Change in %Predicted FVC (Imputed)

	Pirfenidone		Placebo		Treatment Comparison		
Week	N Observed (Death)	Mean [a] (STD)	N Observed (Death)	Mean [a] (STD)	Absolute Diff. [c]	Relative Diff. [d]	p-value [b]
Study 004							
Baseline	174 (0)	74.5 (14.5)	174 (0)	76.2 (15.5)	-1.7	--	--
Week 12	170 (1)	-1.2 (6.8)	166 (3)	-2.7 (9.5)	1.4	53.5	0.061
Week 24	168 (1)	-1.4 (7.5)	164 (5)	-3.9 (12.1)	2.5	65.2	0.014
Week 36	160 (2)	-2.6 (9.1)	156 (10)	-7.2 (15.6)	4.6	63.7	<.001
Week 48	159 (4)	-4.4 (12.1)	154 (13)	-9.2 (17.2)	4.8	52.3	<.001
Week 60	156 (7)	-6.6 (15.5)	148 (14)	-10.7 (17.6)	4.1	38.3	<.001
Week 72	**154 (8)**	**-8.0 (16.5)**	**150 (16)**	**-12.4 (18.5)**	**4.4**	**35.3**	**0.001**
Study 006							
Baseline	171 (0)	74.9 (13.2)	173 (0)	73.1 (14.2)	1.7	--	--
Week 12	167 (2)	-1.5 (10.7)	168 (0)	-1.1 (4.5)	-0.4	-31.5	0.021
Week 24	168 (2)	-1.7 (11.2)	165 (5)	-4.5 (12.7)	2.8	62.1	<.001
Week 36	159 (4)	-2.5 (13.4)	158 (7)	-4.9 (15.0)	2.4	48.2	0.011
Week 48	157 (6)	-5.0 (15.6)	156 (8)	-6.9 (15.4)	1.9	27.3	0.005
Week 60	151 (10)	-7.4 (18.2)	148 (11)	-8.0 (17.2)	0.6	7.6	0.172
Week 72	**148 (13)**	**-9.0 (19.6)**	**149 (15)**	**-9.6 (19.1)**	**0.6**	**6.5**	**0.501**

[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).
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 0 was imputed for the assessment.

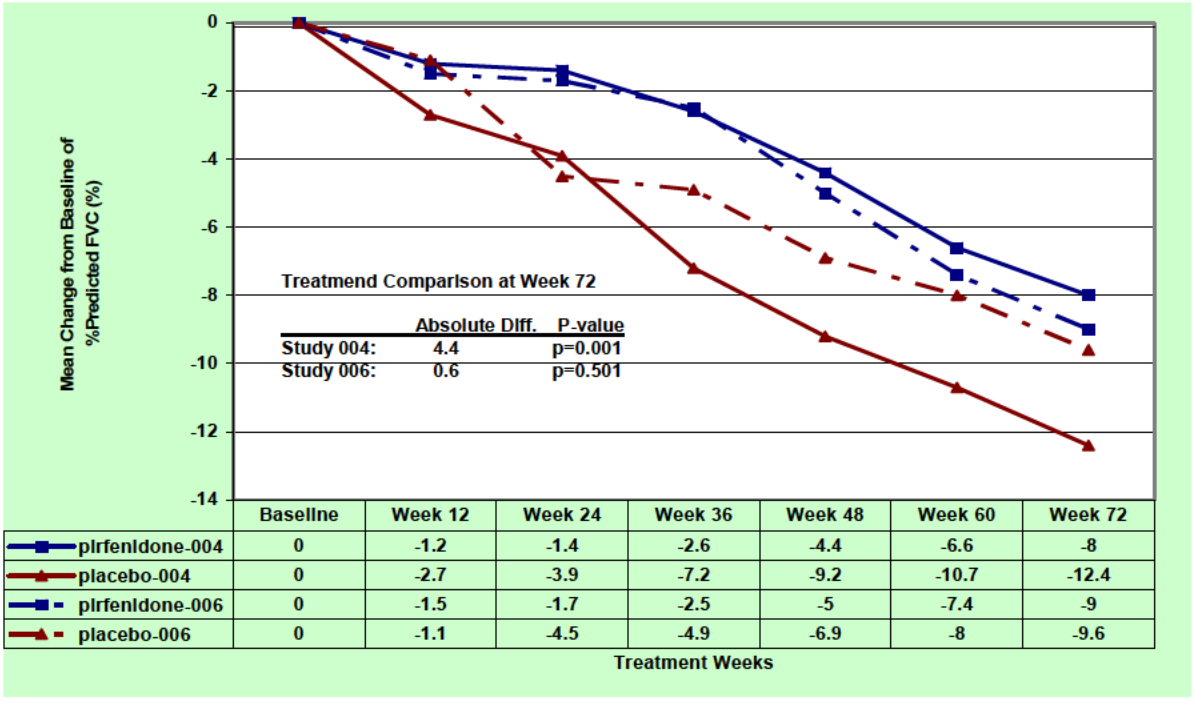
In Figure 3, the solid blue line represents the pirfenidone arm and the solid red line represents the placebo arm from Study 004. The dotted blue line represents the pirfenidone arm and the dotted red line is the placebo arm from Study 006. The x-axis shows the corresponding weeks the FVC measures were collected and reported, and the y-axis shows the mean change from baseline in %Predicted FVC. There is evidence that the mean change from baseline in %Predicted FVC in the pirfenidone arm is almost identical in both studies. In contrast, the mean change from baseline in %Predicted FVC in the placebo arms are not the same and the placebo arm (dotted red line) appears to come together with the pirfenidone arm (dotted blue line) in Study 006. (For the graphic display of observed data, please see Figure 15 in the Appendix.)

The pirfenidone groups appear to decline at the same rate in both studies while the placebo groups behaved differently. The placebo group declined at a faster rate in Study 004 (solid red line) compared to that in Study 006 (dashed red line), particularly after Week 24.

The Applicant tried to explain the reasons for the difference in results between these two studies. They claimed that a smaller proportion of patients taking pirfenidone use salbutamol compared to placebo patients (28% vs. 41%, respectively) in Study 006. They also claimed that more patients in Study 006 than in Study 004 were diagnosed with IPF within 1 year prior to study entry (60% vs. 48%).

I also noticed that Study 006 had a higher proportion of US patients than Study 004, but no definitive conclusion can be made on which factor contributed to the difference of two placebo groups and which placebo group was more representative of the true status.

Figure 3. Mean Change from Baseline in %Predicted FVC (Imputed)



	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

The Applicant's primary approach in handling missing data is reasonable. The Applicant also conducted additional analyses and results were displayed in Table 8 (two were pre-specified marked with * and two were done post-hoc marked with †).

In Study 004, the Applicant's different analytic techniques for data imputation resulted in similar conclusions (i.e. significant p-value in favor of pirfenidone). Estimates of treatment effect (depending on imputation or estimation methods) ranged from 3.1 to 4.4.

With the exception of the post-hoc analysis using rank repeated measures, the results using other analytic approaches in Study 006 resulted in similar conclusion (i.e. no significant difference between pirfenidone and placebo) and the estimates of treatment effect using these approaches ranged from 0.6 to 1.13 (Table 8). The Applicant's rationale for conducting an additional post-hoc analysis using rank repeated measures is as follows:

> A repeated measures mixed linear model was prespecified to integrate the assessments of change in percent predicted FVC across all study visits. Recognizing the dependency of this model on normally distributed data, missing FVC data due to death were assigned a value of 30% as opposed to the 0% used in the mean change from baseline analysis. Once the studies were unblinded, it was determined that even with this alternative imputation, the data were not normally distributed: the Shapiro-Wilk test rejected the hypothesis that the data was normally distributed at week 72 ($p < 0.0001$). To address this unexpected analytic finding and preserve the integrity of the model, we conducted a repeated measures analysis on FVC data ranked at each study timepoint, using the prespecified methodology for the primary endpoint FVC ranking. For completeness of the presentation of the findings from the repeated measures analysis and to avoid the challenges around interpreting differences in mean ranks, the p-values from the analysis of the ranked data will be presented along with graphs of the LS mean estimates of FVC change from the originally prespecified model based on FVC data with missing data due to death imputed as 30%.

Although we find this approach reasonable, the objective of this analysis method is to test the null hypothesis that the observations come from the same distribution and not exactly testing whether there is difference in treatment effect at Week 72. Furthermore, this analysis is one of many secondary analyses performed on the primary endpoint and this approach was conceptualized after studies were unblinded.

Table 8. Estimate of Treatment Effect of %Predicted FVC at Week-72

	Study 004			Study 006		
	Pirfenidone	Placebo	Difference	Pirfenidone	Placebo	Difference
Pre-specified Rank ANCOVA Model with SSD Imputation (primary analysis)						
Mean (STD)	-8.0 (16.5)	-12.4 (18.5)	4.4	-9.0 (19.6)	-9.6 (19.1)	0.6
p-value	--	--	0.001	--	--	0.501
Repeated measure model with imputing death to 30%, no other imputation was made * [a]						
LS Mean (SE)	-6.5 (0.82)	-9.5 (0.84)	3.1 (0.8, 5.4)	-6.5 (1.00)	-7.2 (1.00)	0.7 (-1.9, 3.3)
p-value	--	--	0.009			0.576
Overall Mean Change from Baseline to Week 72 Using ANCOVA Model with SSD Imputation * [b]						
LS Mean (SE)	-3.6 (0.8)	-6.8 (0.8)	3.3 (1.2, 5.3)	-3.4 (1.0)	-4.5 (1.0)	1.13 (-1.2, 3.5)
p-value	--	--	0.002	--	--	0.338
Rank Repeated Measure Model with SSD Imputation † [c]						
LS Mean (SE)	--	--	--	--	--	--
p-value	--	--	<0.001	--	--	0.007
Rank ANCOVA Model with LOCF to Week 72 and imputing death to 0 † [d]						
Mean (STD)	-7.9 (16.5)	-12.2 (18.5)	4.4	-9.0 (19.6)	-9.6 (19.2)	0.6
p-value			0.001	--	--	0.503

[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), and assessment week as fixed effects; covariates of baseline percent predicted FVC, and a repeated effect of assessment week, unstructured covariance structure and patient as the subject factor.
[b] ANCOVA model comparing Pirfenidone 2403 mg/d to Placebo, with mean change from baseline to week 72 as the outcome variable. Treatment, geographical region (USA and ROW), and baseline percent predicted FVC as covariates.
[c] Base on ranked %FVC change using the same mixed linear model as [a].
[d] Base on rank ANCOVA model using LOCF imputation to week 72.

I also performed continuous responder analysis. In each study, continuous responder curves for each treatment arm were plotted. In these plots, all patients who drop out from treatment due to death or lung transplantation are considered non responders (i.e. highest decline in %Predicted FVC) and other missing values were imputed using SSD method. Note that 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 decline in %Predict FVC from baseline (or worsening) at Week 72, and the y-axis show the corresponding percentage of patients achieving that level of %Predicted FVC decline or greater. The positive treatment effect of pirfenidone was demonstrated by consistent separation of the curve across different level of response in Study 004. As an example, only 20% of pirfenidone-treated patients have at least 10% decline in %Predicted FVC compared to 35% in placebo (Figure 4). This evidence is not seen in Study 006 (Figure 5). (For continuous responder analyses at Week 24 and Week 48 for both studies, please see Figure 16, Figure 17, Figure 18, and Figure 19 in the Appendix.)

In consultation with the clinical team, the cut off point of at least 10% decline in %Predicted FVC was chosen to perform a two category responder analysis. This responder analysis confirmed the primary analysis result, which is pirfenidone shows some benefit in reducing lung function decline in Study 004, but not in Study 006 (Figure 6).

Figure 4. Cumulative % of Patients of Change from baseline in %Predicted FVC (Imputed)

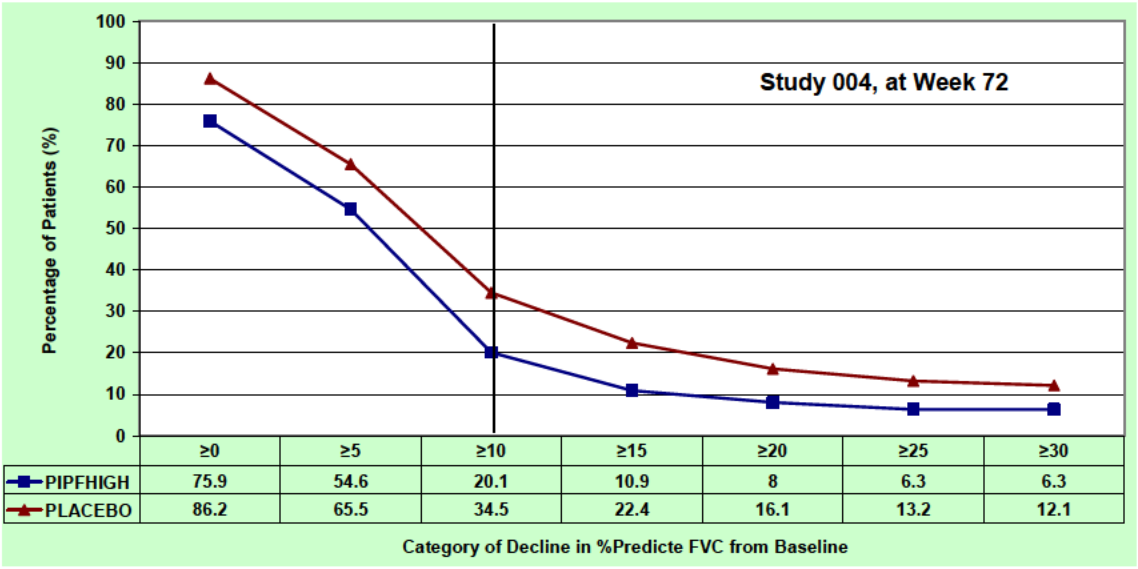


Figure 5. Cumulative % of Patients of Change from baseline in %Predicted FVC (Imputed)

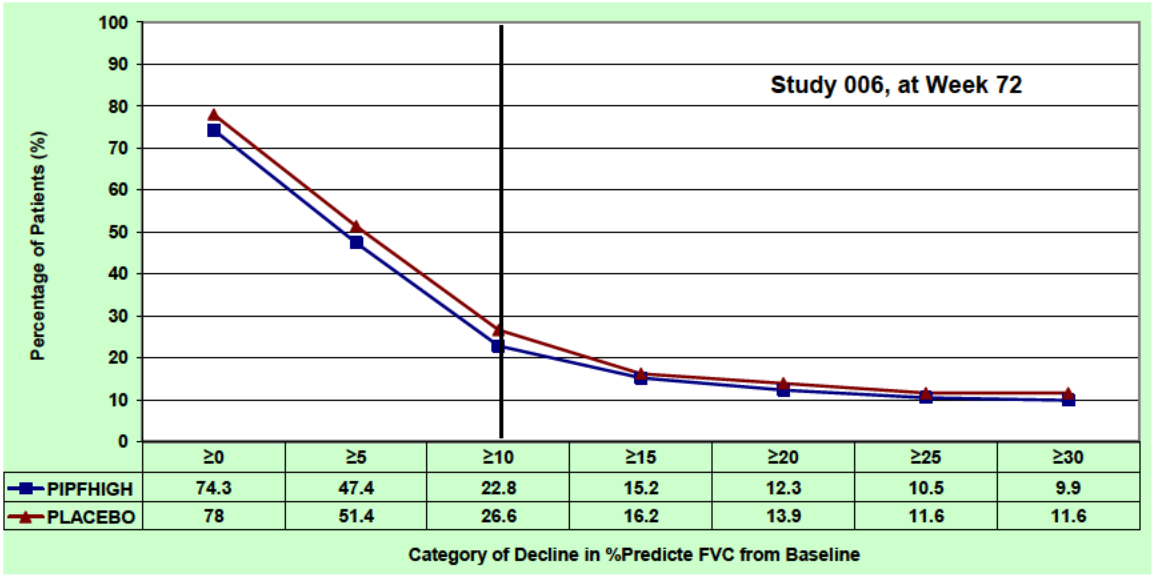
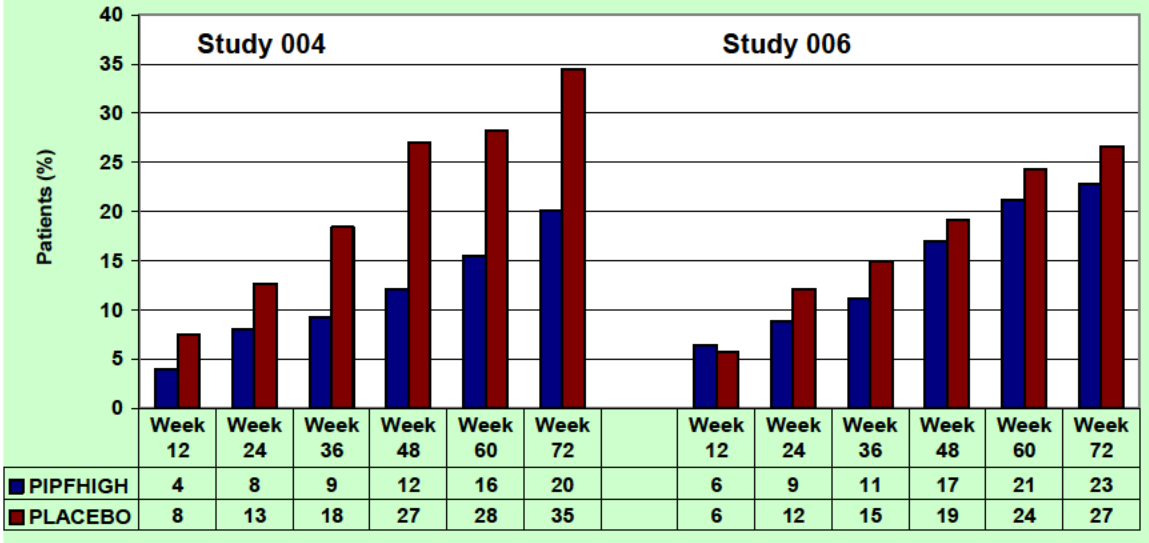


Figure 6. Responder Analysis of At Least 10% Decline in %Predicted FVC (Imputed)



	Week 12	Week 24	Week 36	Week 48	Week 60	Week 72		Week 12	Week 24	Week 36	Week 48	Week 60	Week 72
PIPFHIGH	4	8	9	12	16	20		6	9	11	17	21	23
PLACEBO	8	13	18	27	28	35		6	12	15	19	24	27

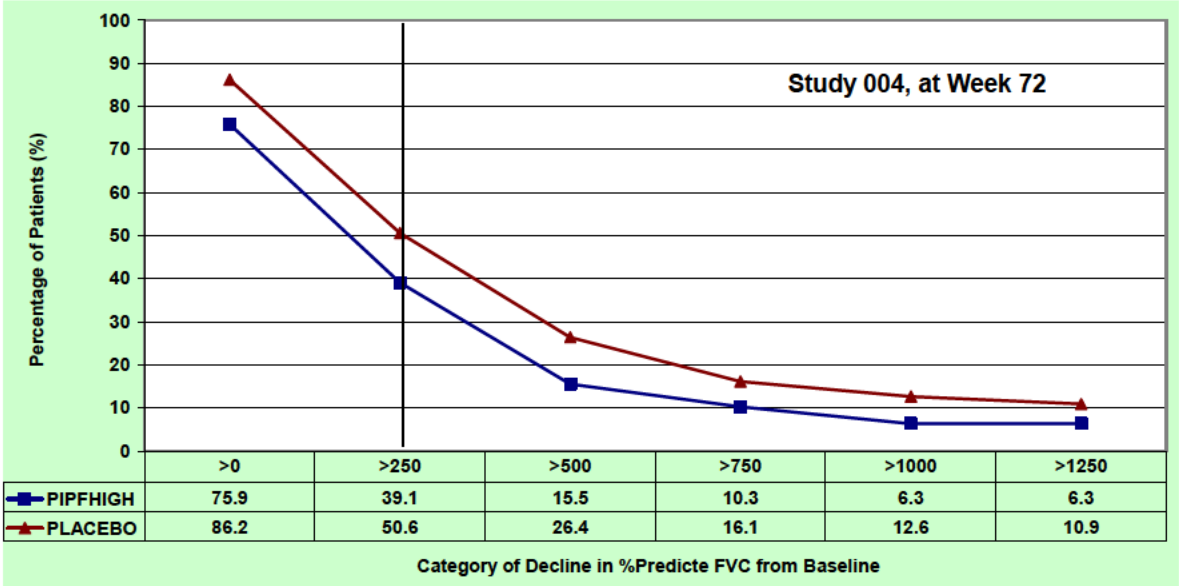
I conducted the analyses on the FVC (mL) with the same rank ANCOVA model using imputed data at each visit with protocol specified imputation method (Table 9). An absolute difference of 156.6 (mL) [-5.4 (mL)] and a relative difference of 33.0% (-1.4%) between the two treatment groups for Study 004 (Study 006) were observed. (For the graphic display of observed data, please see Figure 20 in the Appendix.) From the cumulative responder plot, the positive treatment effect of pirfenidone on change was demonstrated by consistent separation of the curve for Study 004 and only 39% of pirfenidone-treated patients have at least 250 (mL) decline in FVC (mL) compared to 51% in placebo (Figure 7).

Table 9. Mean Change from Baseline in FVC (mL) (Imputed)

	Pirfenidone		*Placebo* [a]		*Treatment Comparison*		
week	***N Observed (Death)***	***Mean*** [a]	***N Observed (Death)***	***Mean*** [a]	***Absolute Difference***	***Relative Difference***	***p-value*** [b]
Study 004							
Baseline	174 (0)	2872	174 (0)	2914	-42.0	--	--
Week 12	170 (1)	-47	166 (3)	-108	60.8	56.3	0.025
Week 24	168 (1)	-62	164 (5)	-153	90.9	59.4	0.034
Week 36	160 (2)	-111	156 (10)	-284	173.1	60.9	0.001
Week 48	159 (4)	-181	154 (13)	-350	169.0	48.3	0.002
Week 60	156 (7)	-266	148 (14)	-403	137.0	34.0	0.001
Week 72	**154 (8)**	**-318**	**150 (16)**	**-475**	**156.6**	**33.0**	**0.004**
Study 006							
Baseline	171 (0)	2940	173 (0)	2855	85	--	--
Week 12	167 (2)	-65	168 (0)	-39	-26.3	-67.8	0.047
Week 24	168 (2)	-70	165 (5)	-175	104.9	60.0	<.001
Week 36	159 (4)	-108	158 (7)	-190	81.6	43.0	0.021
Week 48	157 (6)	-220	156 (8)	-274	54.2	19.8	0.006
Week 60	151 (10)	-316	148 (11)	-323	6.2	1.9	0.184
Week 72	**148 (13)**	**-379**	**149 (15)**	**-373**	**-5.4**	**-1.4**	**0.533**

Footnotes are the same as in Table 7.

Figure 7. Cumulative % of Patients of Change from baseline in FVC (mL) (Imputed)



In summary, only one of the two phase 3 studies in patients with IPF, showed statistically significant evidence in favor of pirfenidone on the change in lung function (primary efficacy endpoint). The primary efficacy endpoint was not met in Study 006. In both studies, several secondary analyses were conducted on the primary efficacy endpoint to assess the robustness of the primary analysis. Although the magnitude of treatment effects varies depending on the methods of imputation and the statistical approaches used, the conclusions from these analyses were consistent.

Secondary Efficacy Endpoints

I was able to confirm the results of the Applicant's analyses of the secondary endpoints. The Applicant proposed to analyze the secondary outcome variables using the pooled data from both studies, when the primary efficacy analyses (absolute change in percent predicted FVC) from Study 004 and from Study 006 each showed efficacy ($p \leq 0.0498$). Given that Study 006 did not meet its primary endpoint, in accordance with the protocol-specified multiplicity plan, analyses of secondary endpoints using pooled data should not be considered confirmatory.

A review of some of the pre-specified secondary efficacy endpoints is described in the next subsections, for each individual study.

The Time to Progression-Free Survival

The Applicant's results of the progression-free survival analysis are summarized in Table 10 and Figure 8. Kaplan-Meier estimates were used to summarize progression-free survival, and treatment differences were analyzed using the log-rank test stratified by geographic region (USA and ROW). The hazard ratio (HR) was determined based on the Cox proportional hazard model, with geographic region (USA and ROW) as a stratum, to estimate the magnitude of the effect. Patients with no post-Baseline FVC or DLCO values were excluded from the analysis.

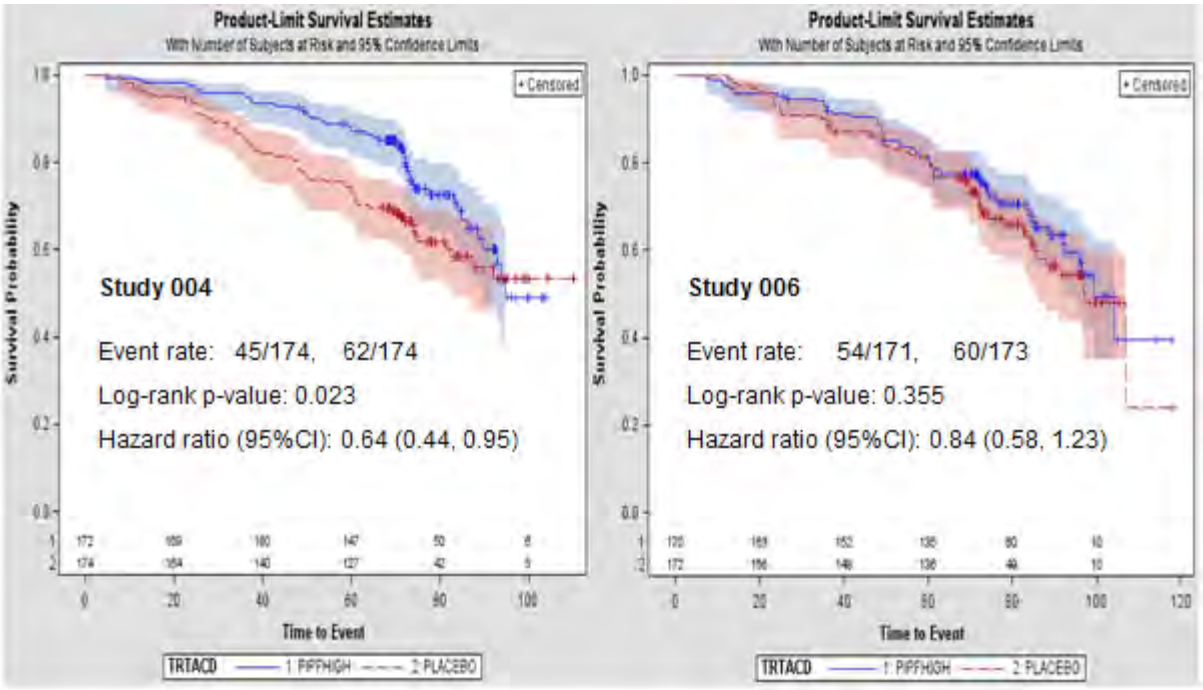
Overall, treatment with pirfenidone resulted in a higher proportion of progression-free survival than treatment with placebo (74%, 127/172 vs. 64%, 111/173 of patients, respectively) in Study 004. Treatment with pirfenidone was associated with a 36% relative reduction of the combined risk of disease progression or death before disease progression compared to placebo (HR [95% CI]: 0.64 [0.44–0.95]). Exploring the individual components of this combined endpoint, the reduction appears to be mainly due to disease progression. In particular, a ≥10% decline in percent predicted FVC occurred in 16% of patients in the pirfenidone group compared to 23% of patients in the placebo group (Table 10). There was also evidence of a treatment effect of pirfenidone 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 8). This evidence is not seen in Study 006.

Table 10. Survival Analysis on Progression-Free Survival during the Treatment Period

	Pirfenidone	***Placebo***	***Hazard Ratio (95% CI)*** [c]
	N of Event (%)	***N of Event (%)***	***p-value*** [b]
Study 004			
N of Randomized	174 [a]	174 [a]	--
Death or Disease Progression [d]	45 (26.2)	62 (35.8)	0.64 (0.44, 0.94), 0.023
Decline in %Predicted FVC≥10%	28 (16.3)	39 (22.5)	--
Decline in %Predicted DL_{CO}≥15%	9 (5.2)	9 (5.2)	--
Death before disease progression [e]	8 (4.7)	14 (8.1)	--
Study 006			
N of Randomized	171	173	--
Death or Disease Progression [d]	54 (31.8)	60 (34.9)	0.84 (0.58, 1.23), 0.355
Decline in %Predicted FVC≥10%	31 (18.2)	41 (23.8)	--
Decline in %Predicted DL_{CO}≥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 from Study 004; 1 patient in the pirfenidone 2403-mg/d group and 1 patient in the placebo group from Study 006).
[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.

Figure 8. Kaplan-Meier Curve of Time to Progression-Free Survival during the TRT Period



Note: Footnotes are same as in Table 15

The Time to Worsening of IPF

The Applicant's results of the time to worsening of IPF analysis are summarized in Table 11 and Figure 9. Kaplan-Meier estimates were used to summarize progression-free survival, and treatment differences were analyzed using the log-rank test stratified by geographic region (USA and ROW). The hazard ratio (HR) was determined based on the Cox proportional hazard model, with geographic region (USA and ROW) as a stratum, to estimate the magnitude of the effect. Patients with no post-Baseline FVC or DL_{CO} values were excluded from the analysis.

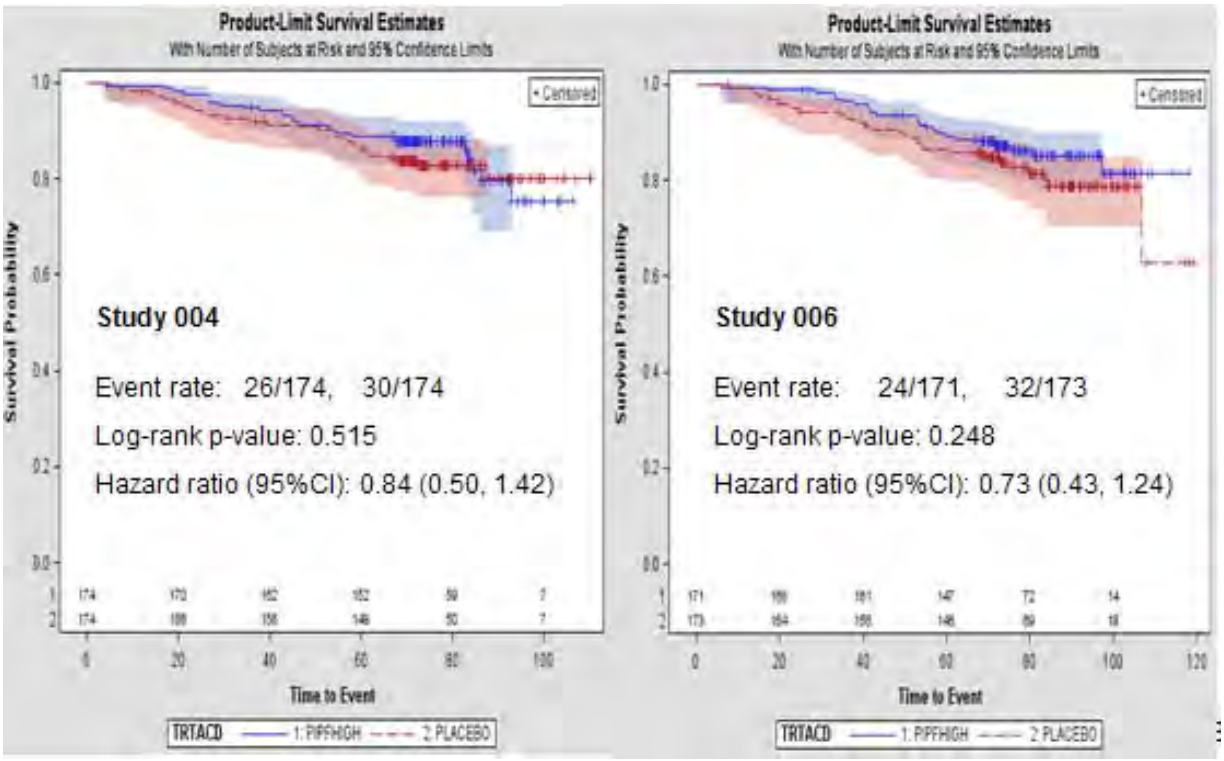
Overall, the majority of patients in the pirfenidone 2403-mg/d and placebo groups did not experience worsening of IPF in both studies (85%, 295/345 and 82%, 285/347 of patients, respectively). Treatment with pirfenidone resulted in a lower proportion of patients that experience worsening of IPF compared to placebo in both studies. Exploring the individual components of this combined endpoint, worsening of IPF was primarily due to respiratory hospitalizations, which occurred in 12.1% (21/174) and 13.8 (24/174) of patients in the pirfenidone 2403-mg/d and placebo group in Study 004 and 9.9% (17/171) and 13.3% (23/173) of patients in the pirfenidone 2403-mg/d and placebo groups, respectively in Study 006.

Table 11. Survival Analysis on Worsening IPF during the Treatment Period

	Pirfenidone N of Event (%)	Placebo N of Event (%)	Hazard Ratio (95% CI) [d] p-value [c]
Study 004			
N of Randomized	174	174	--
Worsening IPF [a]	26 (14.9)	30 (17.2)	0.84 (0.50, 1.42), 0.515
Acute IPF exacerbation	2 (1.1)	3 (1.7)	--
Lung transplantation	2 (1.1)	2 (1.1)	--
Respiratory hospitalization	21 (12.1)	24 (13.8)	--
IPF-related death [b]	1 (0.6)	1 (0.6)	--
Study 006			
N of Randomized	171	173	--
Worsening IPF [a]	24 (14.0)	32 (18.5)	0.73 (0.43, 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] p-value was based on the log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d with placebo.
[d] Hazard ratio was based on the Cox proportional hazard model.

Figure 9. Kaplan-Meier Curve of Time to Worsening IPF during the Treatment Period



Note: 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 end of the Treatment Period.

%Predicted Hgb-corrected DLco and Six-Minute Walk Test (6MWT)

The results from the analyses of the mean change from baseline in %Predicted Hgb-corrected DLco and Six-Minute Walk Test are summarized in Table 12 and Table 13, respectively. Both these endpoints were analyzed using rank ANCOVA model, stratified by geographic region (USA and ROW). For the summary of mean change, missing data were not imputed.

In Study 004, the decline from baseline in the mean percent predicted Hgb-corrected DLCO at Week72 was not different between the treatment groups (mean changes of -6.3% in the pirfenidone group and -6.6% in the placebo group; p = 0.584). In Study 006, the decline from baseline was slightly higher in the pirfenidone group (6.8%) compared to placebo group (5.9%), and this difference was numerically in favor of placebo. (For the graphic display of observed data, please see Figure 21 in the Appendix.)

In Study 006, the mean decline in 6MWT distance in patients treated with pirfenidone is numerically lower compared to patients treated with placebo (-45.1 vs. -76.9 meters, respectively; difference of 31.8 meters). This evidence is not seen in Study 004. (For the graphic display of observed data, please see Figure 22 in the Appendix.)

Table 12. Mean Change from Baseline in %Predicted DLco (%) (Imputed)

	Pirfenidone 2403 mg/d		Placebo [a]		Treatment Comparison		
Week	N Observed (Death)	Mean [a]	N Observed (Death)	Mean [a]	Absolute Difference	Relative Difference	p-value [b]
Study 004							
Baseline	174 (0)	46.4	172 (0)	46.1	0.3	--	--
Week 12	169 (1)	-1.3	166 (3)	-2.9	1.6	53.6	0.121
Week 24	166 (1)	-2.2	161 (5)	-3.5	1.3	37.8	0.393
Week 36	158 (2)	-3.4	152 (10)	-5.0	1.6	32.5	0.227
Week 48	157 (4)	-5.5	152 (13)	-7.5	2.0	27.1	0.216
Week 60	155 (7)	-6.3	146 (14)	-7.9	1.6	20.6	0.304
Week 72	**152 (8)**	**-7.9**	**149 (16)**	**-9.9**	**2.0**	**20.4**	**0.145**
Study 006							
Baseline	171 (0)	47.8	173 (0)	47.4	0.4	--	--
Week 12	167 (2)	-1.7	166 (0)	-1.3	-0.4	-34.9	0.634
Week 24	167 (2)	-2.7	165 (5)	-3.6	0.8	23.0	0.485
Week 36	157 (4)	-4.7	158 (7)	-5.2	0.6	11.2	0.580
Week 48	157 (6)	-6.1	154 (8)	-6.3	0.2	3.6	0.548
Week 60	151 (10)	-8.4	148 (11)	-8.6	0.3	3.4	0.540
Week 72	**147 (13)**	**-9.8**	**147 (15)**	**-9.2**	**-0.5**	**-5.9**	**0.996**

Footnotes [a], [b], [c], and [d] are same as in Table 7.

Table 13. Mean Change from Baseline in 6MWT Distance (m) (Imputed)

	Pirfenidone 2403 mg/d		Placebo [a]		Treatment Comparison		
Week	N Observed (Death)	Mean [a]	N Observed (Death)	Mean [a]	Absolute Difference	Relative Difference	p-value [b]
Study 004							
Baseline	170 (0)	411.1	170 (0)	410.0	1.1	--	--
Week 12	164 (1)	-8.2	166 (3)	-15.2	7.0	46.0	0.690
Week 24	163 (1)	-14.3	163 (5)	-31.4	17.1	54.4	0.420
Week 36	152 (2)	-17.4	151(10)	-33.8	16.4	48.5	0.468
Week 48	155 (4)	-34.5	152 (13)	-52.6	18.0	34.3	0.068
Week 60	150 (7)	-43.6	142 (14)	-65.9	22.4	33.9	0.059
Week 72	**150 (8)**	**-60.4**	**148 (16)**	**-76.8**	**16.4**	**21.3**	**0.171**
Study 006							
Baseline	169 (0)	378.0	168 (0)	399.1	-21.1	--	--
Week 12	161 (2)	-8.3	168 (0)	-9.0	0.7	8.1	0.975
Week 24	164 (2)	-7.7	162 (5)	-27.7	20.1	72.3	0.034
Week 36	155 (4)	-16.4	156 (7)	-37.4	21.0	56.2	0.044
Week 48	154 (6)	-23.5	152 (8)	-44.9	21.5	47.8	0.023
Week 60	150 (10)	-31.9	146 (11)	-56.0	24.1	43.1	0.014
Week 72	**145 (13)**	**-45.1**	**147 (15)**	**-76.9**	**31.8**	**41.3**	**0.001**

Footnotes [a], [b], [c], and [d] are same as in Table 7.

Death

As stated in Drs. Banu Karimi-Shah and Sally Seymour's review, 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. 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. The Agency noted that 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 also noted that efficacy would be assessed by the totality of the data, including secondary endpoints.

Because of the importance of this endpoint, we have examined the Applicant's results on mortality, as well as conducted additional analyses using the pooled and the individual study data.

The Applicant conducted an analysis comparing death (includes all death except those occurring after lung transplantation) between the treatment groups in both studies. Kaplan-Meier estimates were used to summarize survival time up to the end of the study treatment period. Survival time is measured by time from randomization to death. Treatment differences were analyzed using the log-rank test stratified by geographic region (USA and ROW). The hazard ratio (HR) was determined based on the Cox proportional hazard model, with geographic region (USA and ROW) as a factor. The results are displayed in Table 14. The overall number of deaths in this analysis is based on the "treatment period" deaths (defined on the next page). The reported number of death is different from the safety summary of deaths in the Study Report, because of

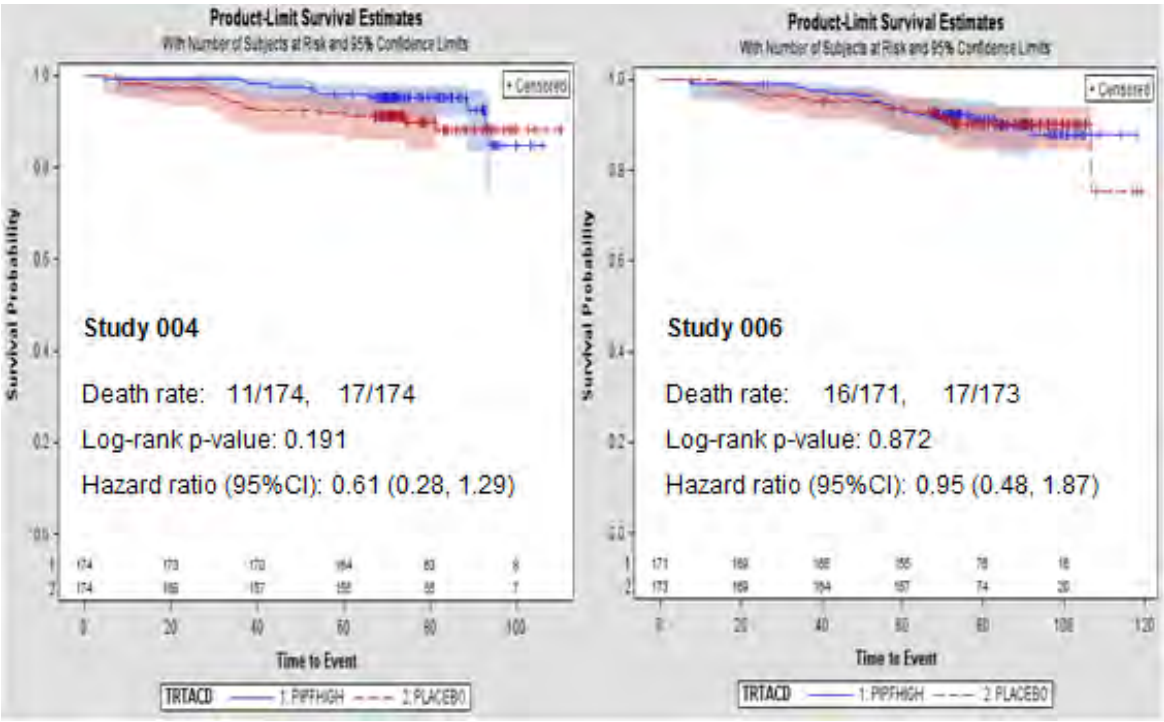
the pre-specified censoring algorithm used in this analysis. Neither study demonstrated a mortality benefit. (Figure 10)

Table 14. Survival Time during the Treatment Period (All Randomized Patients)

Fatal Adverse Event	Pirfenidone 2403 N of Event [a] (%)	Placebo N of Event [a] (%)	Hazard Ratio [c] (95% CI) p-value [b]
Study 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)	
Study 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)	

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.
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.

Figure 10. Kaplan-Meier Curve of Time to All Cause Mortality during the Treatment Period



Note: the footnotes are the same as Table 12.

In each study, I also performed several analyses on fatal adverse events (including lung transplantation) and IPF-related deaths using three different datasets.

Treatment period – data for all patients up to then September 2008 cutoff used by the Applicant; some patients would have >72 weeks treatment; this is the dataset used for the primary efficacy analysis. Note of, the Applicant's survival analysis was based on this period (Table 14).
On-Treatment – data for all patients while on study medication and 28 days after the last dose of treatment; primary dataset for safety endpoints.
Vital Status at End of Study – data including the Treatment Period (September 2008 cutoff) and subsequent follow up; used for vital status only.

The results are summarized in Table 15, Table 16, and Table 17. Of note, IPF-related deaths are based on investigator report and were not adjudicated. It is difficult to assess whether the reported cause of death is truly IPF-related. For each individual study, no benefit was demonstrated either on all-cause mortality, fatal adverse events, or IPF-related death. For reference, pooled analyses of the mortality data are presented in the Appendix (Table 26, Table 27, and Table 28). Of note, because Study 006 failed to meet its primary endpoint and all deaths (including IPF-related deaths) were not adjudicated, it is difficult to make definitive conclusion about the result from the pooled analyses.

Table 15. Survival Analysis on All Cause Mortality

	Study 004			Study 006		
	Pirfenidone (N=174)	Placebo (N=174)	HR (95%CI) [b] p-value [c]	Pirfenidone (N=171)	Placebo (n=173)	HR (95%CI) [b] p-value [c]
Treatment Period						
Number of Event (%)	11 (6.3)	17 (9.8)	0.61 (0.29, 1.30)	16 (9.4)	17 (9.8)	0.96 (0.48, 1.89)
Probability of event by end of the period [a]	12.7 (6.0, 25.5)	11.1 (6.8, 17.8)	0.201	11.8 (7.0, 19.3)	16.5 (7.0, 36.1)	0.897
On-Treatment						
Number of Event (%)	10 (5.7)	14 (8.0)	0.71 (0.32, 1.60)	9 (5.3)	15 (8.7)	0.59 (0.26, 1.36)
Probability of event by end of the period [a]	11.5 (5.3, 23.7)	12.0 (6.3, 22.2)	0.413	7.5 (3.7, 14.9)	9.2 (5.6, 14.8)	0.217
Vital Status at End of Study						
Number of Event (%)	14 (8.0)	20 (11.5)	0.68 (0.34, 1.34)	18 (10.5)	17 (9.8)	1.06 (0.55, 2.07)
Probability of event by end of the period [a]	19.8 (10.5, 35.4)	19.0 (10.8, 32.2)	0.268	23.1 (9.8, 48.6)	22.8 (7.6, 57.1)	0.856

[a] Kaplan Meier estimated event rate at end of 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

Table 16. Survival Analysis on Fatal Adverse Event (Deaths + Lung Transplantations)

	Study 004			Study 006		
	Pirfenidone (N=174)	Placebo (N=174)	HR (95%CI) [b] p-value [c]	Pirfenidone (N=171)	Placebo (n=173)	HR (95%CI) [b] p-value [c]
Treatment Period						
Number of Event (%)	14 (8.0)	21 (12.1)	0.65 (0.33, 1.29)	20 (11.7)	22 (12.7)	0.90 (0.49, 1.64)
Probability of event by end of the period [a]	17.8 (8.7, 34.4)	16.4 (9.9, 26.3)	0.220	15.8 (9.9, 24.6)	31.1 (10.7, 70.6)	0.722
On-Treatment						
Number of Event (%)	13 (7.5)	19 (10.9)	0.68 (0.34, 1.37)	11 (6.4)	20 (11.6)	0.54 (0.26, 1.14)
Probability of event by end of the period [a]	13.2 (6.8, 24.9)	21.2 (11.3, 37.5)	0.281	8.7 (4.6, 16.1)	12.9 (8.4, 19.5)	0.105
Vital Status at End of Study						
Number of Event (%)	17 (9.8)	24 (13.8)	0.69 (0.37, 1.29)	22 (12.9)	22 (12.7)	1.00 (0.55, 1.80)
Probability of event by end of the period [a]	21.3 (11.9, 36.5)	27.6 (14.8, 47.8)	0.244	25.7 (12.2, 49.4)	26.1 (10.3, 56.9)	0.988

[a] Kaplan Meier estimated event rate at end of 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

Table 17. Survival Analysis on IPF Related Death

	Study 004			Study 006		
	Pirfenidone (N=174)	Placebo (N=174)	HR (95%CI) [b] p-value [c]	Pirfenidone (N=171)	Placebo (n=173)	HR (95%CI) [b] p-value [c]
Treatment Period						
Number of Event (%)	6 (3.4)	13 (7.5)	0.45 (0.17, 1.19)	12 (7.0)	15 (8.7)	0.79 (0.37, 1.69)
Probability of event by end of the period [a]	9.7 (3.4, 25.9)	9.7 (5.4, 17.2)	0.108	10.4 (5.6, 19.0)	27.1 (7.6, 72.1)	0.542
On-Treatment						
Number of Event (%)	5 (2.9)	11 (6.3)	0.45 (0.16, 1.31)	7 (4.1)	14 (8.1)	0.49 (0.20, 1.23)
Probability of event by end of the period [a]	5.9 (2.0, 16.8)	10.3 (4.9, 20.9)	0.143	6.3 (2.8, 13.9)	8.6 (5.2, 14.1)	0.129
Vital Status at End of Study						
Number of Event (%)	8 (4.6)	15 (8.6)	0.51 (0.22, 1.21)	14 (8.2)	15 (8.7)	0.94 (0.45, 1.95)
Probability of event by end of the period [a]	12.9 (5.7, 27.9)	14.3 (7.3, 27.2)	0.127	21.1 (8.2, 48.3)	21.9 (6.9, 57.4)	0.863

[a] Kaplan Meier estimated event rate at end of 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

Results from the analyses of the secondary endpoints (including progression-free survival) for each study are summarized in Table 18. The primary time point for all landmark analyses was Week 72.

Table 18. Applicant's Results of Primary and Secondary Endpoints in Study 004 and 006

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	●					

6MWT = Six-minute walk test, DLCO = Carbon monoxide diffusing capacity; FVC = Forced vital capacity; SpO2 = Oxygen saturation by pulse oximetry; UCSD SOBQ = University of San Diego Shortness of Breath Questionnaire
Note: Solid circle represents a result directionally favorable to pirfenidone (• $p > 0.05$; •• $p < 0.05$). An open circle represents a result directionally favorable to placebo.

3.1.2 Dose Response

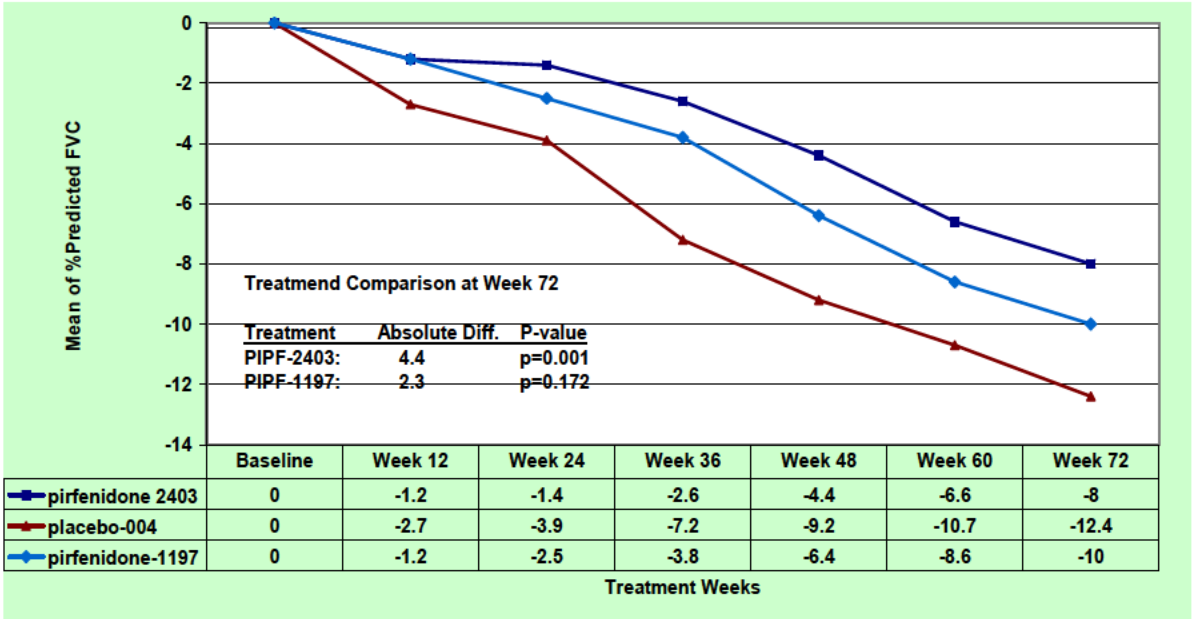
A lower dose of pirfenidone, 1197 mg/d, was included in Study 004 to qualitatively explore a dose-response relationship of pirfenidone in the treatment of patients with IPF. There was a numerical reduction in the mean decline from baseline in %Predicted FVC in patients receiving pirfenidone 1197 mg/d compared with those receiving placebo at week 72 (p=0.172, rank ANCOVA) in Study PIPF 004 (Table 19). This represents an absolute difference of 2.3% and a relative difference of 23.4% between the two treatment groups. The treatment effect (without any imputation) of pirfenidone 1197 mg/d (light blue) appeared to be intermediate to that of pirfenidone 2403 mg/d (dark blue) and placebo (red) in the primary efficacy analysis (Figure 11).

Table 19. Mean Change in %Predicted FVC (Imputed)

	Pirfenidone 1197 mg/d		Placebo		Treatment Comparison		
Week	N Observed (Death)	Mean [a] (STD)	N Observed (Death)	Mean [a] (STD)	Absolute Diff. [c]	Relative Diff. [d]	p-value [b]
Study 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**

Footnotes are the same as in Table 7

Figure 11. Mean Change from Baseline in %Predicted FVC (Imputed)



Death

I did an analysis of time to death or lung transplantation (whichever occurs first) at the end of treatment period and at the end of follow-up period (included additional 4 week follow-up), and the results are summarized in Figure 12. Similar to the high dose pirfenidone (2403 mg/d), low dose pirfenidone (1197 mg/d) demonstrated no mortality benefit. In Study 004, the treatment effect of pirfenidone 1197 mg/d on progression-free survival appeared to be intermediate to that of pirfenidone 2403 mg/d and placebo. (Figure 13)

Figure 12. Kaplan-Meier Curve of Time to Death and Lung Transplantation during Study Period

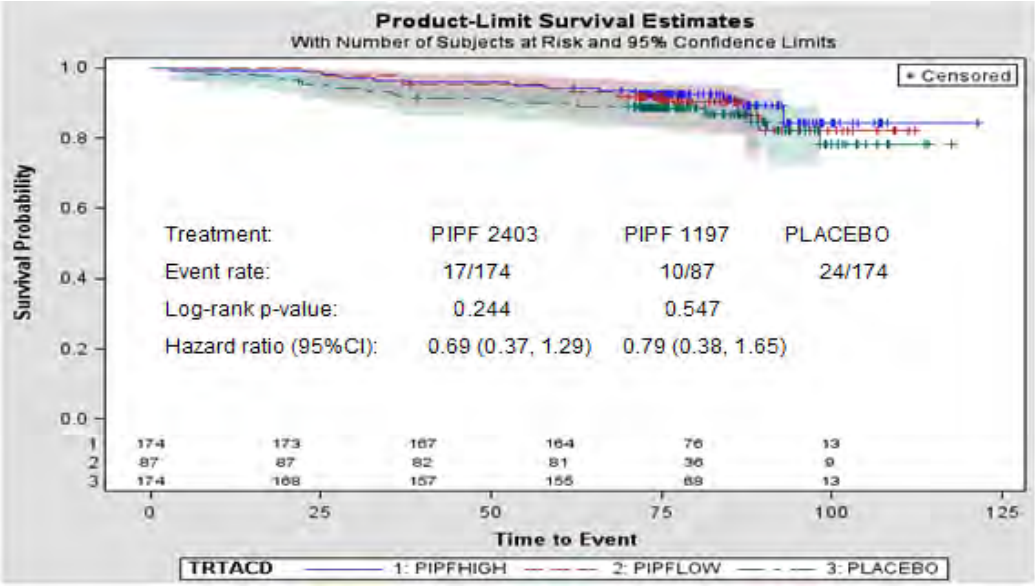
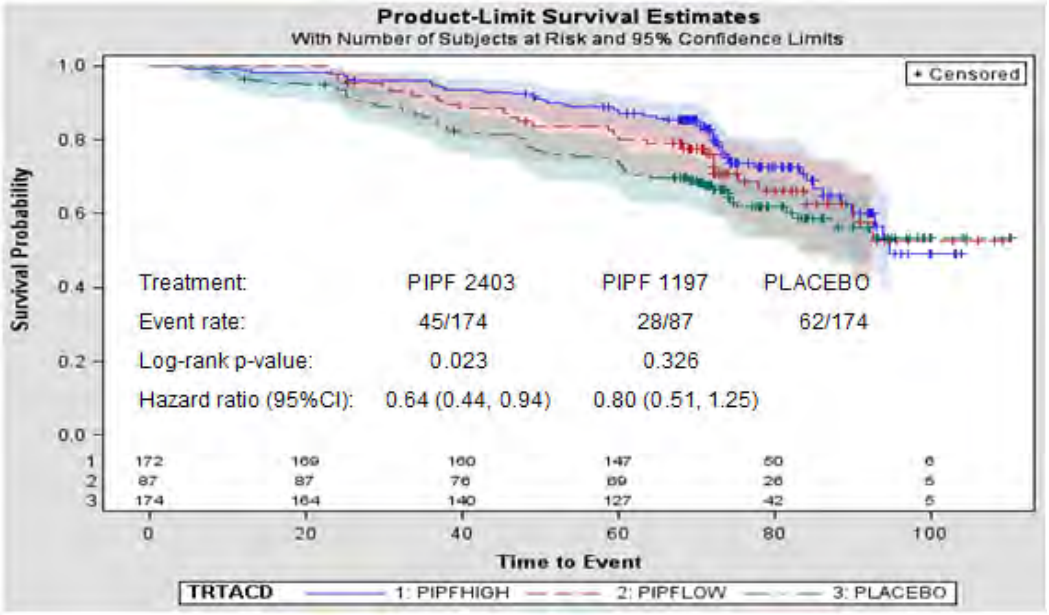


Figure 13. Kaplan-Meier Curve of Time to Progression-Free Survival during the TRT Period



3.2 Evaluation of Safety

Dr. Banu Karimi-Shah, conducted the evaluation of the safety data in detail. The reader is referred to Dr. Karimi-Shah's review for information regarding the safety profile of the drug.

4. FINDINGS IN SPECIFAL/SUBGROUP POPULATIONS

The Applicant performed subgroup analyses of mean change from baseline to week 72 in %Predicted FVC using the rank ANCOVA model and these analyses were conducted in the pooled data (Study 004 and Study 006). The absolute differences between pirfenidone and placebo by subgroup are presented in Figure 14.

Quantitative interactions between treatment and time from IPF diagnosis to randomization and between treatment and baseline supplemental oxygen use during 6MWT) are observed. The treatment effect varies in magnitude in these subgroups but all were in favor of the pirfenidone group.

Because the results of Study 004 and Study 006 were different, I conducted separate subgroup analyses for each of the studies on the mean change from baseline to week 72 in %Predicted FVC (Table 20). In Study 004, there were some quantitative interactions between treatment and the following subgroups: region, smoking history, and the time from IPF diagnosis to randomization. Because there was no treatment effect in Study 006, the results from subgroup analyses are considered exploratory.

I also conducted analyses of time to death or lung transplantation (whichever occurs first) at the end of study period by subgroup (Table 21). In Study 004, there were imbalances in the

proportion of patients who died between the treatment group that favors the pirfenidone group in the following subgroups: female (1% vs. 5%), age<65 yrs (6% vs. 12%), and Baseline %Predicted DLco (6% vs. 15%). In Study 006, there was no difference between two treatment groups in all subgroups.

Figure 14. The Applicant's Subgroup Analyses Results (Pooled Two Studies)

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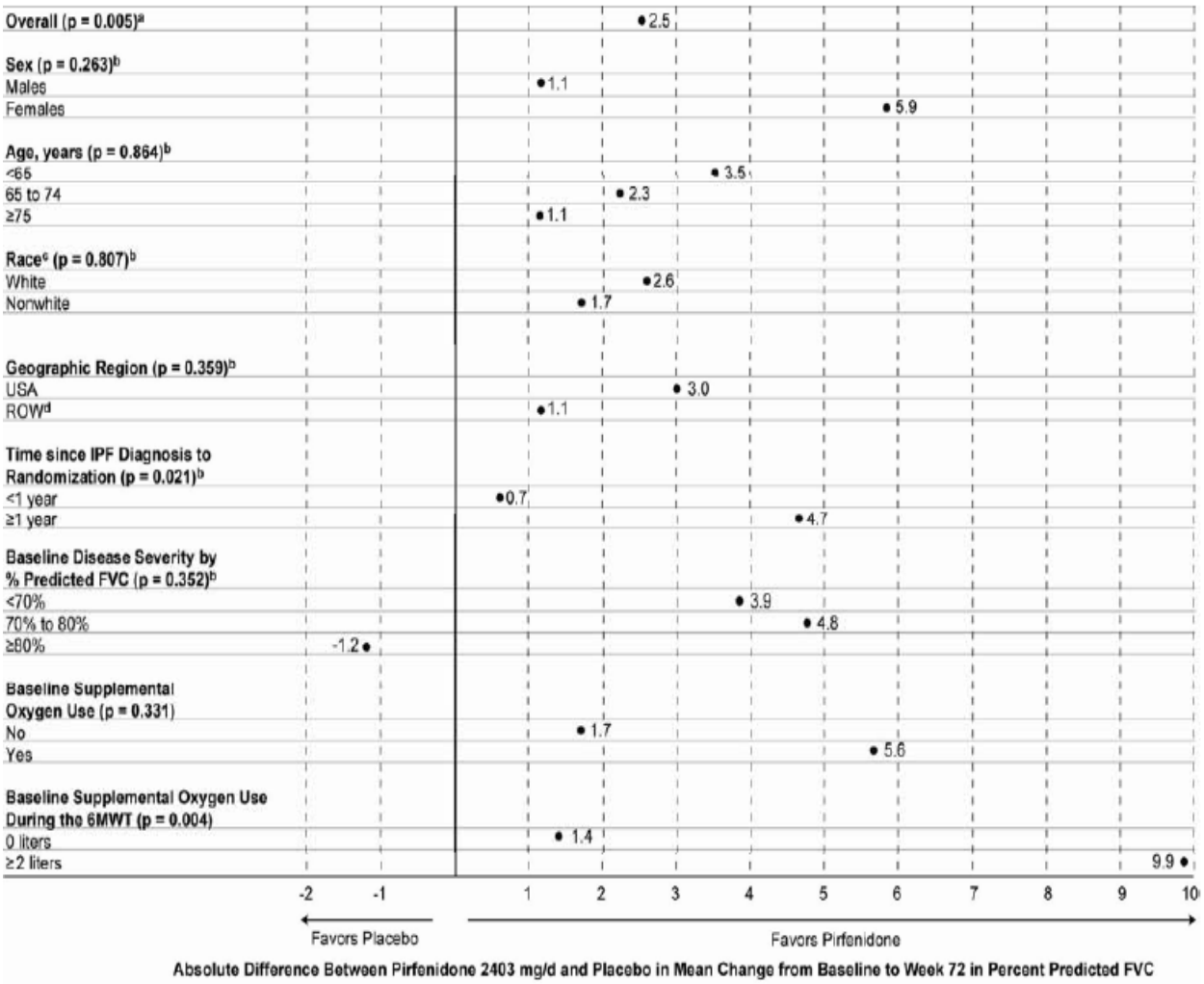


Note: For missing values, if the patient was alive on the protocol-specified visit the imputation was by the smallest SSD method. If the patient died on or before the protocol-specified date then zero was imputed for the assessment.

Table 20. Mean Change in %Predicted FVC at Week-72

	Study 004					Study 006				
	Pirfenidone 2403 mg/d		Placebo		ABS Diff	Pirfenidone 2403 mg/d		Placebo		ABS Diff
Week	N (D)	Mean	N (D)	Mean	Mean	N (D)	Mean	N (D)	Mean [a]	Mean [a]
Overall (p=0.001) [a]						**Overall (p=0.501) [a]**				
	174 (14)	-8.0	174 (20)	-12.4	4.4	171 (18)	-9.0	173 (17)	-9.6	0.6
Sex (p=0.468) [b]						**Sex (p=0.397) [b]**				
Males	118 (14)	-9.6	128 (15)	-11.9	2.4	123 (13)	-9.4	124 (11)	-9.2	-0.2
Female	56 (0)	-4.7	46 (5)	-13.5	8.9	48 (5)	-7.8	49 (6)	-10.6	2.8
Age (p=0.729) [b]						**Age (p=0.598) [b]**				
<65 yrs	75 (3)	-5.7	73 (9)	-13.2	7.5	70 (10)	-12.1	61 (7)	11.1	-0.9
≥65 yrs	99 (11)	-9.8	101 (11)	-11.7	2.0	101 (8)	-6.8	112 (10)	-8.7	1.9
Region (p=0.090) [b]						**Region (p=0.964) [b]**				
ROW [d]	60 (4)	-9.7	60 (8)	-12.0	2.3	23 (2)	-7.6	23 (1)	-5.4	-2.2
USA	114 (10)	-7.1	114 (12)	-12.5	5.4	148 (16)	-9.2	148 (16)	-10.2	1.1
Race [c] (p=0.894) [b]						**Race (p=0.838)**				
White	168 (14)	-8.1	168 (20)	-12.6	4.4	169 (18)	-9.0	171 (17)	-9.7	0.6
N-White	6 (0)	-4.3	6 (0)	-6.5	2.2	2 (0)	-1.0	2 (0)	0.3	-1.3
Baseline %Predicted FVC (P=0.847) [b]						**Baseline %Predicted FVC (P=0.071) [b]**				
<70%	73 (6)	-8.2	68 (11)	-14.6	6.4	64 (12)	-9.8	83 (12)	-11.3	1.5
≥70%	101 (8)	-7.8	106 (9)	-10.9	3.1	107 (6)	-8.4	90 (5)	-8.0	-0.5
Baseline %Predicted DLco (P=0.853) [b]						**Baseline %Predicted DLco (P=0.063) [b]**				
<40%	50 (5)	-11.6	60 (12)	-17.5	5.9	39 (9)	-11.4	41 (8)	-15.9	1.8
≥40%	124 (9)	-6.5	114 (8)	-9.6	3.1	132 (9)	-7.4	132 (9)	-7.6	0.2
Smoke History (P=0.006) [b]						**Smoke History (P=0.452) [b]**				
Never S	56 (0)	-6.7	51 (3)	-8.8	2.1	59 (8)	-10.5	64 (7)	-9.9	-0.6
Smoke	118 (14)	-8.6	123 (17)	-13.8	5.2	112 (10)	-8.1	109 (10)	-9.4	1.3
Baseline Oxygen Use (P=0.981) [b]						**Baseline Oxygen Use (P=0.108) [b]**				
Yes	29 (4)	-8.5	25 (3)	-10.5	2.0	48 (6)	-8.9	49 (8)	-16.2	7.4
No	145 (10)	-7.9	149 (17)	-12.7	4.8	123 (12)	-9.0	124 (9)	-6.9	-2.0
Time Since IPF Diagnosis (P=0.014) [b]						**Time Since IPF Diagnosis (P=0.654) [b]**				
<1 yrs	83 (5)	-8.4	61 (7)	-10.3	1.9	100 (13)	-10.7	107 (12)	-10.3	-0.4
≥1 yrs	91 (9)	-7.6	93 (13)	-14.2	6.5	71 (5)	-6.4	65 (5)	-8.5	2.0

a Rank ANCOVA, comparing pirfenidone 2403 mg/d to placebo.
b Rank ANCOVA for interaction between treatment arm and subgroup.
c Hispanic/Latino ethnicity grouped with nonwhite for subgroup analyses.
d ROW includes Australia, Belgium, Canada, France, Germany, Ireland, Italy, Mexico, Poland, Spain, Switzerland, and the United Kingdom.

Table 21. Survival Analysis on Fatal Adverse Event (Deaths + Lung Transplantations)

	Study 004			Study 006			Pooled two studies
	PIPF	PLB	HR [a] 95%CI	PIPF	PLB	HR [a] 95%CI	HR [a] 95%CI
Sex							
Males	118 (16)	128 (19)	*0.9 (0.4, 1.7)*	123 (15)	124 (13)	*1.1 (0.5, 2.4)*	*1.0 (0.6, 1.6)*
Female	56 (1)	46 (5)	*0.2 (0.0, 1.4)*	48 (7)	49 (9)	*0.7 (0.3, 2.0)*	*0.5 (0.2, 1.2)*
Age							
<65 yrs	75 (6)	73 (12)	*0.4 (0.2, 1.2)*	70 (13)	61 (11)	*1.0 (0.5, 2.3)*	*0.7 (0.4, 1.3)*
≥65 yrs	99 (11)	101 (12)	*0.9 (0.4, 2.1)*	101 (9)	112 (11)	*0.9 (0.4, 2.1)*	*0.9 (0.5, 1.7)*
Region							
ROW [d]	60 (5)	60 (8)	*0.6 (0.2, 1.8)*	23 (2)	23 (1)	*2.1 (0.2, 23)*	*0.8 (0.3, 2.1)*
USA	114 (12)	114 (16)	*0.7 (0.3, 1.5)*	148 (20)	148 (21)	*0.9 (0.5, 1.7)*	*0.8 (0.5, 1.3)*
Race [c]							
White	168 (17)	168 (24)	*0.7 (0.4, 1.2)*	169 (18)	171 (17)	*1.0 (0.6, 1.8)*	*0.8 (0.5, 1.3)*
N-White	6 (0)	6 (0)	*1.0 (1.0, 1.0)*	2 (0)	2 (0)	*1.0 (1.0, 1.0)*	*1.0 (1.0, 1.0)*
Baseline %Predicted FVC							
<70%	73 (9)	68 (14)	*0.6 (0.3, 1.4)*	64 (13)	83 (15)	*1.1 (0.5, 2.2)*	*0.8 (0.5, 1.4)*
≥70%	101 (8)	106 (10)	*0.7 (0.3, 1.9)*	107 (9)	90 (7)	*1.1 (0.4, 3.0)*	*0.9 (0.5, 1.8)*
Baseline %Predicted DLco							
<40%	50 (6)	60 (15)	*0.5 (0.2, 1.2)*	39 (9)	41 (9)	*1.0 (0.4, 2.5)*	*0.7 (0.4, 1.3)*
≥40%	124 (11)	114 (9)	*1.0 (0.4, 2.5)*	132 (13)	132 (13)	*1.0 (0.5, 2.2)*	*1.0 (0.6, 1.8)*
Smoke History							
Never S	56 (1)	51 (3)	*0.3 (0.0, 2.9)*	59 (10)	64 (9)	*1.2 (0.5, 3.0)*	*0.9 (0.4, 2.1)*
Smoke	118 (16)	123 (21)	*0.7 (0.4, 1.4)*	112 (12)	109 (13)	*0.9 (0.4, 1.9)*	*0.8 (0.5, 1.3)*
Baseline Oxygen Use							
Yes	29 (6)	25 (6)	*0.8 (0.3, 2.6)*	48 (8)	49 (12)	*0.6 (0.2, 1.5)*	*0.7 (0.4, 1.4)*
No	145 (11)	149 (18)	*0.6 (0.3, 1.2)*	123 (14)	124 (10)	*1.4 (0.6, 3.2)*	*0.9 (0.4, 1.4)*
Time Since IPF Diagnosis							
<1 yrs	83 (6)	61 (9)	*0.6 (0.2, 1.8)*	100 (15)	107 (16)	*1.0 (0.5, 2.0)*	*0.9 (0.5, 1.5)*
≥1 yrs	91 (11)	93 (15)	*0.7 (0.3, 1.5)*	71 (7)	65 (6)	*1.0 (0.3, 3.0)*	*0.8 (0.4, 1.5)*

[a]: HR: Hazard Ratio. CI: Confident Interval, which were based on the Cox proportional hazard model.

A total of 127 (16.3%) patients in studies 004 and 006 had previously been enrolled in the INSPIRE trial. The Applicant submitted the summary of patients demographics, baseline characteristics, and primary endpoint by INSPIRE subgroup on February 1, 2010 upon my request (Table 22). The duration of IPF before the randomization were different between the patients who were enrolled in INSPIRE trial (2.3 years) and patients who did not enrolled in INSPIRE trial (1 years), but it was balance between the treatment groups.

In both studies, there is no interaction between treatment and patients enrollment in the INSPIRE trial (the p-values for interaction are 0.207 and 0.583 for Studies 004 and 006, respectively).

In Study 004, patient who were enrolled in INSPIRE trial had a larger treatment effect (7.2%) compared to patient who were not enrolled in the INSPIRE trial (3.8%). In contrast, there appears to be a negative treatment effect in patients enrolled in the INSPIRE trial in Study 006 and had a very small treatment effect in favor of pirfenidone in patients not enrolled in the INSPIRE trial. However, because of the small numbers of patients enrolled in the INSPIRE trial; any claims of disparity may not be supported.

Table 22. Summary of Patients Information by Previously Enrolled in the INSPIRE Trial or Not

	Study 004				Study 006			
	Pirfenidone 2403		Placebo		Pirfenidone 2403		Placebo	
	Enrolled (N=28)	Not Enrolled (N=146)	Enrolled (N=32)	Not Enrolled (N=142)	Enrolled (N=20)	Not Enrolled (N=151)	Enrolled (N=31)	Not Enrolled (N=142)
Age (years)								
Mean	66.2 (9.2)	65.7 (8.0)	67.0 (6.7)	66.1 (7.7)	68.0 (9.4)	66.6 (7.7)	68.2 (7.3)	66.7 (7.9)
Range	(46, 80)	(45, 80)	(52, 79)	(40, 79)	(45, 78)	(46, 80)	(46, 79)	(42, 80)
<55	4 (14)	12 (8)	2 (6)	8 (6)	2 (10)	9 (6)	1 (3)	9 (6)
55 – 64	7 (25)	52 (36)	10 (31)	53 (37)	5 (25)	54 (36)	6 (19)	45 (32)
65 – 74	13 (46)	59 (40)	14 (44)	55 (39)	5 (25)	59 (39)	18 (58)	65 (46)
≥75	4 (14)	23 (16)	6 (19)	26 (18)	8 (40)	29 (19)	6 (19)	23 (16)
Sex [n (%)]								
Male	19 (68)	99 (68)	22 (69)	106 (75)	16 (80)	107 (71)	21 (68)	103 (72)
Female	9 (32)	47 (32)	10 (31)	36 (25)	4 (20)	44 (29)	10 (32)	39 (27)
Race [n (%)]								
White	26 (93)	142 (97)	31 (97)	137 (96)	10 (100)	149 (99)	31 (100)	140 (99)
Non-white	2 (7)	4 (3)	1 (3)	5 (4)	0	1 (1)	0	2 (1)
BMI – Male								
Mean	29.7 (4.0)	29.8 (4.1)	28.3 (4.1)	30.1 (4.5)	32.1 (5.7)	30.9 (4.5)	28.9 (3.5)	30.7 (4.2)
Range	(22, 37)	(23, 44)	(23, 38)	(22, 48)	(24, 44)	(24, 42)	(24, 36)	(23, 46)
BMI – Female								
Mean	29.6 (2.9)	30.8 (4.6)	29.9 (4.7)	30.4 (5.3)	28.9 (4.4)	30.0 (5.4)	32.1 (4.4)	29.7 (5.4)
Range	(26, 34)	(21, 41)	(23, 39)	(20, 42)	(25, 35)	(22, 47)	(25, 39)	(15, 41)
Smoking Status at Screening [n (%)]								
Never	7 (25)	49 (34)	9 (28)	42 (30)	7 (35)	52 (34)	12 (39)	52 (37)
Previously	18 (64)	92 (63)	22 (69)	92 (65)	13 (65)	99 (66)	17 (55)	84 (59)
Currently	3 (11)	5 (3)	1 (3)	8 (6)	0	0	2 (6)	6 (4)
Oxygen Used at Baseline [n (%)]								
Yes	5 (18)	24 (16)	5 (16)	20 (14)	9 (45)	39 (26)	10 (32)	39 (27)
No	23 (82)	122 (84)	27 (84)	122 (86)	11 (55)	112 (74)	21 (68)	103 (72)
% Predicted FVC at Baseline								
Mean	76 (14.6)	74 (14.5)	74 (14.9)	77 (15.7)	75 (15.3)	75 (12.9)	73 (10.9)	73 (14.9)
Range	(58, 118)	(52, 124)	(51, 100)	(48, 136)	(50, 98)	(51, 108)	(53, 90)	(52, 128)
% Predicted DLco at Baseline								
Mean	46 (8.9)	46 (9.6)	45 (7.9)	46 (10.7)	45 (6.2)	48 (10.2)	48 (8.2)	47 (9.4)
Range	(34, 69)	(30, 81)	(34, 64)	(30, 90)	(31, 58)	(32, 81)	(35, 68)	(33, 78)
Time from IPF Diagnosis to Randomization (years)								
Mean	2.2 (0.6)	1.1 (0.9)	2.4 (0.6)	1.2 (1.1)	2.3 (0.8)	1.0 (1.0)	2.2 (0.7)	0.8 (0.9)
Range	(1, 3)	(>0, 4)	(1, 4)	(>0, 4)	(1, 4)	(>0, 4)	(1,4)	(>0, 4)
< 6 mon	0	48 (33)	0	46 (32)	0	63 (42)	0	71 (50)
6 m-<1 y	0	35 (24)	0	35 (25)	0	37 (24)	0	36 (25)
1 - <2 yrs	12 (43)	41 (28)	10 (31)	32 (22)	9 (45)	28 (18)	16 (52)	19 (13)
≥2 yrs	16 (57)	22 (15)	22 (69)	29 (20)	11 (55)	23 (15)	15 (48)	15 (11)
Missing	0	0	0	0	0	0	0	1 (1)
Primary Endpoint – Mean Change from Baseline at Week 72 in %Predicted FVC								
#Observed	26	128	28	122	17	131	29	120
#Death	1	7	3	13	2	11	2	13
#Imputed	1	11	1	7	1	9	0	9
Mean (SD)	-5.6 (13)	-8.5 (17)	-12.8 (17)	-12.3 (19)	-8.0 (17)	-9.1 (20)	-7.5 (21)	-10.0 (26)
Range	(-65, 8)	(-91, 13)	(-63, 4)	(-83, 10)	(-56, 11)	(-99, 18)	(-88, 19)	(-87, 13)
Difference in Mean Change	7.2	3.8	--	--	-0.5	0.9	--	--

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The main issue for this application is that only one of the two Phase 3 studies in patients with IPF, Study 004, showed statistically significant evidence in favor of pirfenidone on the primary outcome variable of change in lung function. In other words, positive findings from Study 004 were not replicated in Study 006. From a statistical perspective, this application failed to provide substantial evidence of pirfenidone's efficacy benefit.

During my review of the application, several potential statistical issues were identified, including the approach to handle missing data, multiplicity, and change in study design (sample size).

Upon review of the Applicant's pre-specified approach to handle missing data when analyzing the primary endpoint, that is, to impute the worst rank to patients who died, and applying sum of square difference to missing data due to reason other than death, I find that this approach is acceptable and not a statistical issue.

In terms of multiplicity, the Applicant did not apply any formal adjustments for the secondary and exploratory endpoints. They stated that:

> Because of the limited information in the literature about assessing IPF and the lack of regulatory precedent to guide in the selection of endpoints for IPF, there were no adjustments for multiple comparisons of secondary and exploratory endpoints.

Instead, they analyzed the secondary outcome variables using the pooled data from both studies, when the primary efficacy analyses (absolute change in percent predicted FVC) from PIPF-004 and from PIPF-006 each showed efficacy ($p \leq 0.0498$). They considered the results from the analyses of pooled data to be primary to that of the individual study results.

This is an issue, in particular, when a study failed to show significant treatment difference on the primary endpoint (Study 006). In the strictest sense of alpha spending, he entire alpha has been spent by the primary efficacy analyses. Furthermore, the Applicant stated that they will only analyze secondary outcome variables using the pooled data from both studies, when each study showed efficacy.

Multiplicity is also an issue in Study 004, because the Applicant would like to add the result from the analysis of secondary endpoint (i.e. progression-free survival) in the label. Of note, PFS is one of many secondary endpoints analyzed by the Applicant.

The Applicant also made some changes in the conduct of the study prior to unblinding. Some of these changes are extending the duration of blinded therapy and increasing the total sample size from 325 to 400 patients. Because these changes were made prior to unblinding and no efficacy analyses were conducted, these changes are not an issue.

Findings from the review of Study 004 and Study 006 are summarized below.

Primary Endpoint - %Predicted FVC

Patients receiving pirfenidone had a smaller mean decline from Baseline in %Predicted FVC compared to those receiving placebo at Week 72 ($p < 0.001$, rank ANCOVA) in Study 004. This represents an absolute difference of 4.4% and a relative difference of 35% between the two treatment groups.

In contrast, there was no statistically significant reduction in the mean decline from Baseline in %Predicted FVC in patients receiving pirfenidone compared to those receiving placebo at Week 72 in Study 006.

Table 23. Mean Change in %Predicted FVC (Imputed)

	Pirfenidone		Placebo		Treatment Comparison		
Week	N Observed (Death)	Mean [a] (STD)	N Observed (Death)	Mean [a] (STD)	Absolute Diff. [c]	Relative Diff. [d]	p-value [b]
Study 004							
Baseline	174 (0)	74.5 (14.5)	174 (0)	76.2 (15.5)	-1.7	--	--
Week 72	**154 (8)**	**-8.0 (16.5)**	**150 (16)**	**-12.4 (18.5)**	**4.4**	**35.3**	**0.001**
Study 006							
Baseline	171 (0)	74.9 (13.2)	173 (0)	73.1 (14.2)	1.7	--	--
Week 72	**148 (13)**	**-9.0 (19.6)**	**149 (15)**	**-9.6 (19.1)**	**0.6**	**6.5**	**0.501**

[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).

Secondary endpoint – Time to Progression-Free Survival

Overall, treatment with pirfenidone resulted in a higher proportion of progression-free survival than treatment with placebo (74%, 127/172 vs. 64%, 111/173 of patients, respectively) in Study 004. Treatment with pirfenidone was associated with a 36% relative reduction of the combined risk of disease progression or death before disease progression compared to placebo (HR [95% CI]: 0.64 [0.44–0.95]). However, this finding was not replicated in Study 006. Furthermore, exploring the individual components of this combined endpoint, the reduction appears to be mainly due to disease progression.

Table 24. Survival Analysis on Progression-Free Survival during the Treatment Period

	Pirfenidone	Placebo	Hazard Ratio (95% CI) [c]
	N of Event (%)	N of Event (%)	p-value [b]
Study 004			
N of Randomized	174 [a]	174	--
Death or Disease Progression [d]	45 (26.2)	62 (35.8)	0.64 (0.44, 0.94), 0.023
Decline in %Predicted FVC≥10%	28 (16.3)	39 (22.5)	--
Decline in %Predicted DL_{CO}≥15%	9 (5.2)	9 (5.2)	--
Death before disease progression [e]	8 (4.7)	14 (8.1)	--
Study 006			
N of Randomized	171	173	--
Death or Disease Progression [d]	54 (31.8)	60 (34.9)	0.84 (0.58, 1.22), 0.355
Decline in %Predicted FVC≥10%	31 (18.2)	41 (23.8)	--
Decline in %Predicted DL_{CO}≥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 from Study 004; 1 patient in the pirfenidone 2403-mg/d group and 1 patient in the placebo group from Study 006).
[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.

Post Hoc Endpoint – IPF-Related Deaths

IPF-related deaths were analyzed post-hoc by the Applicant. When data from both studies were pooled, the Applicant stated there is some evidence of survival benefit in the pirfenidone group compared to placebo on on-treatment IPF-related death. However, because all deaths (including IPF-related deaths) were not adjudicated, it is difficult to make definitive conclusion about this result.

Table 25. Survival Analysis on IPF Related Death

	Study 004		Study 006		Pooled Study 004/006	
	Pirfenidone (N=174)	Placebo (N=174)	Pirfenidone (N=171)	Placebo (n=173)	Pirfenidone (N=345)	Placebo (n=347)
Treatment Period						
Number of Event (%)	6 (3.4)	13 (7.5)	12 (7.0)	15 (8.7)	18 (5.2)	28 (8.1)
Probability of event by end of the period [a]	9.7 (3.4, 25.9)	9.7 (5.4, 17.2)	10.4 (5.6, 19.0)	27.1 (7.6, 72.1)	9.7 (5.5, 16.7)	22.1 (7.1, 57.1)
Hazard ratio [b] (95%CI)	0.45 (0.17, 1.19)	--	0.79 (0.37, 1.69)	--	0.63 (0.35, 1.14)	--
Log-rank p-value [c]	0.108	--	0.542	--	0.130	--
On-Treatment						
Number of Event (%)	5 (2.9)	11 (6.3)	7 (4.1)	14 (8.1)	12 (3.5)	25 (7.2)
Probability of event by end of the period [a]	5.9 (2.0, 16.8)	10.3 (4.9, 20.9)	6.3 (2.8, 13.9)	8.6 (5.2, 14.1)	6.0 (3.1, 11.3)	9.0 (5.8, 13.7)
Hazard ratio [b] (95%CI)	0.45 (0.16, 1.31)	--	0.49 (0.20, 1.23)	--	0.48 (0.24, 0.95)	--
Log-rank p-value [c]	0.143	--	0.129	--	0.035	--
Vital Status at End of Study						
Number of Event (%)	8 (4.6)	15 (8.6)	14 (8.2)	15 (8.7)	22 (6.4)	30 (8.6)
Probability of event by end of the period [a]	12.9 (5.7, 27.9)	14.3 (7.3, 27.2)	21.1 (8.2, 48.3)	21.9 (6.9, 57.4)	19.6 (8.4, 41.7)	20.8 (8.1, 47.4)
Hazard ratio [b] (95%CI)	0.51 (0.22, 1.21)	--	0.94 (0.45, 1.95)	--	0.72 (0.42, 1.25)	--
Log-rank p-value [c]	0.127	--	0.863	--	0.246	--

[a] Kaplan Meier estimated event rate at end of 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

5.2 Conclusion

Based on my collective evaluation of Study 004 and 006, I conclude that only one of the two studies in patients with IPF, Study 004, showed statistically significant evidence in favor of pirfenidone on the primary outcome variable of change in lung function. Most of the secondary endpoints in Study 004 were also numerically in favor of pirfenidone providing additional support.

Positive findings from Study 004 were not replicated in Study 006. Therefore from a statistical perspective, the overall package failed to provide substantial evidence of pirfenidone's efficacy benefit.

6. LABELING

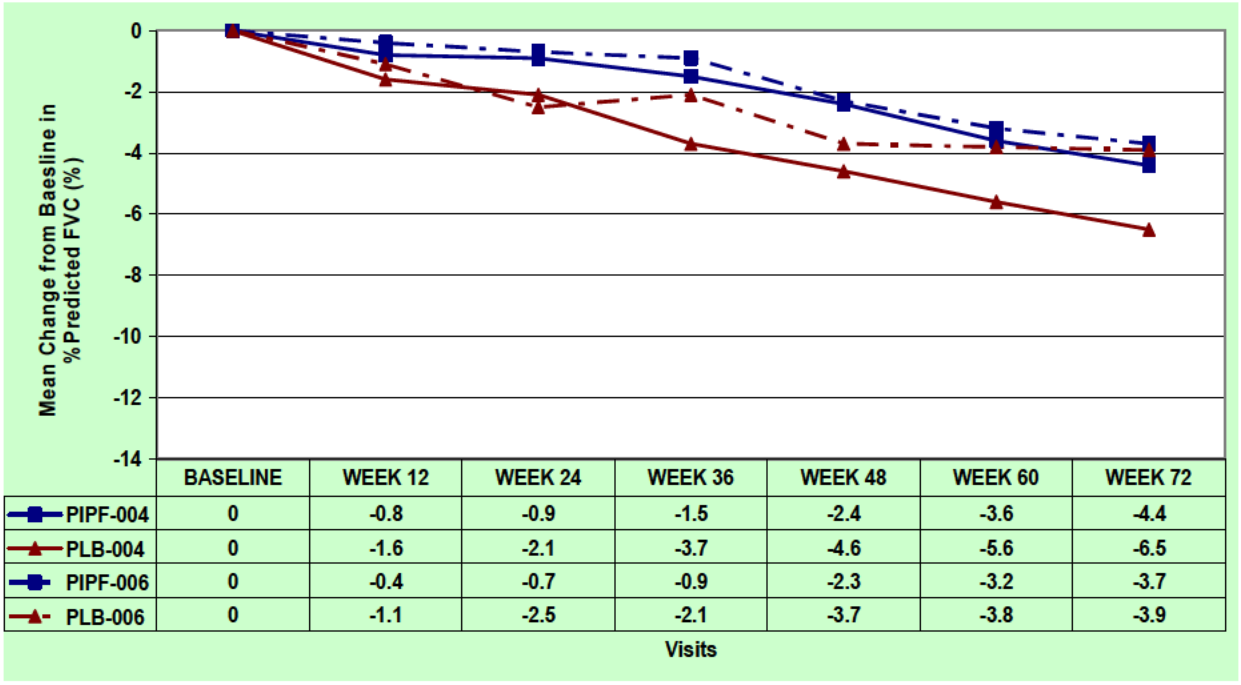
I recommend the labeling changes as follows:

(b) (4)

3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

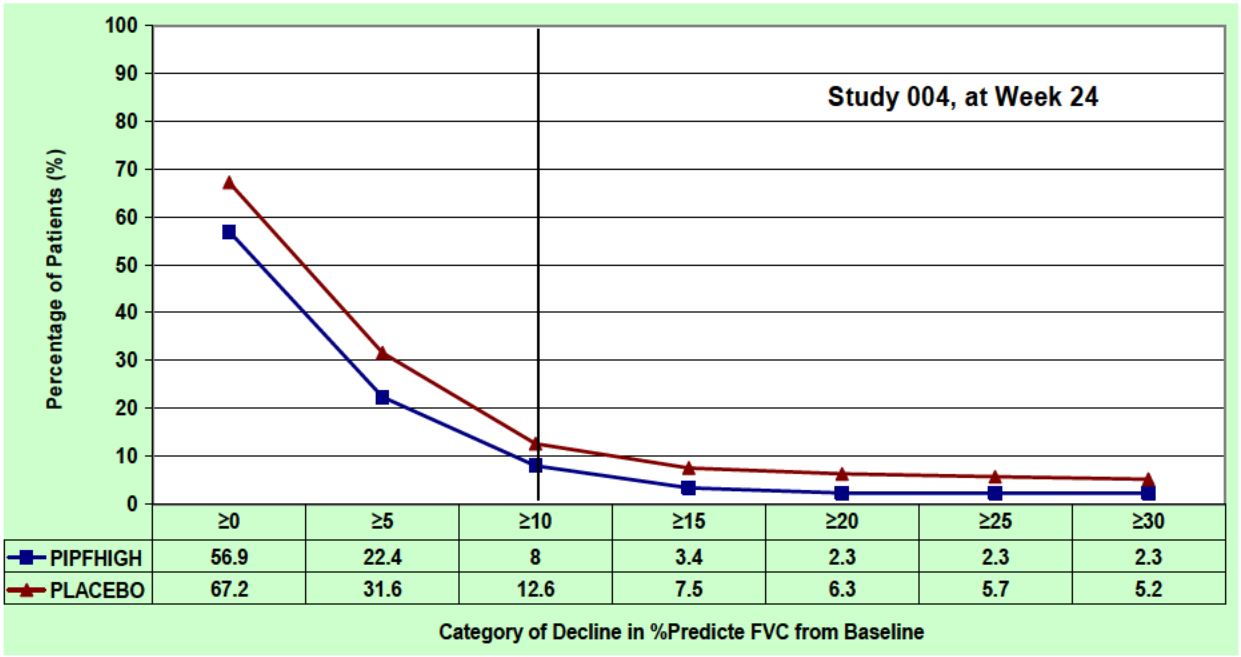
APPENDIX

Figure 15. Mean Change from Baseline in %Predicted FVC (Observed)



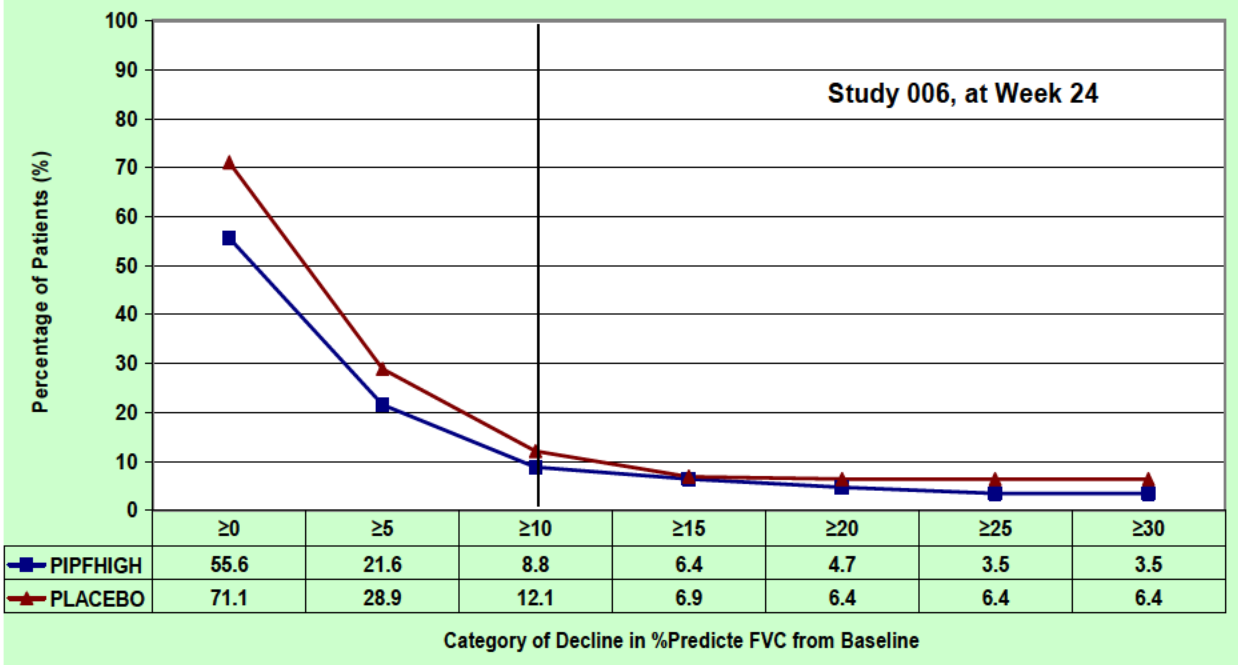
	BASELINE	WEEK 12	WEEK 24	WEEK 36	WEEK 48	WEEK 60	WEEK 72
PIPF-004	0	-0.8	-0.9	-1.5	-2.4	-3.6	-4.4
PLB-004	0	-1.6	-2.1	-3.7	-4.6	-5.6	-6.5
PIPF-006	0	-0.4	-0.7	-0.9	-2.3	-3.2	-3.7
PLB-006	0	-1.1	-2.5	-2.1	-3.7	-3.8	-3.9

Figure 16. Cumulative % of Patients of Change from baseline in %Predicted FVC (Imputed)



	≥0	≥5	≥10	≥15	≥20	≥25	≥30
PIPFHIGH	56.9	22.4	8	3.4	2.3	2.3	2.3
PLACEBO	67.2	31.6	12.6	7.5	6.3	5.7	5.2

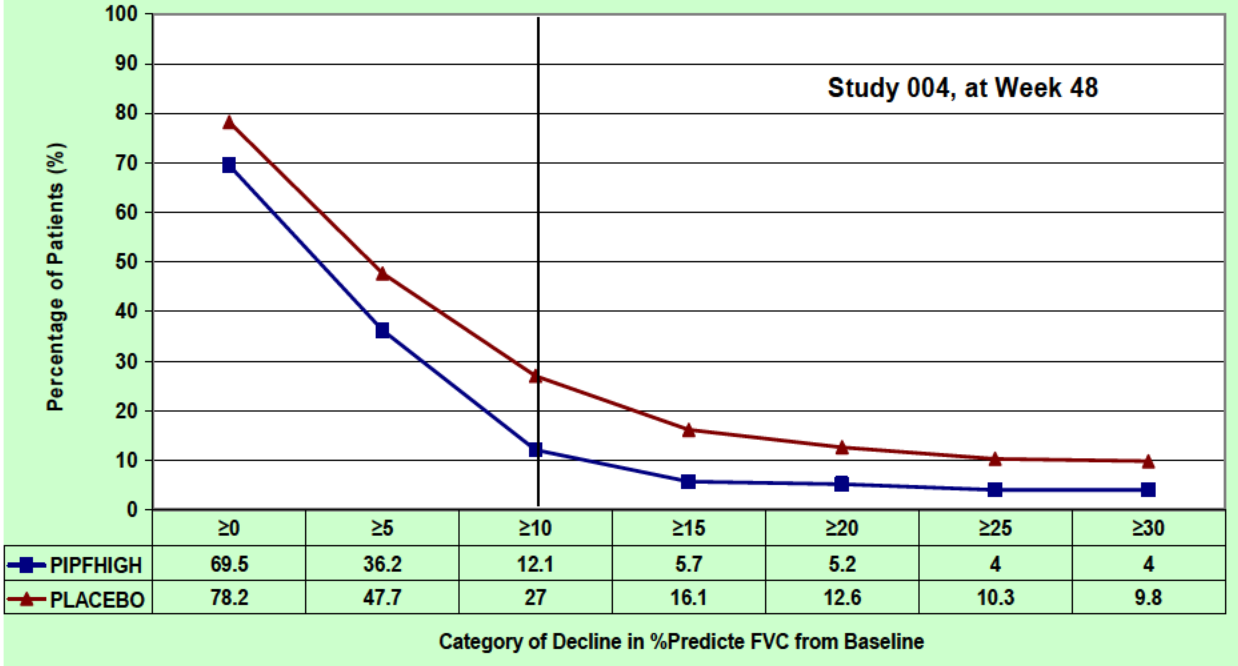
Figure 17. Cumulative % of Patients of Change from baseline in %Predicted FVC (Imputed)



	≥0	≥5	≥10	≥15	≥20	≥25	≥30
PIPFHIGH	55.6	21.6	8.8	6.4	4.7	3.5	3.5
PLACEBO	71.1	28.9	12.1	6.9	6.4	6.4	6.4

Category of Decline in %Predicte FVC from Baseline

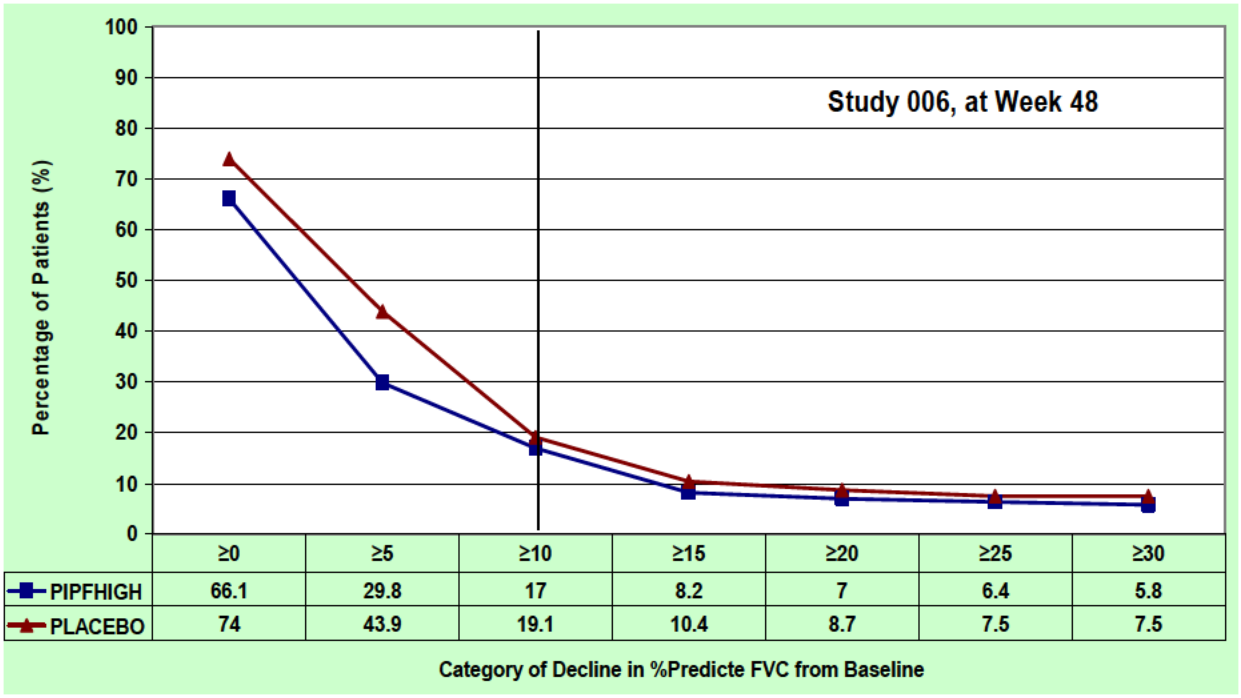
Figure 18. Cumulative % of Patients of Change from baseline in %Predicted FVC (Imputed)



	≥0	≥5	≥10	≥15	≥20	≥25	≥30
PIPFHIGH	69.5	36.2	12.1	5.7	5.2	4	4
PLACEBO	78.2	47.7	27	16.1	12.6	10.3	9.8

Category of Decline in %Predicte FVC from Baseline

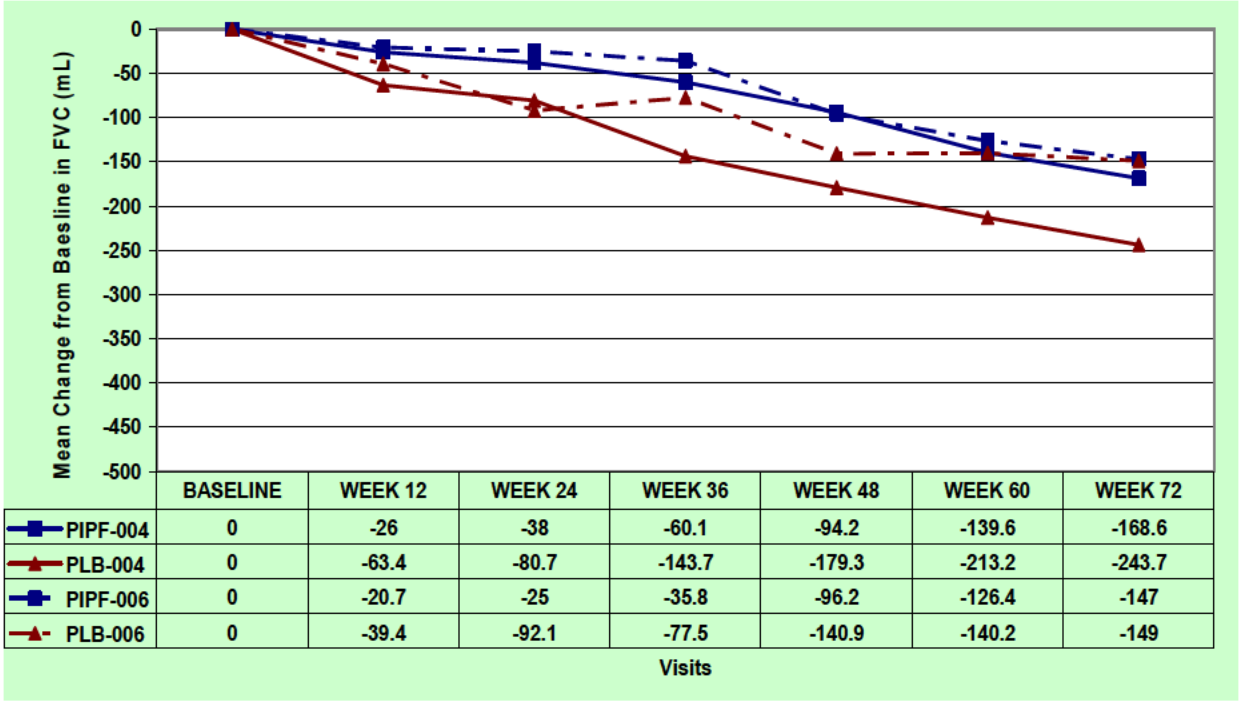
Figure 19. Cumulative % of Patients of Change from baseline in %Predicted FVC (Imputed)



	≥0	≥5	≥10	≥15	≥20	≥25	≥30
PIPFHIGH	66.1	29.8	17	8.2	7	6.4	5.8
PLACEBO	74	43.9	19.1	10.4	8.7	7.5	7.5

Category of Decline in %Predicte FVC from Baseline

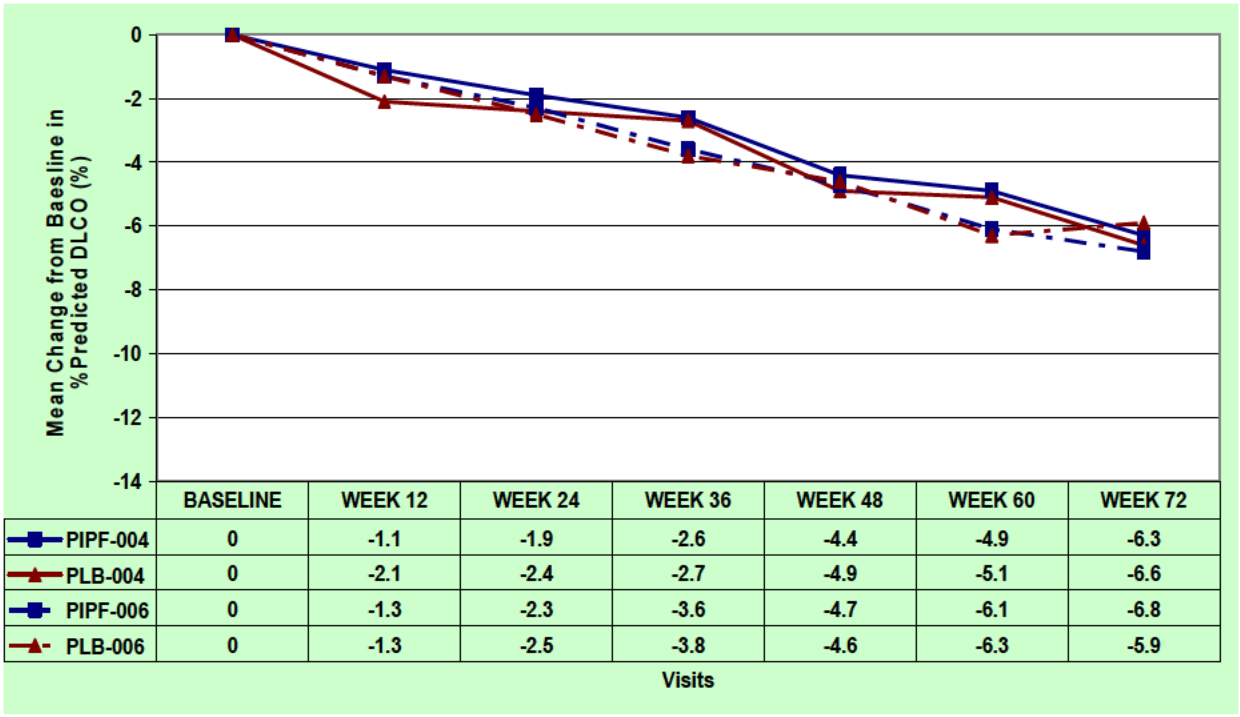
Figure 20. Mean Change from Baseline in FVC (mL) (Observed)



	BASELINE	WEEK 12	WEEK 24	WEEK 36	WEEK 48	WEEK 60	WEEK 72
PIPF-004	0	-26	-38	-60.1	-94.2	-139.6	-168.6
PLB-004	0	-63.4	-80.7	-143.7	-179.3	-213.2	-243.7
PIPF-006	0	-20.7	-25	-35.8	-96.2	-126.4	-147
PLB-006	0	-39.4	-92.1	-77.5	-140.9	-140.2	-149

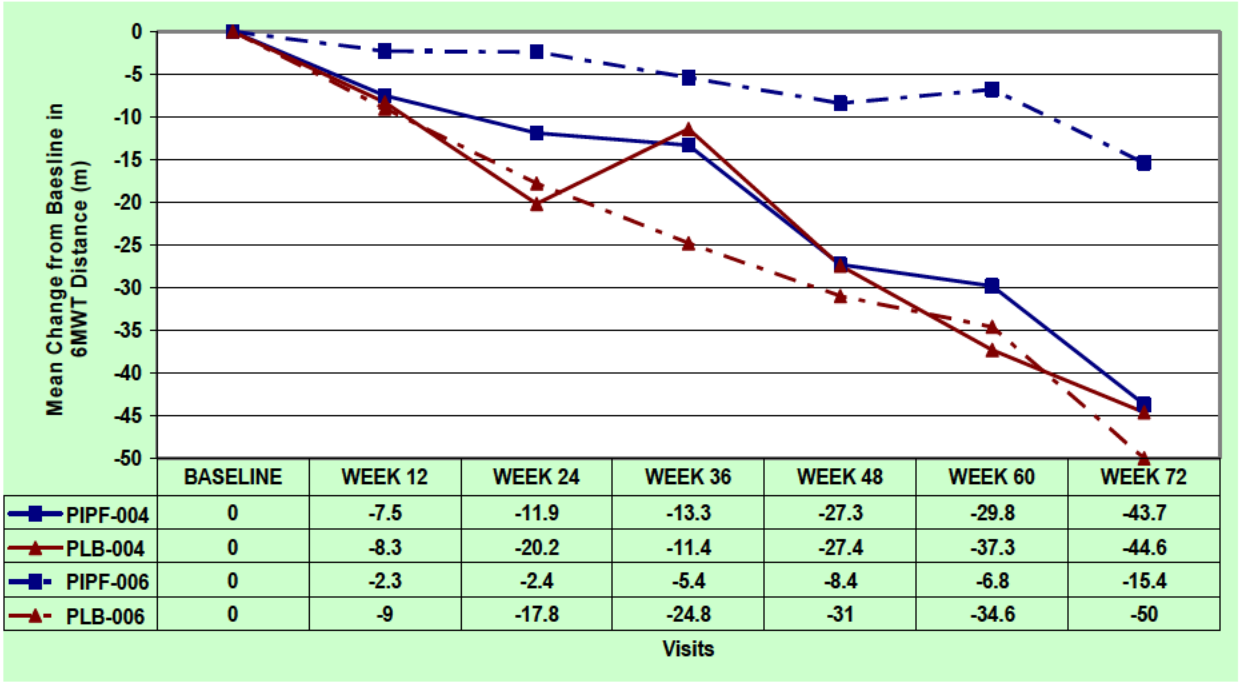
Visits

Figure 21. Mean Change from Baseline in %Predicted DLco (%) (Observed)



	BASELINE	WEEK 12	WEEK 24	WEEK 36	WEEK 48	WEEK 60	WEEK 72
PIPF-004	0	-1.1	-1.9	-2.6	-4.4	-4.9	-6.3
PLB-004	0	-2.1	-2.4	-2.7	-4.9	-5.1	-6.6
PIPF-006	0	-1.3	-2.3	-3.6	-4.7	-6.1	-6.8
PLB-006	0	-1.3	-2.5	-3.8	-4.6	-6.3	-5.9

Figure 22. Mean Change from Baseline in 6MWT Distance (m) (Observed)



	BASELINE	WEEK 12	WEEK 24	WEEK 36	WEEK 48	WEEK 60	WEEK 72
PIPF-004	0	-7.5	-11.9	-13.3	-27.3	-29.8	-43.7
PLB-004	0	-8.3	-20.2	-11.4	-27.4	-37.3	-44.6
PIPF-006	0	-2.3	-2.4	-5.4	-8.4	-6.8	-15.4
PLB-006	0	-9	-17.8	-24.8	-31	-34.6	-50

Table 26. Survival Analysis on All Cause Mortality

	Study 004		Study 006		Pooled Study 004/006	
	Pirfenidone (N=174)	Placebo (N=174)	Pirfenidone (N=171)	Placebo (n=173)	Pirfenidone (N=345)	Placebo (n=347)
Treatment Period						
Number of Event (%)	11 (6.3)	17 (9.8)	16 (9.4)	17 (9.8)	27 (7.8)	34 (9.8)
Probability of event by end of the period [a]	12.7 (6.0, 25.5)	11.1 (6.8, 17.8)	11.8 (7.0, 19.3)	16.5 (7.0, 36.1)	11.7 (7.6, 17.9)	14.9 (7.7, 27.7)
Hazard ratio [b] (95%CI)	0.61 (0.29, 1.30)	--	0.96 (0.48, 1.89)	--	0.78 (0.47, 1.29)	--
Log-rank p-value [c]	0.201	--	0.897	--	0.333	--
On-Treatment						
Number of Event (%)	10 (5.7)	14 (8.0)	9 (5.3)	15 (8.7)	19 (5.5)	29 (8.4)
Probability of event by end of the period [a]	11.5 (5.3, 23.7)	12.0 (6.3, 22.2)	7.5 (3.7, 14.9)	9.2 (5.6, 14.8)	9.0 (5.4, 14.9)	10.1 (6.8, 14.9)
Hazard ratio [b] (95%CI)	0.71 (0.32, 1.60)	--	0.59 (0.26, 1.36)	--	0.65 (0.37, 1.16)	--
Log-rank p-value [c]	0.413	--	0.217	--	0.146	--
Vital Status at End of Study						
Number of Event (%)	14 (8.0)	20 (11.5)	18 (10.5)	17 (9.8)	32 (9.3)	37 (10.7)
Probability of event by end of the period [a]	19.8 (10.5, 35.4)	19.0 (10.8, 32.2)	23.1 (9.8, 48.6)	22.8 (7.6, 57.1)	23.3 (11.7, 43.2)	23.2 (10.1, 47.8)
Hazard ratio [b] (95%CI)	0.68 (0.34, 1.34)	--	1.06 (0.55, 2.07)	--	0.85 (0.53, 1.37)	--
Log-rank p-value [c]	0.268	--	0.856	--	0.509	--

[a] Kaplan Meier estimated event rate at end of 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

Table 27. Survival Analysis on Fatal Adverse Event (Deaths + Lung Transplantations)

	Study 004		Study 006		Pooled Study 004/006	
	Pirfenidone (N=174)	Placebo (N=174)	Pirfenidone (N=171)	Placebo (n=173)	Pirfenidone (N=345)	Placebo (n=347)
Treatment Period						
Number of Event (%)	14 (8.0)	21 (12.1)	20 (11.7)	22 (12.7)	34 (9.9)	43 (12.4)
Probability of event by end of the period [a]	17.8 (8.7, 34.4)	16.4 (9.9, 26.3)	15.8 (9.9, 24.6)	31.1 (10.7, 70.6)	16.0 (10.7, 23.6)	27.0 (11.1, 56.6)
Hazard ratio [b] (95%CI)	0.65 (0.33, 1.29)	--	0.90 (0.49, 1.64)	--	0.78 (0.50, 1.22)	--
Log-rank p-value [c]	0.220	--	0.722	--	0.274	--
On-Treatment						
Number of Event (%)	13 (7.5)	19 (10.9)	11 (6.4)	20 (11.6)	24 (7.0)	39 (11.2)
Probability of event by end of the period [a]	13.2 (6.8, 24.9)	21.2 (11.3, 37.5)	8.7 (4.6, 16.1)	12.9 (8.4, 19.5)	10.5 (6.7, 16.3)	15.6 (10.7, 22.2)
Hazard ratio [b] (95%CI)	0.68 (0.34, 1.37)	--	0.54 (0.26, 1.14)	--	0.61 (0.37, 1.01)	--
Log-rank p-value [c]	0.281	--	0.105	--	0.054	--
Vital Status at End of Study						
Number of Event (%)	17 (9.8)	24 (13.8)	22 (12.9)	22 (12.7)	39 (11.3)	46 (13.3)
Probability of event by end of the period [a]	21.3 (11.9, 36.5)	27.6 (14.8, 47.8)	25.7 (12.2, 49.4)	26.1 (10.3, 56.9)	25.5 (13.7, 44.3)	27.8 (14.2, 50.1)
Hazard ratio [b] (95%CI)	0.69 (0.37, 1.29)	--	1.00 (0.55, 1.80)	--	0.84 (0.55, 1.28)	--
Log-rank p-value [c]	0.244	--	0.988	--	0.411	--

[a] Kaplan Meier estimated event rate at end of 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

Table 28. Survival Analysis on IPF Related Death

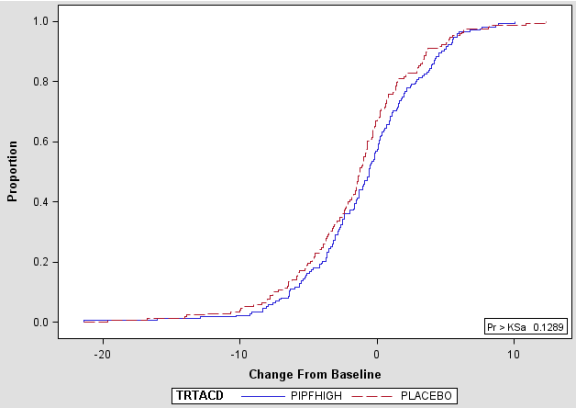
	Study 004		Study 006		Pooled Study 004/006	
	Pirfenidone (N=174)	Placebo (N=174)	Pirfenidone (N=171)	Placebo (n=173)	Pirfenidone (N=345)	Placebo (n=347)
Treatment Period						
Number of Event (%)	6 (3.4)	13 (7.5)	12 (7.0)	15 (8.7)	18 (5.2)	28 (8.1)
Probability of event by end of the period [a]	9.7 (3.4, 25.9)	9.7 (5.4, 17.2)	10.4 (5.6, 19.0)	27.1 (7.6, 72.1)	9.7 (5.5, 16.7)	22.1 (7.1, 57.1)
Hazard ratio [b] (95%CI)	0.45 (0.17, 1.19)	--	0.79 (0.37, 1.69)	--	0.63 (0.35, 1.14)	--
Log-rank p-value [c]	0.108	--	0.542	--	0.130	--
On-Treatment						
Number of Event (%)	5 (2.9)	11 (6.3)	7 (4.1)	14 (8.1)	12 (3.5)	25 (7.2)
Probability of event by end of the period [a]	5.9 (2.0, 16.8)	10.3 (4.9, 20.9)	6.3 (2.8, 13.9)	8.6 (5.2, 14.1)	6.0 (3.1, 11.3)	9.0 (5.8, 13.7)
Hazard ratio [b] (95%CI)	0.45 (0.16, 1.31)	--	0.49 (0.20, 1.23)	--	0.48 (0.24, 0.95)	--
Log-rank p-value [c]	0.143	--	0.129	--	0.035	--
Vital Status at End of Study						
Number of Event (%)	8 (4.6)	15 (8.6)	14 (8.2)	15 (8.7)	22 (6.4)	30 (8.6)
Probability of event by end of the period [a]	12.9 (5.7, 27.9)	14.3 (7.3, 27.2)	21.1 (8.2, 48.3)	21.9 (6.9, 57.4)	19.6 (8.4, 41.7)	20.8 (8.1, 47.4)
Hazard ratio [b] (95%CI)	0.51 (0.22, 1.21)	--	0.94 (0.45, 1.95)	--	0.72 (0.42, 1.25)	--
Log-rank p-value [c]	0.127	--	0.863	--	0.246	--

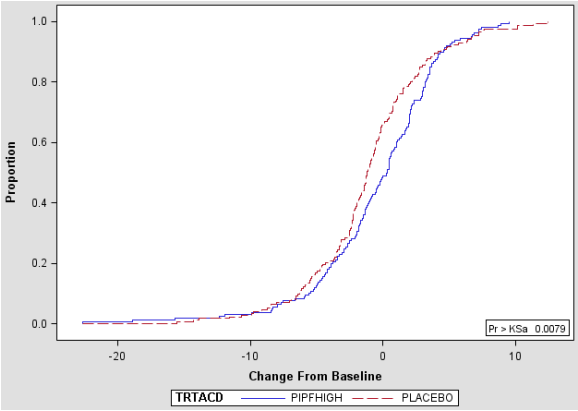
[a] Kaplan Meier estimated event rate at end of period.
[b] Hazard ratio was based on the Cox proportional hazard model
[c] p-value was based on the log-rank test, stratified by geographic region (USA and ROW) comparing pirfenidone 2403 mg/d with placebo

Figure 23. Empirical Distribution with Kolmogorov-Smirnov Two-Sample Test of Change in Percent Predicted FVC

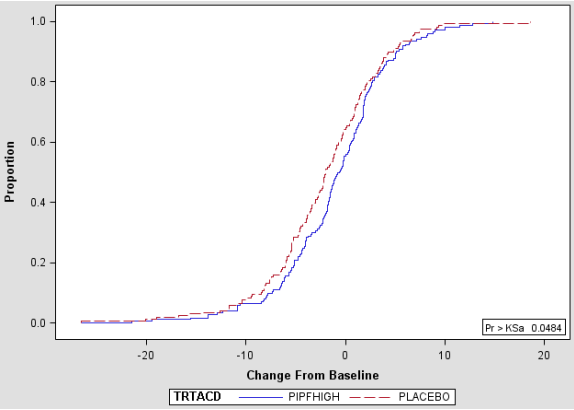
Study 004 Study 006

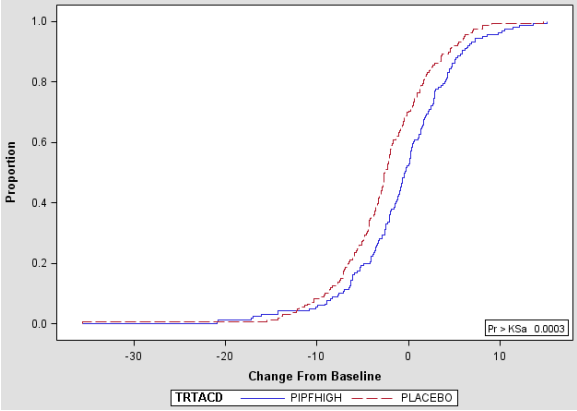
Week 12



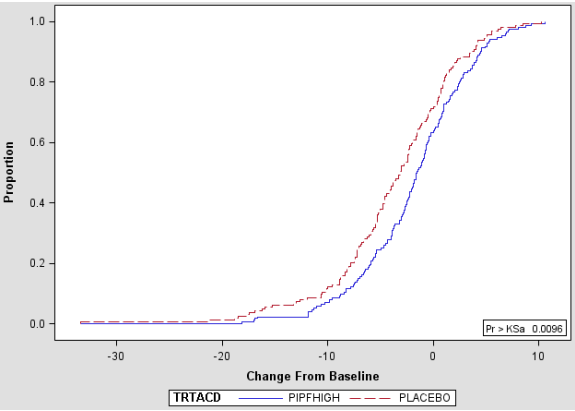


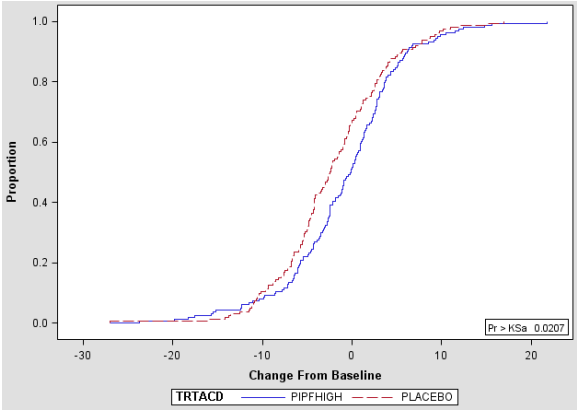
Week 24





Week 36





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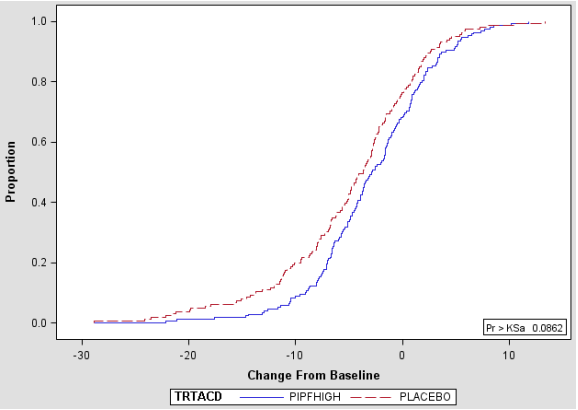

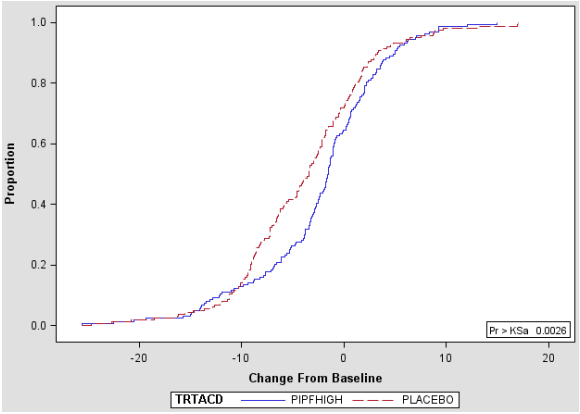

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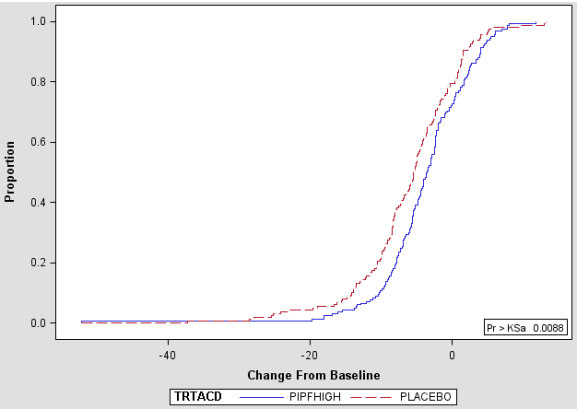

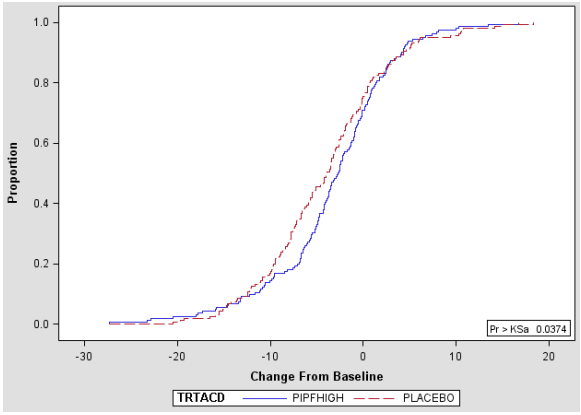

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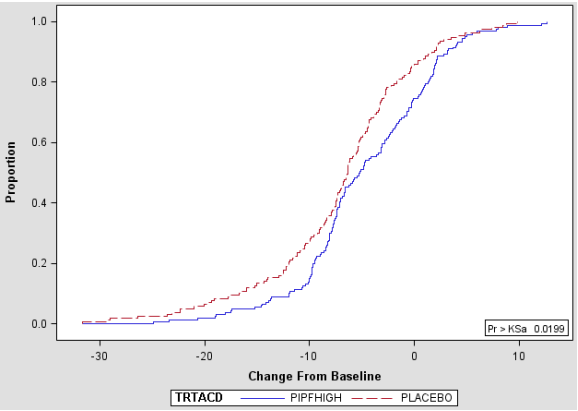

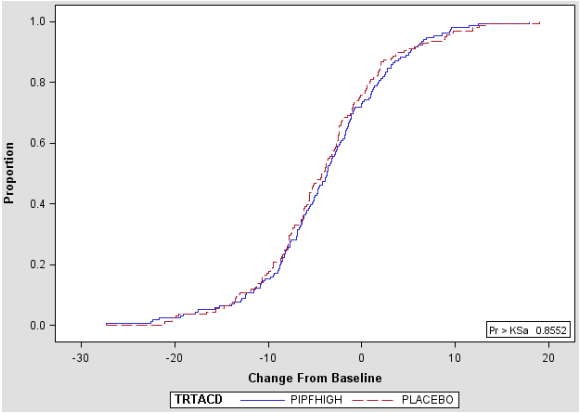

-EOF-

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/

FENG ZHOU
04/05/2010

JOAN K BUENCONSEJO
04/05/2010
I concur with Feng Zhou's statistics review of NDA 22535 (Pirfenidone).

THOMAS J PERMUTT
04/05/2010
concur

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

Statistical Review and Evaluation

CLINICAL STUDIES

NDA/Serial Number:	NDA22-535
Drug Name:	Pirfenidone capsules
Indication(s):	Treatment of patients with idiopathic pulmonary fibrosis to reduce decline in lung function
Applicant:	InterMune, Inc.
Date(s):	Received 11/4/09; User Fee 05/4/10
Review Priority:	6-months
Biometrics Division:	Division of Biometrics II/Office of Biostatistics
Statistical Team:	Zhou, Feng, M.S. (Statistical Reviewer) Buenconsejo, Joan, Ph.D. (Acting Statistical Team Leader) Permutt, Thomas J, Ph.D. (Division Director of Biometrics II)
Medical Division:	Division of Pulmonary and Allergy Products
Clinical Team:	Karimi-Shah, Banu, M.D. (Medical Reviewer) Seymour, Sally, M.D. (Medical Team Leader) Chowdhury, Badrul A, M.D., Ph.D. (Medical Division Director)
Project Manager:	Chung, Eunice

Keywords: Clinical Studies, NDA review, Dropouts

FILING CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	Yes
Original protocols & subsequent amendments available in the NDA	Yes
Safety and efficacy for gender, racial, and geriatric subgroups investigated	Yes
Data sets in EDR conform to applicable guidance.	Yes

From a statistical perspective, the submission can be filed.

Reviewer's comment:

1. *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.*
2. *On December 18, 2009, the missing information for some interim analyses data for studies PIPF-004 and PIPF-006 was requested from the Applicant. The Applicant responded on December 24, 2009 that they submitted the eleven tables and figure, along with the electronic data for three DMC meetings. Therefore application was FILEABLE.*

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/

FENG ZHOU
01/11/2010

JOAN K BUENCONSEJO
01/11/2010
I concur