CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022535Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY:
CLINICAL PHARMACOLOGY REVIEW

NDA	22535
Submission Date:	May 23, 2014
Brand Name:	Esbriet
Generic Name:	Pirfenidone
OCP Reviewer:	Dinko Rekić, M.Sc., Ph.D.
OCP Team Leader:	Satjit Brar, Pharm.D., Ph.D.
Pharmacometrics Reviewer:	Dinko Rekić, M.Sc., Ph.D.
Pharmacometrics Team Leader:	Liang Zhao, Ph.D.
OCP Division:	Division of Clinical Pharmacology II
OND Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor:	InterMune
Submission Type; Code:	Class 2 Resubmission
Dosing regimen:	Maintenance regimen: 801 mg (three 267 mg capsules) orally three times a day with food.
Indication:	Treatment of patients with idiopathic pulmonary fibrosis to reduce decline in lung function

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1 EXECUTIVE SUMMARY

InterMune has submitted a Class 2 resubmission for NDA 22535 seeking the marketing approval for pirfenidone capsules (proposed tradename ESIBRET) for the treatment of patients with idiopathic pulmonary fibrosis to reduce decline in lung function. The original NDA submission for pirfenidone was not approved due to failure to show replicable evidence of effectiveness. A complete review of all clinical pharmacology trials was conducted at time of the original NDA submission (see clinical pharmacology review by Drs. Elizabeth Y. Shang, Yun Xu, Venkatesh Bhattaram, Michael A Pacanowski, and Issam Zineh, DARRTS date April 5, 2010). This assessment included ADME, extrinsic/intrinsic factors, dose selection, and drug-drug interactions. The current submission contains a new phase III trial (PIPF-016) and a drug-drug-interaction trial with ciprofloxacin (PIPF-017).

The following points are the major findings from the Office of Clinical Pharmacology:

1) Pirfenidone reaches its maximum concentration (T_{max}) ~0.5 hours after a single dose. A high fat meal decreases the maximum concentration (C_{max}) by ~49% and increases T_{max} to 3.5 hr. Area under the curve ($AUC_{0\text{-}inf}$) is decreased by ~16% due to a high fat meal.

2) The elimination half-life ($t_{1/2}$) is estimated at ~3 hr., after multiple dose administration. The main metabolite of pirfenidone, 5-carboxy pirfenidone, is formed by CYP1A2 and is inactive. Approximately 80% of a pirfenidone dose is eliminated in urine; with less than 1% as parent compound and majority as the 5-carboxy metabolite.

3) $AUC_{0\text{-}\infty}$ and C_{max} was 46% and 68% of the exposure in non-smokers. Smoking is known to induce CYP1A2, which is the chief metabolizing enzyme of pirfenidone.

4) Fluvoxamine (a strong CYP1A2 inhibitor) and ciprofloxacin (a moderate CYP1A2 inhibitor) increased pirfenidone $AUC_{0\text{-}inf}$ by 400% and 81% and C_{max} by 70% and 23%, respectively. The reviewer finds the proposed dosing regimen changes for the following drug-interactions acceptable.

    a. Fluvoxamine: decrease the pirfenidone dose to 1 capsule three times a day (a total of 801 mg daily).
    b. Ciprofloxacin: decrease the pirfenidone dose to two capsules three times a day (a total of 1602 mg daily).

5) A reviewer initiated analysis of the submitted registration trials shows that the treatment effect, defined as placebo adjusted treatment response in the rate of decline in lung function, is found to vary across trials. The treatment response within the active arms was found to be consistent across trials. However, the decrease in lung function in the placebo arm varied across trials.

   An analysis of the placebo response across trials found three covariates that significantly correlate with the rate of disease progression; %predicted Forced Vital Capacity (FVC) at baseline, baseline bodyweight, and use of supplemental oxygen at baseline. Patients on supplemental oxygen use had a higher rate of disease progression, while patients with higher bodyweight at baseline (up to ~85 kg), had a slower rate of disease progression. Patients with higher baseline FVC had slower rate of disease progression.

   With regard to trial design for treatments of IPF, future trials should aim to keep the following patient characteristics balanced across treatment arms; bodyweight, baseline supplemental oxygen use, and baseline FVC.

For complete assessment of efficacy and safety, the reader is referred to the medical and statistical reviews by Dr. Banu A. Karimi-Shah and Zhou Feng for the original NDA22535 and Dr. Banu A. Karimi-Shah and Dr. Yongman Kim for this submission.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 22535 and finds the application acceptable.

1.2 Phase IV Commitments

None.

2 PERTINENT REGULATORY BACKGROUND

Pirfenidone was designated as an orphan drug on March 5, 2004. The applicant (InterMune) submitted an NDA application (NDA 22535) for pirfenidone in 2009. The Agency sent a complete response (CR) letter in 2010 stating that the applicant has failed to show significant treatment effect in two replicate trials. Reference is made to CR letter from Dr. Rosebraugh dated, May 4, 2010.

The current submission contains results from a new phase III trial (PIPF-016) as well as one additional drug-drug interaction trial (PIPF-017).

No therapy for idiopathic pulmonary fibrosis has been approved in the United States. Pirfenidone is approved in Japan (daily dose of 1,800 mg) and the European Union (daily dose of 2,403 mg).

3 SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

A complete review of all clinical pharmacology trials was conducted at time of the original NDA submission (see clinical pharmacology review by Drs. Elizabeth Y. Shang, Yun Xu, Venkatesh Bhattaram, Michael A Pacanowski, and Issam Zineh, dated April 5, 2010). This assessment included ADME, extrinsic/intrinsic factors, dose selection, and drug-drug interactions. Presented in this review is an overview of pirfenidone pharmacokinetics and the external and internal factors influencing systemic exposure of pirfenidone. In addition, a reviewer initiated analysis presents a summary of findings based on new clinical data.

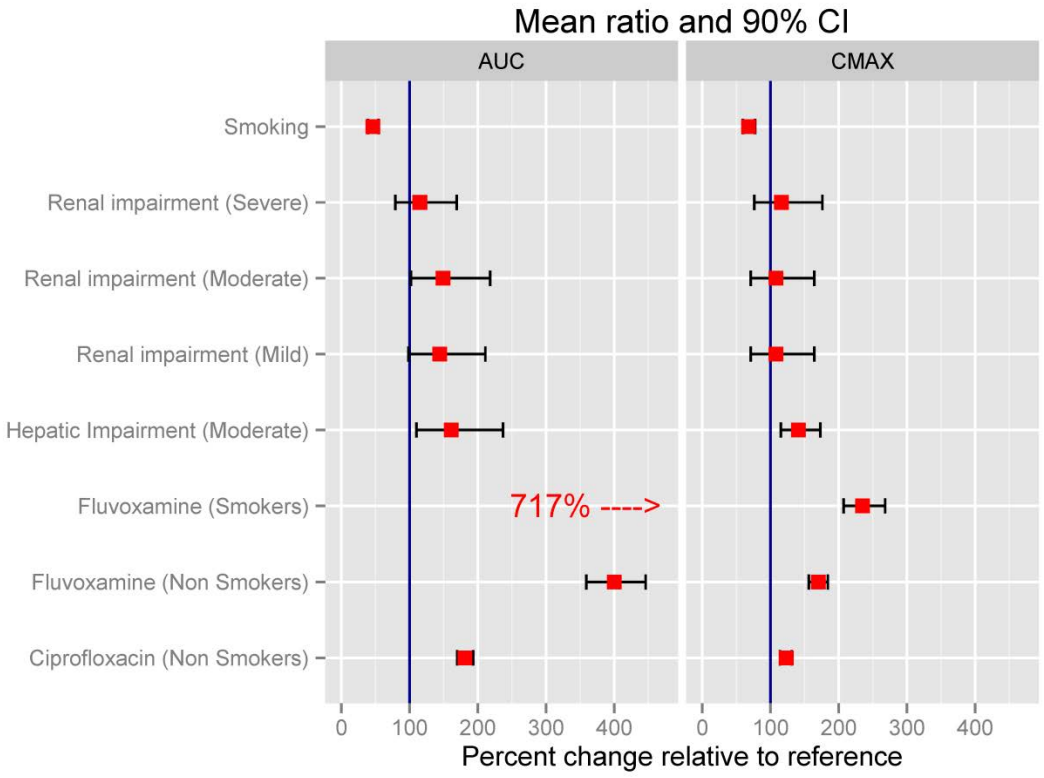
Pirfenidone is a small molecule (MW: 185.23 g/mol) that is purported to reduce the decline in lung function in patients with idiopathic pulmonary fibrosis (IPF). The proposed dosing regimen is 801 mg (three 267 mg capsules) orally three times a day with food after initial dose titration. Food reduces gastrointestinal adverse effects; therefore, it is recommended that pirfenidone is administered after a meal. The mechanism of action is not fully understood. However, it is believed that anti-fibrotic and anti-inflammatory actions mediated by TNF-α and TGT-β affect lung function decline.

Pirfenidone reaches its maximum concentration (T_{max}) 0.5 hr. after a single dose. A high fat meal decreases the maximum concentration (C_{max}) by ~49% and increases T_{max} to 3.5 hr. Area under the curve ($AUC_{0\text{-}inf}$) is decreased by ~16% due to a high fat meal. Pirfenidone is moderately bound to human albumin ~50%. A decrease in binding was noticed with increasing pirfenidone concentrations. The elimination half-life ($t_{1/2}$) is estimated at ~3 hr., after multiple dose administration. The main metabolite of pirfenidone, 5-carboxy pirfenidone, is formed by CYP1A2 and is inactive. Approximately 80% of a pirfenidone dose is eliminated in urine; with less than 1% as parent compound and majority as the 5-carboxy metabolite. With regard to the factors that influence pirfenidone pharmacokinetics, a forest plot depicting the influence of extrinsic and intrinsic factors on pirfenidone exposure based on dedicated clinical pharmacology studies is shown in **Figure 1**.

Most notable are the effects of smoking ($AUC_{0\text{-}\infty}$ 46%) and CYP1A2 inhibitors. $AUC_{0\text{-}\infty}$ and C_{max} was 46% and 68% of the $AUC_{0\text{-}\infty}$ and C_{max} in non-smokers. Fluvoxamine (a strong CYP1A2 inhibitor) and ciprofloxacin (a moderate CYP1A2 inhibitor) increased pirfenidone $AUC_{0\text{-}inf}$ by 400% and 81% and C_{max} by 70% and 23%, respectively. Population pharmacokinetic analysis of Study PITP-004 found that pirfenidone elimination decreases with increasing age, but does not warrant a dose adjustment. Furthermore, smokers were identified to have ~50% less exposure than non-smokers. Smoking is known to induce CYP1A2, which is the chief metabolizing enzyme of pirfenidone. No difference in pirfenidone exposure was observed between African-Americans and Caucasians, or between women and men.

The labeling recommendations and risk mitigation strategies are summarized in **Table 2.**

Figure 1 **Summary of external and internal factors investigated in dedicated clinical pharmacology studies**



Effect of fluvoxamine on pirfenidone AUC in non-smokers is 717% (90%CI: 597; 860). Referenced studies: PIPF-010 (Smoking), PIPF-010 (Fluvoxamine), PIPF-009 (Renal impairment), PIPF-11 (Hepatic impairment)

4 OVERVIEW OF NEW INFORMATION IN THE SUBMISSION

The Sponsor has submitted two new clinical trials for the resubmission; PIPF-017 and PIPF-16. PIPF-17 is a drug-drug interaction trial exploring the influence of the moderate CYP1A2 inhibitor ciprofloxacin on pirfenidone exposure. Trial PIPF-16 is a new phase III trial intended to support the safety and effectiveness of pirfenidone. Inclusion and exclusion criteria were conserved across the pivotal trials in the program. However, maximum baseline FVC was restricted to be less than 90% in PIPF-16 while it was unrestricted in the two previous trials submitted in the original NDA application. The two phase III trials in the original submission, PIPF-004 and PIPF-006, have been previously reviewed. Statistical analysis of the two trials concluded that trial PIPF-004 showed significant benefit over placebo, while trial PIPF-006 failed to show effectiveness.

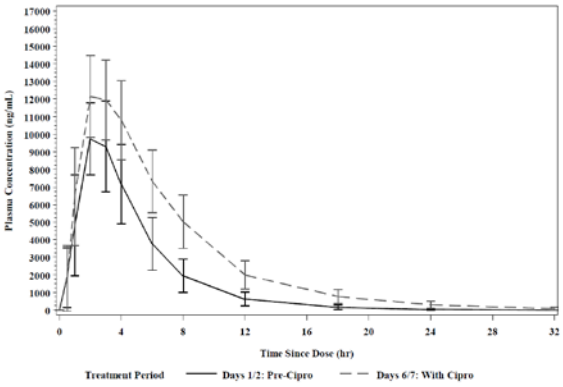
The new phase III trial (PIPF-16), was a randomized, double-blind, placebo-controlled, efficacy and safety study of pirfenidone in patients with IPF. Approximately 500 patients were equally randomized to receive pirfenidone 2403 mg/day or placebo for 52 weeks. The primary efficacy endpoint was change in percent predicted FVC from baseline to week 52. Some difference in the completion rates was observed in the two treatment arms, 80.2% in active and 85.9% in placebo completed the study. The most common reasons patients discontinued treatment early were: AEs (active: 12.6%, placebo: 8.7%), decision by the patient (active: 3.2%, placebo: 2.5%), death (active: 1.4% placebo: 1.8%), lung transplant (active: 2.2%, placebo: 0.4%). No pharmacokinetic data was collected in the trial. The sponsor reports a statistically significant effect from baseline in percent predicted FVC in patients treated with pirfenidone compared with placebo (p-value < 0.000001, rank ANCOVA).

5 REVIEW QUESTIONS

5.1 What is the effect of Ciprofloxacin on pirfenidone exposure?

Ciprofloxacin, a moderate CYP1A2 inhibitor, increases pirfenidone $AUC_{0\text{-inf}}$ and C_{max} by 81% (90%CI: [70, 93]) and 23% (90%CI:[14, 31]), respectively, (**Figure 2 and Figure 1**). This interaction is expected because the strong CYP1A2 inhibitor, fluvoxamine, increased pirfenidone exposure (AUC) by 400% (90%CI: [359,446]). A review of study PIPF-017 can be found in section 7.1.

Figure 2 Mean (+/-SD) Concentrations at Scheduled Time Points (Linear Scale and log scale) Pirfenidone



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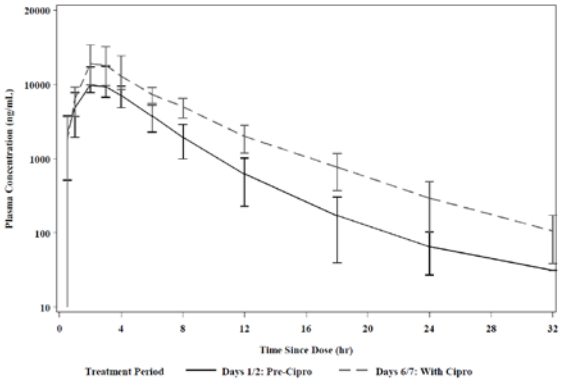

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5.2 Is the treatment response consistent across trials?

Treatment response, defined as the rate of decline in lung function for the active arm, is consistent across trials. However, decrease in lung function in the placebo arm varies across trials. When treatment effect is defined as placebo adjusted treatment effect; it is found to vary across trials.

Absolute change in predicted FVC from baseline for the placebo and the proposed dose in the three trials are shown in **Table 1. Figure 3** shows declining lung function (measured as %predicted FVC) over time. Each panel in a row shows data from each of the phase III trials. The thick lines represent the observed mean FVC value for that time point. The shaded areas represent the 90% CI interval based on linear regression. Each dose or placebo arm is represented by a color. The top row of panels shows absolute FVC change from baseline over time. The bottom row shows observed FVC over time. The placebo arm (red) and the 2403 mg dose arm (blue) have visually different rate of decline in trial PIPF-004 (first panel, top row Figure 3). In trial PIPF-006, the two arms seem to decline in a parallel fashion (second panel, top row, **Figure 3**). Trial PIPF-016 was submitted as part of this submission. Results from that trial are shown in the two right panels in **Figure 3**. The rate of decline seems to be consistent across trials for the 2403 mg dose depicted in blue; however, the placebo response differs significantly across trials

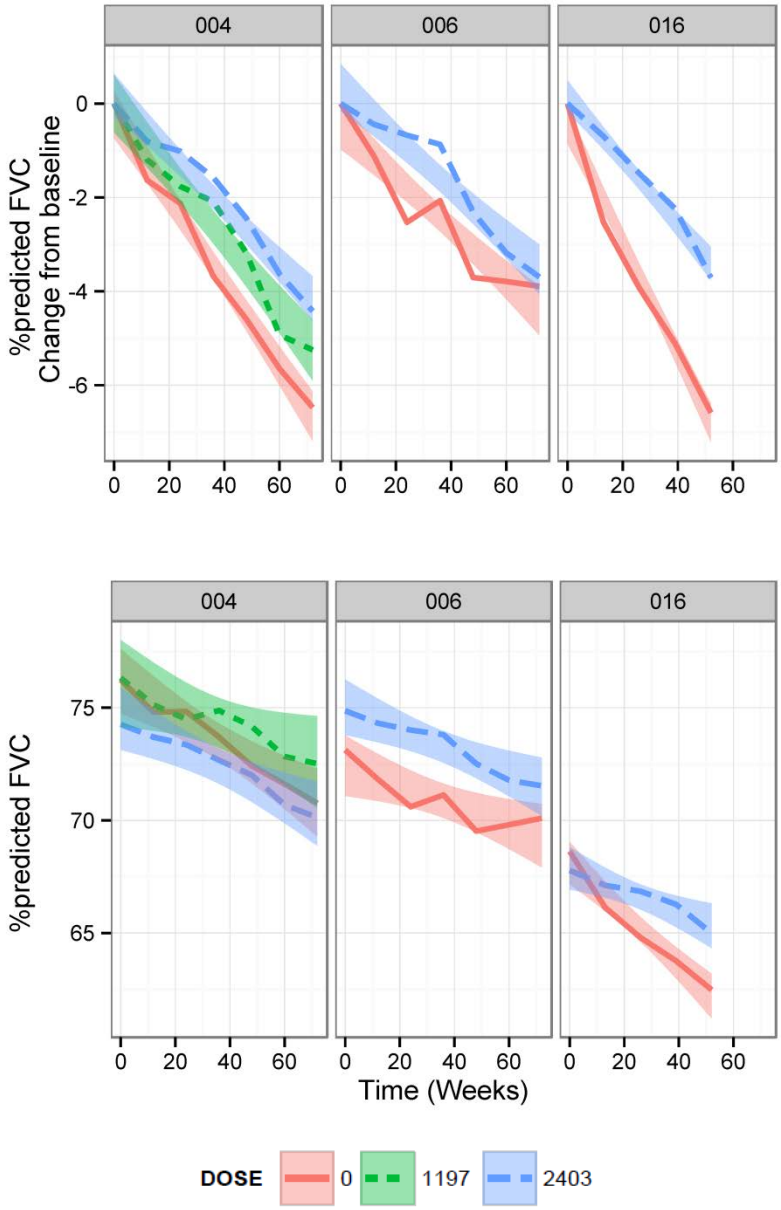
(red lines and areas). The three bottom panels show the unadjusted FVC value over time. The most striking feature of the three bottom plots are the different baseline FVC values which tend to decrease from trial to trial. The sponsor estimates mean (±SD) baseline FVC for the placebo arms to be: 76.2 (±15.51), 73.1 (±14.21), and 68.6 (±10.89) and for the 2403 mg arms to be: 74.5 (±14.47), 74.9 (±13.15), 67.8 (±11.24), in trials PIPF—004, PIPF-006, and PIPF-016, respectively. Understanding that FVC is used as a measure of disease severity, trial PIPF-016 seems to have been conducted in a population with higher disease severity. This may be the result of the slightly different inclusion criteria in trial PIPF-016 where baseline FVC was restricted to be equal or below 90%. Comparison of the same treatment arm across trials is shown in **Figure 4**. The 2403 mg dose seems to result in similar rate of decline across trials, while the placebo arm seems to result in visually different rate of decline in lung function across the three trials. The placebo arm of Trial PIPF-006 shows the slowest rate of decline, which is comparable to treatment effect of the 2403 mg arm in other trials. Adjusting the FVC change from baseline for placebo effects shows different treatment effect for the 2403 mg dose across trials, **Figure 5.** The constancy in treatment effect is further shown in **Table 1,** where trial PIPF-004 and PIPF-006 show similar (-8.0 vs. -9.0) mean change in %predicted FVC. Trial PIPF-016 was 20 weeks shorter compared to trials PIPF-004 and PIPF-006 (52 weeks vs. 72 week). Thus the treatment effect is estimated at a lower number. The most common point of time (close to the end of trial) is week 48 for trials PIPF-004/-006 and week 52 for trial PIPF-016. Comparison of the mean change in %predicted FVC for the most common point in time is also shown in **Table 1.** Although there is a 4 week difference in the point of comparison, the trend that cross trial placebo response differs more than the treatment response is seen. It should be noted that the table below is based on imputed values, e.g. missing FVC value due to death is imputed a 0.

Table 1. Mean Change in %Predicted FVC (imputed)

Trial	Pirfenidone (2403 mg)		Placebo	
	End of trial	Most common time point across trial	End of trial	Most common time point across trials
PIPF-004[c]	-8.0[a]	-4.4[a]	-12.4[a]	-9.2[a]
SD	(16.5)	(12.1)	(18.5)	(17.2)
Week	72	48	72	48
PIPF-006[c]	-9.0[a]	-5.0[a]	-9.6[a]	-6.9[a]
SD	(19.6)	(15.6)	(19.1)	(15.4)
Week	72	48	72	48
PIPF-016[d]	-6.17[b]	-6.17[b]	-10.95[b]	-10.95[b]
SE	(0.875)	(0.875)	(0.877)	(0.877)
Week	52	52	52	52

[a] from, Table 7, statistical review of Mr. Zhou, Feng, M.S
[b] from, Table 14.2.1-2, Clinical Study Report PIPF-016
[c] Mean change from baseline is calculated as study week minus baseline
[d] Mean change from baseline is calculated as study week minus baseline

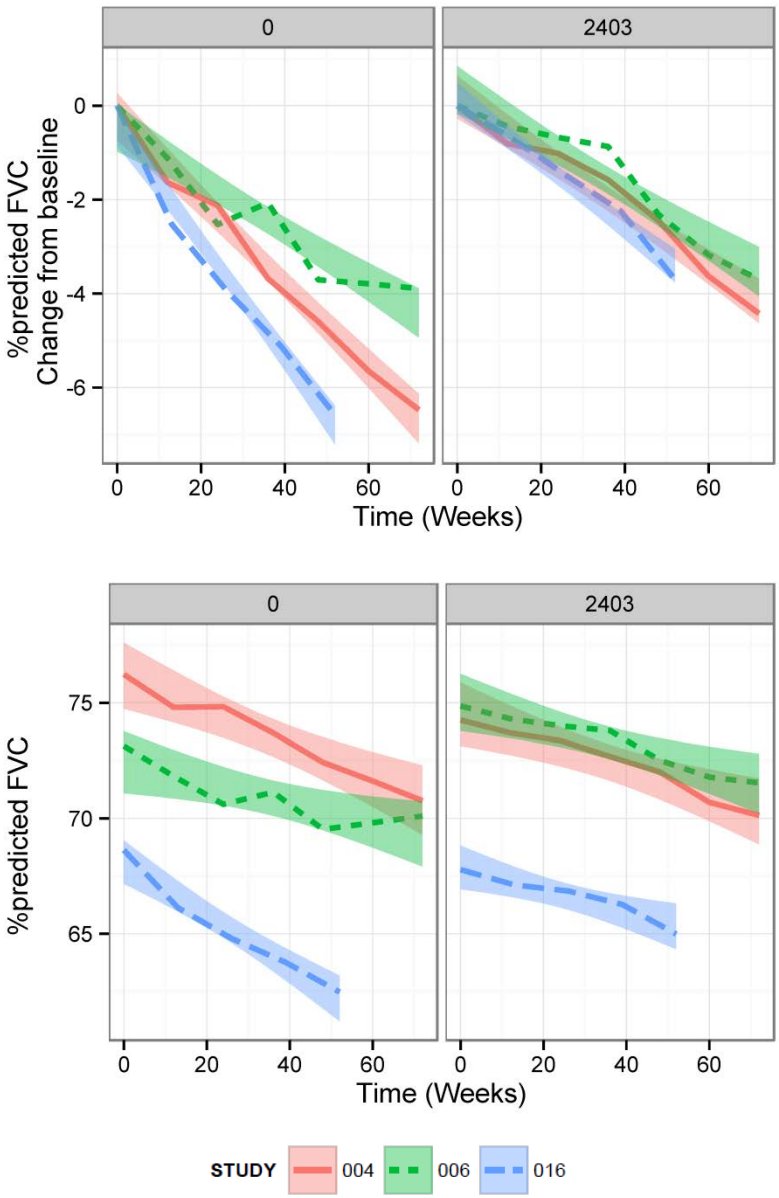
Figure 3 **Mean FVC and mean absolute change in FVC from baseline stratified by study and treatment arm**



Data source adeff datasets from trials PIPF-004, PIPF-006, PIPF-016. Original variables AVAL, CHG, and AVISIT. No imputation, ITT population.

Panels show result from trials; from left to right, PIPF-004, PIPF-006, PIPF-016. Top row shows absolute change from baseline verses time. Bottom row shows FVC versus time. Lines represent mean values at each observation. Shaded areas represent 90% confidence intervals based on fixed effect linear regression.

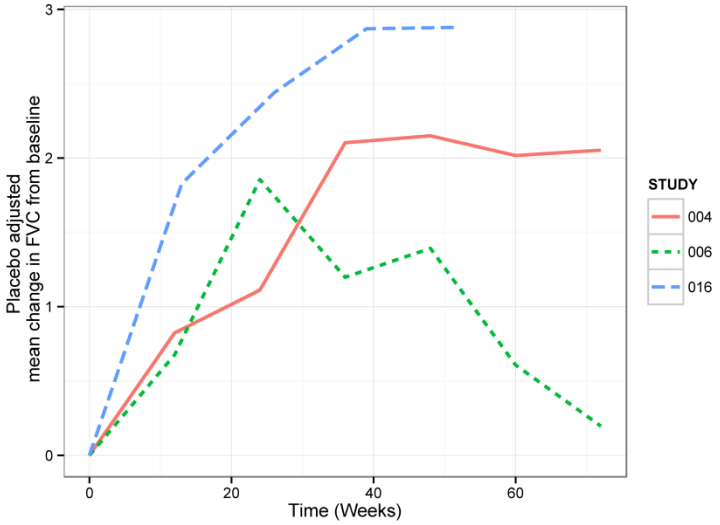
Figure 4 **Mean FVC and mean absolute change in FVC from baseline stratified by treatment arm and study**



Data source adeff datasets from trials PIPF-004, PIPF-006, PIPF-016. Original variables AVAL, CHG, and AVISIT. No imputation, ITT population.

Panels show result from trials; from left to right, PIPF-004, PIPF-006, PIPF-016. Top row shows absolute change from baseline verses time. Bottom row shows FVC versus time. Lines represent mean values at each observation. Shaded area represent 90% confidence intervals based on fixed effect linear regression.

Figure 5. Placebo adjusted mean change in FVC from baseline for the 2403 mg arm in studies PIPF-004, PIPF-006, and PIPF-016.



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Data source adeff datasets from trials PIPF-004, PIPF-006, PIPF-016. Original variables CHG, and AVISIT. No imputation, ITT population.

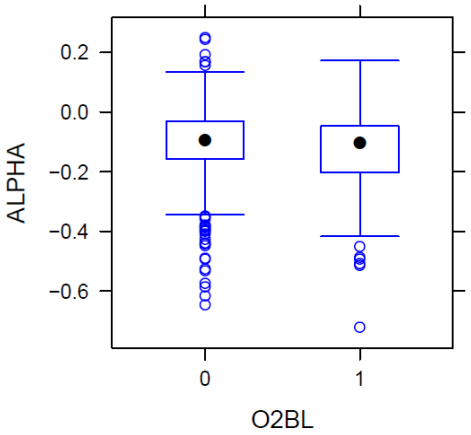
5.3 What are the sources of inter-individual variability in the placebo response?

Three covariates where found to significantly correlate with the rate of disease progression; baseline %predicted FVC, baseline bodyweight, and use of oxygen at baseline, **Figure 6**. Baseline oxygen use as well as %predicted FVC at baseline can be views as measures of disease severity; these covariates correlated with higher rate of disease progression. Patients on supplemental oxygen use had a 29% (95% CI: [2.4 – 60]) higher rate of disease progression. The bodyweight and disease progression relationship was quantified with a power model. Properties of such models are similar to an Emax model where a relationship between two variables is steep in the beginning until it plateaus when Emax is reached. Patients with higher bodyweight at baseline, up to ~85 kg, had a lower rate of disease progression. Patient 85 kg to ~140 kg showed similar rate of disease progression. Patients with higher baseline FVC had slower rate of disease progression. A 10 point increase in baseline FVC resulted in 8.67% slower rate in disease progression. These covariates failed to fully explain why the placebo group in trial PIPF-006 showed a slower rate of disease progression compared to the other trials. The limitations of this analysis are several; however, use of covariates only observed at baseline is perhaps the most severe limitation. Time varying covariates such as supplemental oxygen or other medications used through the study may improve the model. Furthermore, study drop-out due to lung transplantation, death or other reasons may have a significant impact as well.

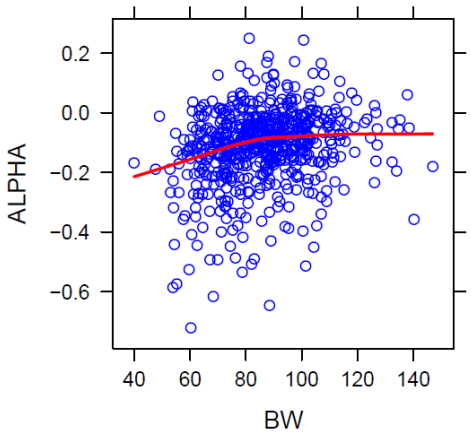
Future trials should aim to keep the following patient characteristic balanced across treatment arms; bodyweight, supplemental oxygen use at baseline, and FVC at baseline.

For further details regarding this review question, see the pharmacometric review in Section 8.

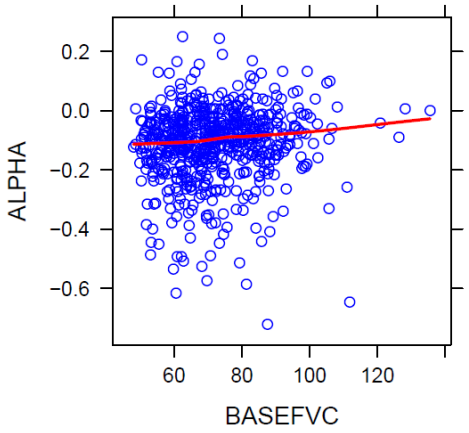
Figure 6 Covariates found to significantly influence rate of disease progression (Alpha). Lower alpha equals higher rate of disease progression.



Supplemental oxygen use at baseline (O2BL=1).
p-value=0.025, based on the log likelihood ratio test.



Bodyweight at baseline=BW (kg)
p-value <0.000003, based on the log likelihood ratio test.



% predicted FVC at baseline = BASEFVC (%)
p-value=0.003, based on the log likelihood ratio test.

6 LABELING RECOMMENDATIONS

Risk mitigation strategies for external and internal factors are summarized in **Table 2.**

Table 2. Labeling recommendations for risk mitigations strategies for internal and external factors.

Internal /external factor	Sponsors recommendations	FDA recommendations
Renal impairment	(b) (4)	Use with caution in patients with mild, moderate or severe renal impairment
Smoking	Smoking may result in decreased pirfenidone exposure (b) (4) (b) (4) patients to stop smoking before treatment with ESBRIET. (b) (4) to avoid smoking when using ESBRIET.	Smoking may result in decreased pirfenidone exposure (b) (4) and may alter the efficacy of ESBRIET.
Hepatic impairment	Use caution in patients with mild to moderate hepatic impairment. Monitor for adverse reactions and consider dose modification or discontinuation of ESBRIET as needed. ESBRIET has not been studied in patients with severe hepatic impairment. ESBRIET is not recommended for use in patients with severe hepatic impairment.	Agree with sponsor
Geriatric Use	(b) (4)	Results of population pharmacokinetic analysis suggest that no dosage adjustment is needed in geriatric patients.
Race	Population pharmacokinetic analysis showed that race has no significant effect on the pharmacokinetics of pirfenidone.	Agree with sponsor
Obesity	Results of population pharmacokinetic analysis showed that obesity (Body Mass Index [BMI] greater than or equal to 30 kg/m^2) has no significant effect on the pharmacokinetics of ESBRIET.	Agree with sponsor

Table 2. Labeling recommendations for risk mitigations strategies for internal and external factors (continued)

Internal /external factor	Sponsors recommendations	FDA recommendations
Gender	Results of population pharmacokinetic analysis of ESBRIET showed no significant differences in pharmacokinetics between males and females.	Agree with sponsor
CYP1A2 inhibitors strong moderate	Moderate (e.g., ciprofloxacin) and strong inhibitors of CYP1A2 (e.g. fluvoxamine) increase systemic exposure of ESBRIET. Discontinue fluvoxamine prior to administration of ESBRIET. Consider dose reduction with use of ciprofloxacin OR. Dose reduction: fluvoxamine; 1 capsule three time a day Ciprofloxacin; 2 capsules three times a day.	Moderate (e.g., ciprofloxacin) and strong inhibitors of CYP1A2 (e.g. fluvoxamine) increase systemic exposure of ESBRIET and may alter the adverse reaction profile of ESBRIET. Discontinue fluvoxamine prior to administration of ESBRIET. Consider dose reduction with use of ciprofloxacin. The reviewer agrees with proposed dosing strategy.

7 INDIVIDUAL STUDY REVIEW

7.1 Clinical study PIPF-017

Study title
An Open-Label Phase 1 Study to Determine the Impact of a Moderate CYP1A2 Inhibitor (Ciprofloxacin) on the Pharmacokinetics and Safety of Pirfenidone in Healthy Subjects

Objectives

1. To determine the impact of a moderate CYP1A2 inhibitor (ciprofloxacin) on the pharmacokinetics of pirfenidone in healthy subjects.
2. To determine the safety of pirfenidone in healthy subjects when concurrently introducing CYP1A2 inhibition.

Study design
Healthy, non-smoking, male (n=17) and female (n=10) volunteers were recruited in a Phase 1, open label, cross-over study. The healthy volunteers were administered a single dose of pirfenidone (801 mg) as three capsules of 267 mg, orally on days 1 and 6. Ciprofloxacin 750 mg was administered on day 2 in the evening and two times daily (750 mg BID) days 3 through 6. The study design is outlined in **Table 3.**

Results
All 27 subjects received all doses of pirfenidone and all doses of ciprofloxacin. The plasma concentration time profiles for pirfenidone and 5-carboxy pirfenidone are shown in **Figure 7** and **Figure 8.** Absolute exposure of pirfenidone, measured as area under the curve from time 0 to infinity ($AUC_{0-\infty}$) increased by 81% (90%CI: [70-93]), while maximum concentration (C_{max}) increased by 23% (90%CI: [14-31]). The 5-carboxy pirfenidone metabolite exposure decreased due to inhibition of its formation pathway (CYP1A2), **Table 4**. Elimination half-life for the metabolite and the parent appears to be similar, suggesting formation rate limited pharmacokinetics of the metabolite, **Table 5**. The sponsor does not shown results of the urine PK. This has no impact on the conclusions regarding this drug-drug interaction.

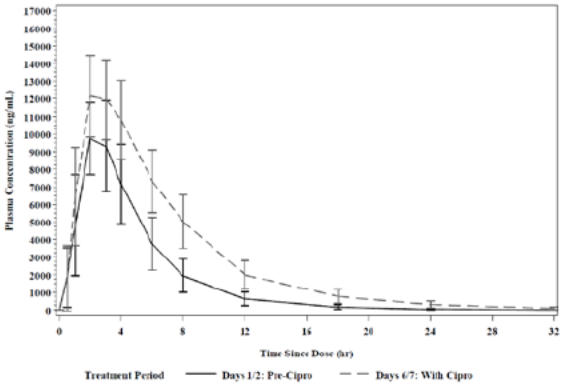
Table 3. Schedule of pharmacokinetic events

Days	1	2	3	4	5	6	7
Victim drug	Pirfenidone 801 mg ~8:00 AM with food					Pirfenidone 801 mg ~8:00 AM with food	
Perpetrating drug		Ciprofloxacin 750 mg in the evening	750 mg twice a day (BID)	750 mg twice a day (BID)	750 mg twice a day (BID)	750 mg twice a day (BID)	
Pharmacokinetic sampling (blood) relative to pirfenidone dosing	Predose 0.5 1 2 3 4 6 8 12 h postdose	18 24 32 h postdose				Predose 0.5 1 2 3 4 6 8 12 h postdose	18 24 32 h postdose
Pharmacokinetic sampling (Urine) relative to pirfenidone dosing	0–12 h postdose	12–24 24–32 h postdose				0–12 h postdose	12–24 24–32 h postdose

Table 4 Effect of Ciprofloxacin Co-administration on Pirfenidone (N = 27)

Analyte/Parameter	Geometric Mean Ratio (90% Confidence Interval)
Pirfenidone	
AUC0-∞	1.81 (1.70, 1.93)
Cmax	1.23 (1.14, 1.31)
5-Carboxy-Pirfenidone	
AUC0-∞	0.96 (0.92, 1.00)
Cmax	0.62 (0.57,0.66)

Figure 7 Mean (+/-SD) Concentrations at Scheduled Time Points (Linear Scale and log scale) Pirfenidone



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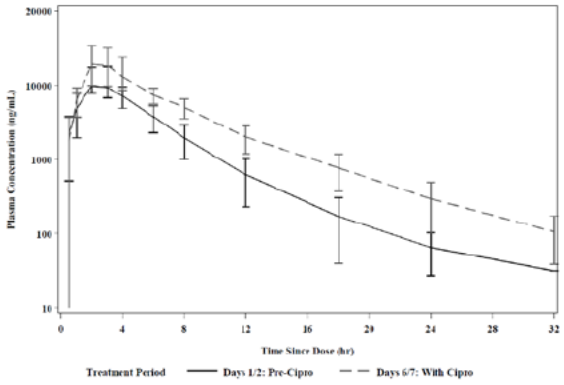

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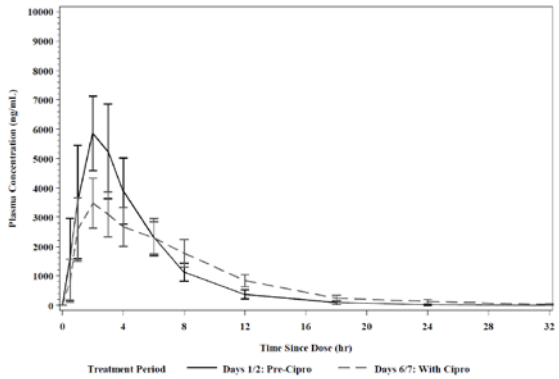
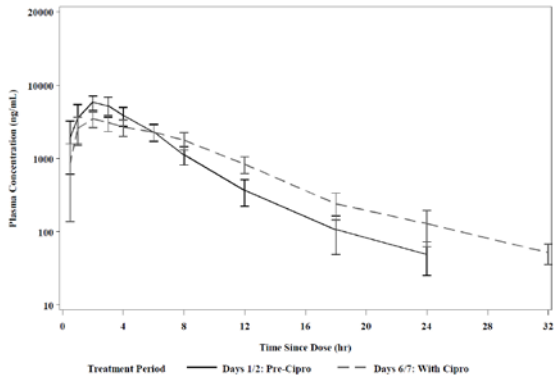
Figure 8. Mean (+/-SD) Concentrations at Scheduled Time Points (Linear Scale and log scale) 5-Carboxy-Pirfenidone



Source: *sponsors pharmacokinetic report, p94 of 254*



Source sponsors pharmacokinetic report, p95 of 254

Sponsors conclusions

A statistically significant increase in both AUC0-∞ and Cmax of pirfenidone was observed with administration of ciprofloxacin 750 mg BID (a high dose of a moderate and relatively selective CYP1A2 inhibitor) for 5 days. However, the magnitude of the effect was relatively modest: an 81% increase (i.e., <2-fold) for AUC0-∞ and a 23% increase in pirfenidone Cmax were observed with coadministration of ciprofloxacin.

No significant effect on 5-carboxy-pirfenidone AUC0-∞ was observed; however, the plasma concentration-time profile was altered such that lower peak and higher 24–32-hour concentrations of 5-carboxy-pirfenidone were observed with ciprofloxacin coadministration.

Source: Clinical Study Report PIPF-017 p59.

Reviewer's conclusions

The trial was adequately designed to investigate the influence of the moderate CYP1A2 inhibitor ciprofloxacin on the pharmacokinetics of pirfenidone. A limitation of the study design is that patients were administered a single dose pirfenidone (801 mg) as opposed 801 three times daily as proposed in the label. Assuming linear kinetics, this has little or no consequence on the conclusions in this trial.

Pirfenidone exposure increased by approximately 80% when concomitant ciprofloxacin.

Table 5 Summary Statistics for Plasma Pharmacokinetic Parameters

Study Day	Statistic	Cmax (µg/mL)	Tmax (h)	T1/2 (h)	AUC0-∞ (µg*hr/mL)
Pirfenidone					
1/2 (Pre- Ciprofloxacin)	Mean (SD)	10.4 (2.14)	2.2 (0.64)	2.5 (0.6)	51.9 (14)
	%CV	20.5	28.8	23.8	27
	Median	10.4	2	2.4	53.2
	Min, Max	6.6, 14.4	1, 3	1.4, 3.6	30, 88.2
	Geometric Mean	10.7	2.2	2.4	50.8
	Geometric %CV	23.9	35.2	32.2	30.5
6/7 (During Ciprofloxacin)	Mean (SD)	12.7 (2.17)	2.6 (0.85)	4 (0.7)	93.2 (20)
	%CV	17.1	33.3	17.5	21.5
	Median	12.8	2	4	95.2
	Min, Max	7.3, 16.3	1, 4.1	2.8, 5.6	47.1, 126.6
	Geometric Mean	13	2.3	4.1	90.3
	Geometric %CV	18.5	39.8	19.1	24.5
5-Carboxy-Pirfenidone					
1/2 (Pre- Ciprofloxacin)	Mean (SD)	6.1 (1.44)	2.3 (0.6)	2.7 (0.73)	30.9 (4.74)
	%CV	23.4	26.3	27.1	15.3
	Median	5.7	2	2.6	30.3
	Min, Max	4.4, 9.4	1, 3	1.4, 4.6	22.4, 42.9
	Geometric Mean	6.5	2.2	2.6	32.6
	Geometric %CV	27.4	35.2	39.2	16.8
6/7 (During Ciprofloxacin)	Mean (SD)	3.8 (0.8)	2 (0.76)	4.2 (0.93)	29.6 (4.52)
	%CV	21.1	38.6	22.3	15.3
	Median	3.8	2	4	29.1
	Min, Max	2.6, 5.4	1, 4	2.6, 6.1	19.7, 39.4
	Geometric Mean	3.8	2.1	4	30.1
	Geometric %CV	23.6	48.6	23.5	16.9

8 APENDIX 1

8.1 Pharmacometric review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

Application Number	22535
Submission Date	May 23, 2014
Drug Name	Pirfenidone
Proposed Indication	Idiopathic Pulmonary Fibrosis
Clinical Division	Division of Pulmonary, Allergy, and Rheumatology Products
Primary CP Reviewer	Dinko Rekić, MSc(Pharm), Ph.D
Primary PM Reviewer	Dinko Rekić, MSc(Pharm), Ph.D
Secondary CP Reviewer	Satjit Brar, Pharm. D., Ph.D.
Secondary PM Reviewer	Liang Zhao, Ph.D.
Sponsor	InterMune

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

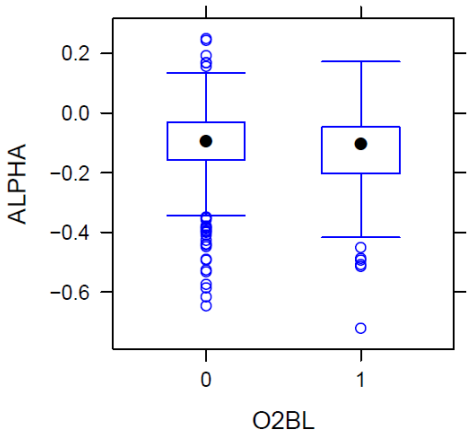
1.1.1 What are the determinants of variability in the placebo response in the perfinedone phase III trials (PIPF-004, PIPF-006, and PIPF-016)?

Patients with higher bodyweight at baseline, up to ~85 kg, had lower rate of disease progression than patients with lower bodyweight at baseline. Patients with higher FVC at baseline had lower rate of disease progression. Furthermore, patients with supplemental oxygen use at baseline had a 29% (95% CI: [2.4 – 60]) higher rate of disease progression, **Figure 1**. However, these covariates failed to fully explain why the placebo group in trial PIPF-004 showed a slower rate of disease progression compared to the placebo groups in other trials.

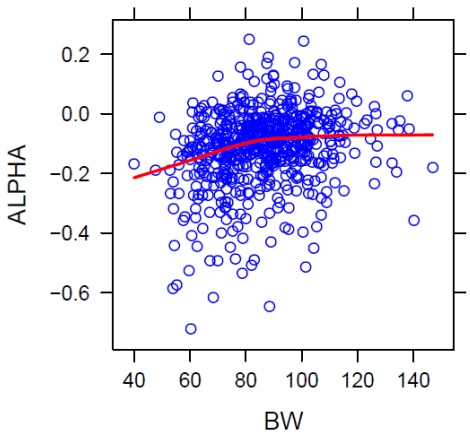
1.2 Recommendations

Randomized studies in the future should consider stratification on bodyweight, supplemental oxygen use at baseline, and FVC at baseline.

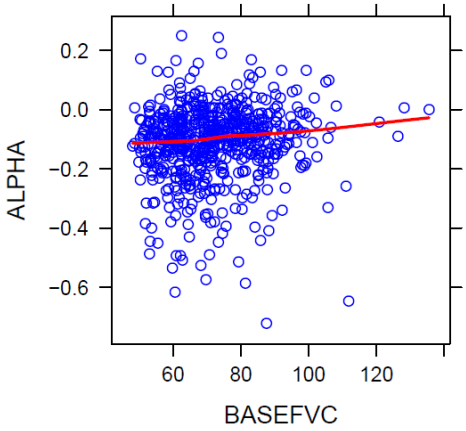
Figure 1. Covariates found to significantly influence rate of disease progression (Alpha). Lower alpha equals higher rate of disease progression.



Supplemental oxygen use at baseline (O2BL=1).
p-value=0.025, based on the log likelihood ratio test.



Bodyweight at baseline=BW (kg)
p-value <0.000003, based on the log likelihood ratio test.



% predicted FVC at baseline = BASEFVC (%)
p-value=0.003, based on the log likelihood ratio test.

2 PERTINENT REGULATORY BACKGROUND

Pirfenidone was designated as an orphan drug on March 5, 2004. The applicant (InterMune) submitted an NDA application (22535) for pirfenidone in 2009. Reference is made to the complete response (CR) letter from Dr. Rosebraugh dated, May 04, 2010, in which the Agency stated that the applicant failed to show significant treatment effect in two replicate trials.

3 RESULTS OF SPONSOR'S ANALYSIS

The sponsor has not conducted a formal analysis to investigate potential covariates that accounted for variability in the placebo response. However, the sponsor tried to explain the reasons for the difference in rate of disease progression between trial PIPF-004 and PIPF-006 by claiming that a smaller proportion of patients taking pirfenidone used

salbutamol in Study 004 compared to placebo patients (28% vs. 41%, respectively) in Study 006. Sponsor 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%).

4 REVIEWER'S ANALYSIS

4.1 Introduction

An independent review of the placebo response was initiated to determine why placebo disease progression differed across trials. The results of this analysis can potentially help design future trials for Idiopathic Pulmonary Fibrosis.

4.2 Objectives

The objectives of the analysis are to quantify and explain the variability in the placebo response.

4.3 Methods

4.3.1 Data Sets

List of datasets and model cod is shown in **Table 1.** Sponsor's datasets used for this analysis is shown in **Table 2**. The variables in the analysis dataset generated by the reviewer are summaries and defined in **Table 4** and **Table 5.**

4.3.2 Software

R, and NONMEM, PsN, Xpose, and Pirana were used for the reviewer's analyses.

4.3.3 Models

Three linear disease progression models were developed for the purpose of characterizing the placebo response across trials. The models were: Base disease progression model (M1), Disease progression model with demographical covariates (M2), Disease progression model with demographical covariates that included study number as a covariate on disease progression (M3). The demongraphical covariates assessed included body weight, baseline FVC, salbutamol use, supplemental oxygen use at baseline, smoking status, IPF diagnosis years, age, gender, and race. The dependent variable (DV) is the baseline adjusted %predicted Forced Vital Capacity (%predicted FVC). The independent variable (IV) is time that is measured in weeks.

The fixed effect parameters (θs) of the base model (M1) are baseline adjusted FVC (L) at time zero (S0) and rate of disease progression (Alpha, [week^{-1}]). The random effect parameters are between subject variability (BSV) of fixed effect parameters, as defined in **Equation 1,** and a proportional residual error component ($\varepsilon \sim N[0, \sigma^2]$). No off diagonal elements of the ω matrix were estimated.

$$\theta_i = \theta + \eta_i, \eta_i \sim N(0, \omega^2) \qquad \textbf{Equation 1}$$

The structural component of the mixed effect model is defined in **Equation 2.**

$$\%predicted\ FVC = S0 + Alpha \times Time \qquad \textbf{Equation 2}$$

Covariates were parameterized as implemented in PSN stepwise covariate modeling (SCM) tool, **Table 6.** The covariate model (M2) included the following covariate-parameter relationships on the slope parameter Alpha.

Covariate	**Relationship**
Baseline FVC	$FVCEffect_i = (1+\theta_{pFVC}[BASEFVC_i – 70.95])$
Baseline Bodyweight	$BWEffect_i = ([BW_i/86.00]^{\theta pBW})$

θ_{pcov} is the population typical parameter value
BASEFVCi is the %predicted FVC at baseline in individual i.
BWi is the observed bodyweight (Kg) *in individual i at baseline.*

The model with study effect included the covariates defined above and those shown below.

Covariate	**Relationship**
Baseline Oxygen use	if O2 use at baseline: $O2Effect_i = (1 + \theta_{pO2})$
Study PIPF-006 vs PIPF-004	if study 006: $S006Effect_i = (1 + \theta_{pS006})$
Study PIPF-016 vs PIPF-004	if study 016: $S016CovEffect_i = (1 + \theta_{pS016})$

Definitions as above

The contributions of all covariates on the structural model were added as multiplicative covariate model according to **Equation 3**, where $TVALPHA_i$ is the population typical parameter for diseases progression (Alpha) for a subject i with all Ncov set equal to median.

$$\text{TVALPHA}_{\,i} = \theta_{Alpha} \times \prod_{Cov=1}^{Ncov} \left(CovEffect_{Pcov,i}\right) \qquad \textbf{Equation 3}$$

4.3.4 Results

4.3.4.1 Assessment of the model

Parameter estimates and their associated precision are shown in **Table 3.** The full covariate model reduced the objective function value by 45.5 points. Shrinkage was low (<10%) for BSV in rate of disease progression. All covariates were significant in the forward inclusion step ($p<0.05$). The backward deletion step had a more stringent cutoff p value (<0.01). The covariate, baseline FVC, was slightly less than significant when the stringer p cutoff was applied and would have been removed from the final model. However, due to the significant difference in baseline FVC across trials it was determined that the covariate should be included in the final model. Parameter precision (RSE%) was

high (6%) for the main parameter of interest; alpha. Covariate effect on disease progression was estimated with precision (RSE%) of 43 to 93%, except for bodyweight which was estimated with high precision (<20%). The visual predictive check (VPC) and basic goodness-of-fit plots for the full covariate model (M2) are shown in **Figure 2, Figure 3, and 4**. Noteworthy, the VPCs were stratified for study although the model did not include a study effect. Some tendencies towards over prediction of disease progression are seen for the median (solid red line and red area). Variability seems to be over predicted towards the end of the studies (dotted red line and blue areas). The basic goodness-of-fit plots indicate no misspecification in the structural model or in the residual model **Figure 4.** Tendencies to over predict rate of disease progression towards the end of the studies are seen. Representative plots of individual predictions and observations are shown in **Figure 5.**

4.3.4.2 Covariates influencing the rate of disease progression.

Three covariates were found to significantly correlate with the rate of disease progression: Baseline FVC, baseline bodyweight, and use of oxygen at baseline. Plots of covariates versus rate of disease progression are shown in **Figure 1.** Baseline oxygen use as well as % predicted FVC at baseline can be viewed as measures of disease severity; these covariates correlated with higher rate of disease progression. Patients on supplemental oxygen use had a 29% (95% CI: [2.4 – 60]) higher rate of disease progression. Patients with higher baseline FVC had slower rate of disease progression. A 10 point increase in baseline FVC, resulted in 8.67% slower rate in disease progression.

Bodyweight at baseline was correlated with decreased rate of disease progression up to ~85 kg, whereas patient of 85 kg to ~140 kg showed similar rate of disease progression.

These covariates failed to fully explain why the placebo group in trial PIPF-006 showed a slower rate of disease progression compared to the other trials. The limitations of this analysis are several; however, use of time-invariant covariates observed at baseline is perhaps the most severe one. Time varying covariates such as 0_2 or other medications used through the study may improve the model. Although body weight was identified as a significant covariate for disease progression, it may reflect the effect(s) of other body size measures such as height and disease severity at baseline. Furthermore, study drop out due to lung transplantation, death or other reasons may be of significant impact.

Model 3 included study as a covariate effect on disease progression (-ΔOFV:14.4 vs [M2]). The disease progression rate in the placebo group of study PIPF-006 was estimated to be 15.7% (95% CI: [43.9 – 12.5]) lower compared to the disease progression in the placebo group of study PIPF-004. Similarly, the rate of disease progression was estimated to be 32% (95% CI: [-1 – 64.1]) higher in study PIPF-006 than in study PIPF-004.

5 LISTING OF MODEL CODES

Table 1. Table of NONMEM models, data set, and R code

File Name	Description	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\
run23.mod	Base model (M1)	X:\Reviews\Ongoing PM Reviews\Pirfenidone_NDA22535_DR\data_and_code
run26.mod	Full covariate model (M2)	X:\Reviews\Ongoing PM Reviews\Pirfenidone_NDA22535_DR\data_and_code
run27.mod	Full covariate model including study effect M(3)	X:\Reviews\Ongoing PM Reviews\Pirfenidone_NDA22535_DR\data_and_code
data4.csv	Derived analysis data file	X:\Reviews\Ongoing PM Reviews\Pirfenidone_NDA22535_DR\data_and_code
Data_gen.R	R code for deriving data4.csv	X:\Reviews\Ongoing PM Reviews\Pirfenidone_NDA22535_DR\data_and_code
scmlog.txt	Stepwise covariate model log	X:\Reviews\Ongoing PM Reviews\Pirfenidone_NDA22535_DR\data_and_code

Table 2. Sponsor's datasets

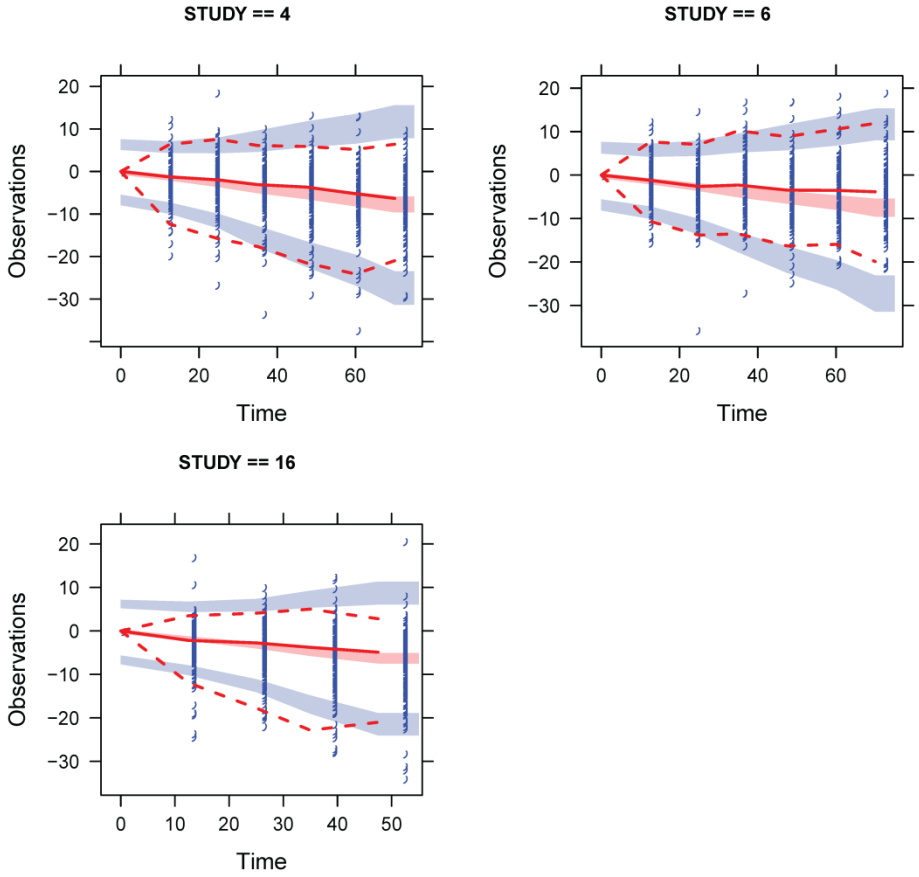
Study Number	Name	Link to EDR
PIPF-004	adeff	\\cdsesub1\evsprod\nda022535\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\pipf-004\analysis\adeff.xpt
PIPF-004	adcm	\\cdsesub1\evsprod\nda022535\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\pipf-004\analysis\addv.xpt
PIPF-004	adsl	\\cdsesub1\evsprod\nda022535\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\pipf-004\analysis\adsl.xpt
PIPF-006	adeff	\\cdsesub1\evsprod\nda022535\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\pipf-006\analysis\adeff.xpt
PIPF-006	adcm	\\cdsesub1\evsprod\nda022535\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\pipf-006\analysis\adcm.xpt
PIPF-006	adsl	\\cdsesub1\evsprod\nda022535\0000\m5\53-clin-stud-rep\537-crf-ipl\datasets\pipf-006\analysis\adsl.xpt
PIPF-016	adeff	\\cdsesub1\evsprod\nda022535\0045\m5\datasets\pipf-016\analysis\adam\datasets\adeff.xpt
PIPF-016	adcm	\\cdsesub1\evsprod\nda022535\0045\m5\datasets\pipf-016\analysis\adam\datasets\adcm.xpt
PIPF-016	adsl	\\cdsesub1\evsprod\nda022535\0045\m5\datasets\pipf-016\analysis\adam\datasets\adsl.xpt
PIPF-004, PIPF-006, and PIPF-016	adtte2	\\cdsesub1\evsprod\nda022535\0045\m5\datasets\pipf-016\analysis\adam\datasets\adtte2.xpt

Table 3. Parameter estimates with their associated precision

	Baseline model (M1) (OFV=13314.4) run23	Covariate model (M2) (OFV=13268.9) run26	Covariate and Study model (M3) (OFV=13254.5) run27
ΔOFV	0	-45.507	-59.949
Parameter (RSE %)			
S0 Intercept (%predicted FVC)	-0.196 (47.20%)	-0.187 (49.40%)	-0.171 (54.30%)
Alpha Rate of disease progression (%predicted FVC/Week)	-0.112 (5.40%)	-0.0995 (6.50%)	-0.0925 (11.20%)
Between subject variability (CV%), (RSE%), [Shrinkage%]			
S0 Intercept[1]	56.8% (15.2%) [54%]	59.8% (14.9 %) [54%]	65.6% (14.9%) [53%]
Alpha Rate of disease progression[1]	121.4% (6.1%) [7%]	131.4 % (6%) [8%]	139.3% (6.1%) [8%]
Covariates on rate of disease progression (RSE%)			
Baseline FVC[2]		-0.00867 (42.70%)	-0.00637 (62.60%)
Baseline Bodyweight[3]		-1.64 (17.80%)	-1.54 (19.70%)
Baseline Oxygen use[4]		+29% (55.20%)	+21.8 % (69.70%)
Study PIPF-006 vs PIPF-004[5]			-15.7% (91.7 %)
Study PIPF-016 vs PIPF-004[5]			+32% (52.1 %)
Residual error			
Proportional error (%)	3.12 (3.4)	3.12 (3.3)	3.12 (3.3)

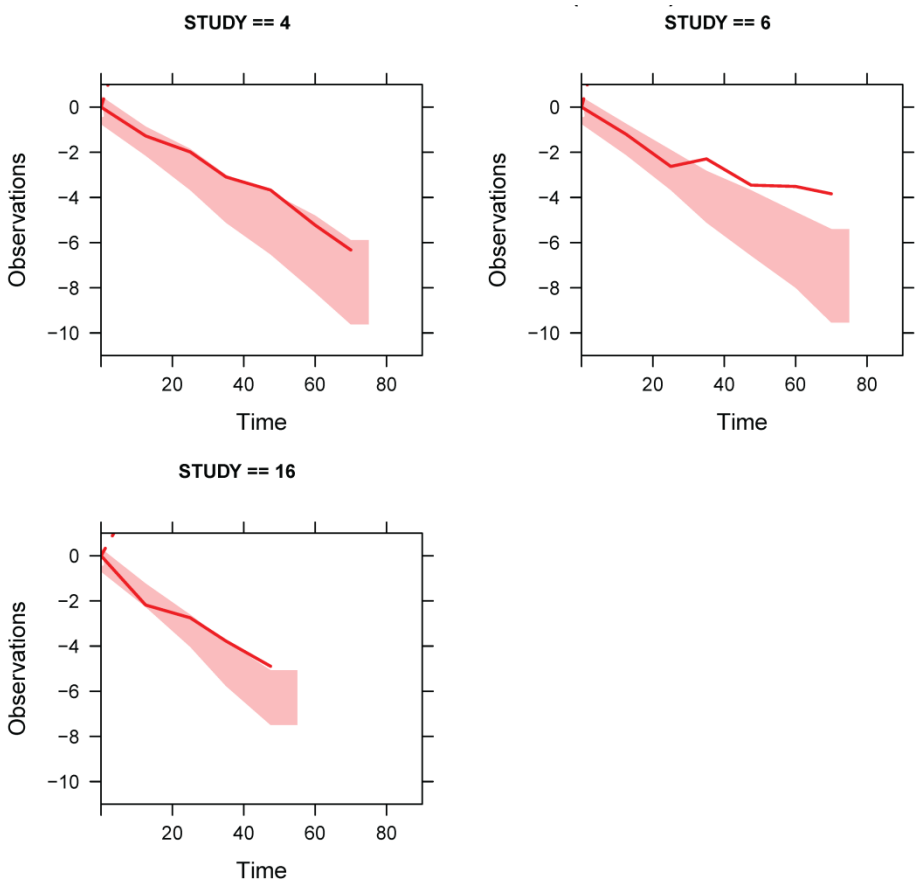
[1]*Between subject variably calculation (additive):* $\boldsymbol{CV\%} = \sqrt{\boldsymbol{\omega^2}}/\boldsymbol{\theta} \times \mathbf{100\%}$
[2]*Linear decrease in rate of disease progression with increase in baseline FVC.*
[3]*Power decrease in rate of disease progression with increase in baseline bodyweight.*
[4]*Percent increase in rate of disease progression with use of supplementary oxygen at baseline.*
[5]*Percent change in rate of disease progression in study PIPF-0XX vs study PIPF-004.*

Figure 2. **Visual predictive check for the full covariate model (M2).**



Circles are observed plasma concentrations, red lines are 5th, 50th, and 95th percentile of the observed data, the shaded areas represent a simulation-based 95% prediction interval of the percentiles. PSN command: c:\perl\bin/vpc -samples=500 -bin_array=0,5,20,30,40,55,65,75 -bin_by_count=0 -dir=vpc_run26 run26.mod -stratify_on=STUDY

Figure 3. **Visual predictive check for the full covariate model (M2). Only the predicted and observed median FVC are shown.**



The shaded areas represent a simulation-based 95% prediction interval of the median; the red line is the observed median. PSN command: c:\perl\bin/vpc -samples=500 -bin_array=0,5,20,30,40,55,65,75 -bin_by_count=0 -dir=vpc_run26 run26.mod -stratify_on=STUDY

Figure 4. Basic goodness-of-fit plots for the full covariate model (M2).

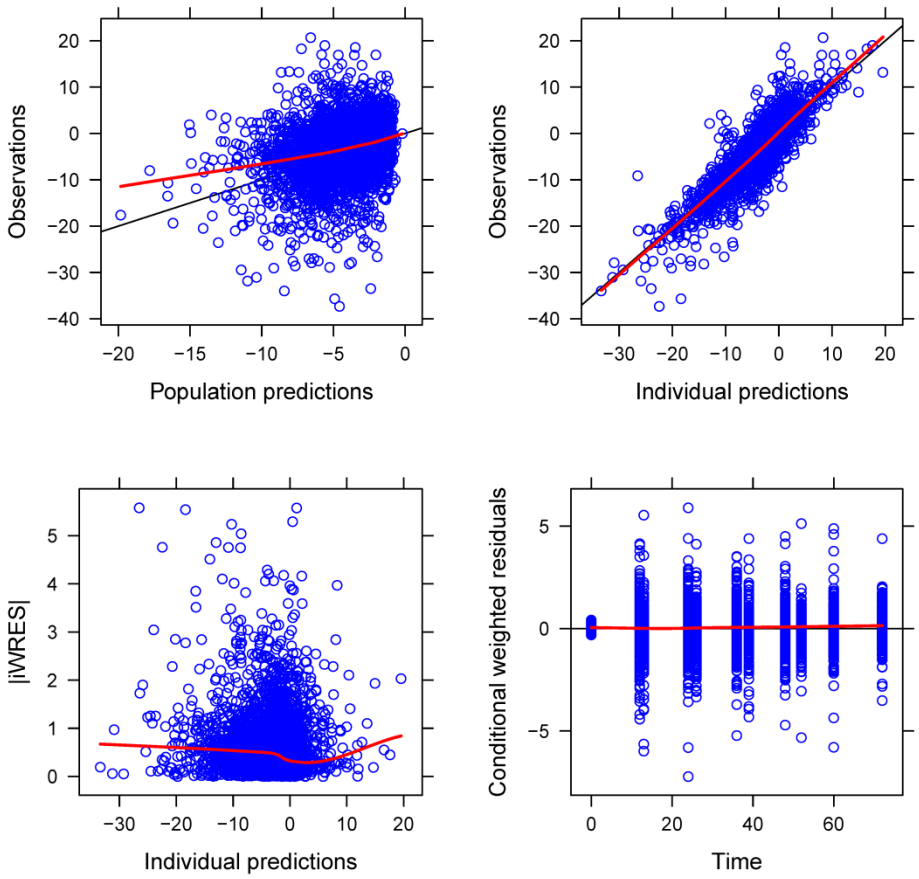


Figure 5. Representative plots of individual predictions and observations for the full covariate model (M2).

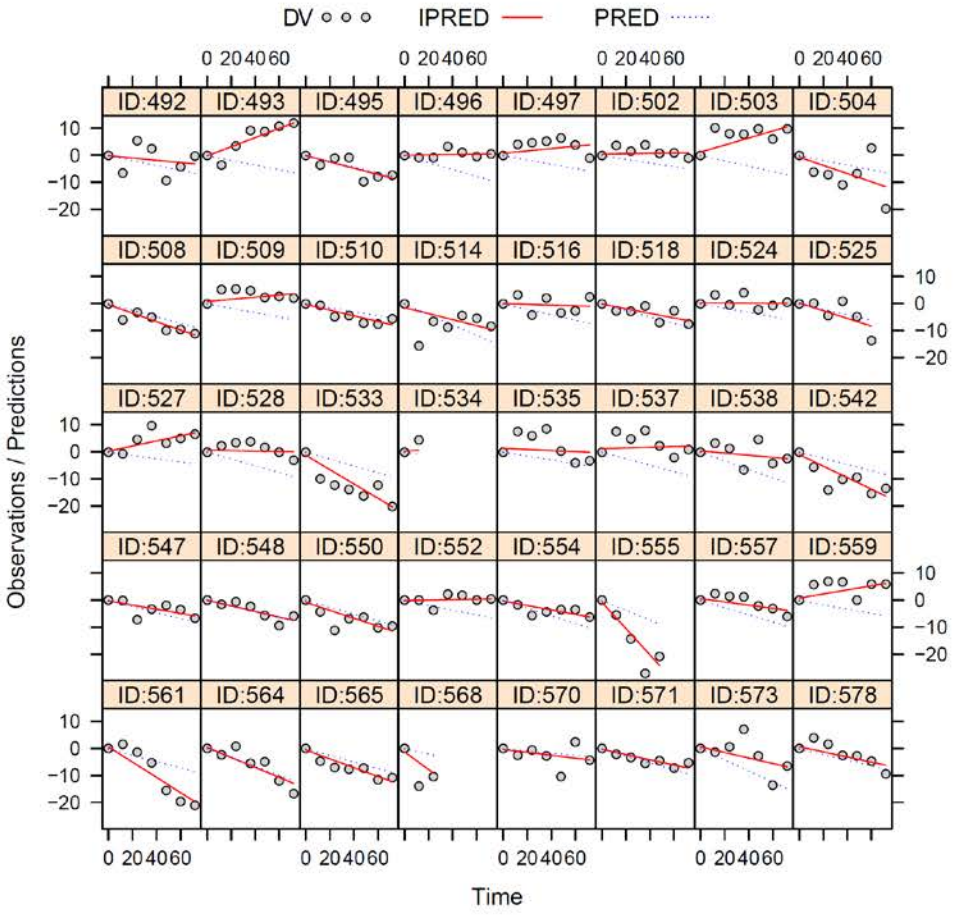


Table 4. Table of data definitions and patient demographics (Categorical variables)

Study		PIPF-004 n=174			PIPF-006 n=173			PIPF-016 n=277			Total n=624		
	Label	Category	N	%	Category	N	%	Category	N	%	Category	N	%
USA	ROW	0	60	34.5	0	23	13.3	0	93	33.6	0	176	28.2
	USA	1	114	65.5	1	150	86.7	1	184	66.4	1	448	71.8
O2BL	Baseline Oxygen Use: No	0	149	85.6	0	124	71.7	0	201	72.6	0	474	76
	Baseline Oxygen Use: Yes	1	25	14.4	1	49	28.3	1	76	27.4	1	150	24
SMOKE	Never Smoked (< 100 Cigarettes In Life)	1	51	29.3	1	64	37	1	108	39	1	223	35.7
	Has Smoked (>=100 Cigarettes In Life)	2	114	65.5	2	101	58.4	2	169	61	2	384	61.5
	Currently Smokes	3	9	5.2	3	8	4.6	3	0	0	3	17	2.7
SALBUTAMOL	Any Salbutamol Use: No	0	151	86.8	0	132	76.3	0	274	98.9	0	557	89.3
	Any Salbutamol Use: yes	1	23	13.2	1	41	23.7	1	3	1.1	1	67	10.7
AGEGRP	Age Group 1: 40-54 Years	1	10	5.7	1	10	5.8	1	15	5.4	1	35	5.6
	Age Group 2: 55-64 Years	2	63	36.2	2	51	29.5	2	73	26.4	2	187	30
	Age Group 3: 65-74 Years	3	69	39.7	3	83	48	3	134	48.4	3	286	45.8
	Age Group 4:>75 Years	4	32	18.4	4	29	16.8	4	55	19.9	4	116	18.6
SEX	Male	1	128	73.6	0	124	71.7	0	213	76.9	0	465	74.5
	Female	0	46	26.4	1	49	28.3	1	64	23.1	1	159	25.5
RACE	White	0	168	96.6	0	171	98.8	0	251	90.6	0	590	94.6
	American Indian Or Alaska Native	1	0	0	1	0	0	1	17	6.1	1	17	2.7
	Asian	2	4	2.3	2	0	0	2	7	2.5	2	11	1.8
	Black Or African American	3	2	1.1	3	2	1.2	3	2	0.7	3	6	1
DIAGRPYRS	Time since diagnosis >=1 Year	0	93	53.4	0	65	37.6	0	183	66.1	0	341	54.6
	Time since diagnosis <1 Year	1	81	46.6	1	108	62.4		94	33.9	1	283	45.4

Table 5. Table of data definitions and patient demographics (Continuous variables)

Study		PIPF-004 n=174			PIPF-006 n=173			PIPF-016 n=277			Total n=624		
		Mean	SD	Range	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
AGE	Age at time of randomization	66.3	7.5	40-79	67.0	7.8	42-80	67.8	7.3	41-80	67.2	7.5	40-80
DIAGYRS	Time since diagnosis	1.4	1.1	0.066-4.06	1.1	1.0	0.044-4	1.7	1.0	0.5-4	1.5	1.1	0.04-4
BW	Body weight at baseline	85.8	16.5	47.6-147	88.8	16.6	39.9-139	84.8	16.4	53-140	86.2	16.5	39.9-147
BASEFVC	Baseline FVC	76.2	15.5	48.02-135.5	73.1	14.2	51.6-128	68.6	10.9	48.64-91	72.0	13.6	48-135.5

Table 6. Default parameterization in PSN.

Replace PAR with the parameter name, e.g. CL, and COV with the covariate name, e.g. WGT or SEX. If the parameter is listed as a logit the offset 1 in default functions for state 1 and 2 will be changed to 0.
Default state 1:Covariate not included on the parameter PARCOV=1
Default state 2, continuous covariates: Linear function PARCOV= (1 + THETA(1)*(COV - median))

Default state 2, categorical covariates: Linear function (will be one extra line for each extra category)
 	
IF(COV.EQ.1) PARCOV = 1 ; Most common
IF(COV.EQ.0) PARCOV = (1 + THETA(1))

Default state 3: Hockey-stick, or piece-wise linear, function. Continuous covariates only.
 	
IF(COV.LE.median) PARCOV = (1 + THETA(1)*(COV - median))
IF(COV.GT.median) PARCOV = (1 + THETA(2)*(COV - median))

Default state 4: Exponential function. Continuous covariates only. PARCOV= EXP(THETA(1)*(COV – median))
Default state 5: Power function. Continuous covariates only. PARCOV= ((COV/median)**THETA(1))

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/s/

DINKO REKIC
08/30/2014

LIANG ZHAO
09/02/2014

SATJIT S BRAR
09/02/2014

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-535	Submission Date(s): November 4, 2009
Brand Name	Esbriet
Generic Name	Pirfenidone (S-7701)
Reviewer	Elizabeth Y. Shang, Ph.D.
Team Leader (Acting)	Yun Xu, M.D., Ph.D.
Pharmacometrics Primary Reviewer	Venkatesh Bhattaram, Ph.D.
Pharmacometrics Team Leader	Yaning Wang, Ph.D.
Pharmacogenomics Reviewer	Michael A. Pacanowski, Pharm.D., M.P.H.
Pharmacogenomics Team Leader	Issam Zineh, Pharm.D., M.P.H.
OCP Division	DCPII
OND division	DPARP
Sponsor	InterMune Inc.
Relevant IND(s)	67,284
Submission Type	Original
Review Priority	Priority
Formulation; Strength(s)	Oral Capsule; 267 mg
Indication	Treatment of patients with idiopathic pulmonary fibrosis to reduce decline in lung function
Proposed Maintenance Dosing Regimen	801 mg (three 267 mg capsules) orally three times a day with food

Table of Contents

1 Executive Summary

1.1 Recommendation

This submission is acceptable from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement can be reached between the sponsor and the Agency regarding the language on the labeling.

Required office level Office of Clinical Pharmacology was held on Friday, March 26, 2009 and the attendees were Drs. Chandrahas G. Sahajwalla, Edward D. Bashaw, Nam Atiqur Rahman, Shiew Mei Huang, Darrell Abernethy, Gilbert Burckart, Sally Choe, Partha Roy, Kellie S. Reynolds, Yun Xu, Michael A. Pacanowski, Venkatesh Bhattaram, Sally Seymour, and Banu Karimi-Shah and Elizabeth Y. Shang.

1.2 Phase IV Commitments

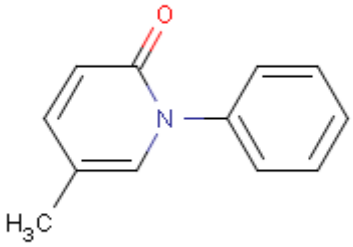
None.

1.3 Summary of Clinical Pharmacology Findings

Although the exact mechanism of action has not been fully established, pirfenidone is thought to have both anti-inflammatory and antifibrotic activity mediated through TNF-α and TGF-β. It is proposed for the treatment of patients with idiopathic pulmonary fibrosis to reduce decline lung function. Pirfenidone is available in 267-mg capsule. The propose dosing regimen is 801 mg orally three times daily with food after initial dose titration.

Pirfenidone has a molecular weight of 185.23 g/mol, empirical formula of $C_{12}H_{11}NO$, and is more soluble in methanol, ethyl alcohol, acetone and chloroform than in water and 1.0 N HCl. The chemical structure is shown in Figure 1.

Figure 1 Chemical Structure of Pirfenidone



Absorption

Pirfenidone is absorbed rapidly under fasted state. The median time (range) to maximum plasma concentration (T_{max}) is 0.5 (0.5 to 4) hour following a single dose administration of 801 mg. The mean (SD) maximum plasma concentration is 15.7 (4.80) mg/L.

Distribution

Pirfenidone binds to human plasma proteins, primarily to serum albumin. *In vitro* study showed that the overall mean binding is ~58% at concentration range of 1 to 10 mg/L, but decreases to ~50% at the highest concentration tested, 100 mg/L. The mean volume of distribution ranges from 59 L to 71 L following multiple doses of administration.

Metabolism and Elimination

Pirfenidone is primarily metabolized in the liver by CYP1A2 (~48%) and multiple other CYPs (each <13%). Oral administration of pirfenidone in humans results in the formation of four metabolites, however, only 5-carboxy-pirfenidone is present in plasma in significant quantities. The sponsor reported no pharmacological activity of the metabolite 5-carboxy-pirfenidone.

Approximately 80% of the dose of pirfenidone is excreted in the urine as parent drug or one of the four metabolites. In urine, majority of pirfenidone is excreted as the 5-carboxy-pirfenidone (~99.6% of that recovered).

Food Effect/Antacid Effect

The rate of pirfenidone absorption is slowed with food, as indicated by increased median T_{max} (range) from 0.5 (0.5 to 4) hour to 3.0 (0.5 to 6) hours. The extent of the absorption is also decreased as evident by ~49% reduction in the maximum pirfenidone plasma concentrations (C_{max}) and a ~16 % reduction in $AUC_{0\text{-}inf}$. The sponsor recommends that pirfenidone should be taken with food to reduce the incidence of nausea and dizziness.

The antacid preparation Mylanta® Maximum Strength Liquid does not affect the absorption of pirfenidone under fed condition.

Hepatic Impairment

Following a single oral dose administration of 801 mg pirfenidone, the geometric means of $AUC_{0\text{-}inf}$ and C_{max} of pirfenidone increased ~1.6 and ~1.4-fold in subjects with moderate hepatic impairment, respectively. The geometric mean of $AUC_{0\text{-}inf}$ of 5-carboxy-pirfenidone did not change significantly.

Renal Impairment

Following a single oral dose administration of 801 mg pirfenidone, the systemic exposure ($AUC_{0\text{-}inf}$) to pirfenidone increased ~1.4, 1.5, and 1.2-fold in subjects with mild, moderate, and severe renal impairment, respectively. The corresponding $AUC_{0\text{-}inf}$ of 5-carboxy-pirfendione increased ~1.7, 3.4, and 5.5-fold, respectively. The renal clearance of 5-carboxy-pirfendone decreased significantly.

Drug-drug Interactions

Co-administration with fluvoxamine resulted in 4.0-fold increase in $AUC_{0\text{-}inf}$ and 1.7-fold increase in C_{max} of pirfenidone in nonsmokers, respectively. No change in $AUC_{0\text{-}inf}$ of 5-carboxy-pirfenidone was observed.

Smoking reduces the systemic exposure ($AUC_{0\text{-}inf}$) to pirfenidone and 5-carboxy-pirfenidone by ~54% and 32%, respectively. Smokers appear to have a more pronounced increase in systemic exposure to pirfenidone with co-administration of fluvoxamine. This is evident that $AUC_{0\text{-}inf}$ of pirfenidone increases ~7-fold in smokers versus ~4-fold in non-smokers.

Thorough QT Study

Although there was no evidence that pirfenidone prolonged the QTc interval in this study, a definitive conclusion may not be drawn for the following reasons: 1) Assay sensitivity can not be established because the study failed to demonstrate the positive control's (moxifloxacin) anticipated effect, 2) The supratherapeutic dose did not cover maximum pirfenidone exposure increase with co-administration of fluvoxamine, a strong CYP1A2 inhibitor.

2 Question Based Review

2.1 General Attributes of the Drug

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

Idiopathic pulmonary fibrosis (IPF) is an orphan disease, with the prevalence estimated to range from 14 to 43 per 100,000 persons in the United States. IPF is a chronic, progressive, diffuse parenchymal lung disease with unknown etiology. Median survival after the diagnosis is less than 3 years. Currently, there is no approved product in US for treatment of IPF, which represents an unmet medical need.

The development of pirfenidone was initiated in the US by Marnac, Inc. InterMune, Inc. acquired the rights to pirfenidone in the US from Marnac and its co-licensor, KDL GmbH, in 2002 and opened an IND in the US in 2003.

Pirfenidone was designated as an orphan drug on March 5, 2004 for the treatment of IPF. InterMune, Inc., submitted its NDA on November 4, 2009. A priority review was subsequently granted on January 4, 2010. It should be noted that pirfenidone has been approved for IPF in Japan on October 16, 2008, under the trade name Pirespa® in a 200 mg tablet. The approved dosing regimen in Japan is 600 mg orally three times daily (1800 mg/day).

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?

This submission contains the manufacture and controls of 267-mg pirfenidone capsules. (b) (4)

2.1.3 What are the proposed mechanism(s) of action and therapeutic indication(s)?

Although the mechanism of action of pirfenidone has not been fully established, the sponsor stated that data from *in vitro* and animal models indicated pirfenidone has both anti-inflammatory and antifibrotic activities. Pirfenidone inhibits the synthesis and release of pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-α) and interleukin-1–beta (IL-1β) and has been shown to reduce the accumulation of inflammatory cells in response to various stimuli.

Pirfenidone also attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as transforming growth factor-beta (TGF-β) and platelet derived growth factor (PDGF).

Pirfenidone is proposed for the treatment of patients with idiopathic pulmonary fibrosis to reduce decline lung function.

2.1.4 What are the proposed dosage(s) and route(s) of administration?

The proposed dosing regimen is 801 mg (three 267 mg capsules) orally three times a day with food. Initial dose titration to the therapeutic dose is recommended. The dose escalation steps are presented in Table 1.

Table 1 Initial Dose Titration Scheme of Pirfenidone Administration

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

2.2 General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

There were no formal dose-ranging and dosing interval studies as a part of the clinical development program. The sponsor stated designing a dose-ranging study in IPF patients is challenging, due to the limited size of the patient population and the long duration needed to evaluate a treatment effect, given the lack of established pharmacodynamic surrogate endpoints.

Food effect on pirfenidone was assessed in the first clinical study. Based on study results, the sponsor recommends that pirfenidone should be taken with food to reduce the incidence of nausea and dizziness. Therefore, all the subsequent clinical studies were conducted under fed condition.

The proposed dosing regimen, 2403 mg/day (801 mg po TID), was derived from a clinical program conducted by Shionogi in Japan with a 1800 mg/day (600 mg po TID) dose. This dose was weight-normalized to the expected body weights of patients in the InterMune clinical trials. A lower dose (1197 mg/day) was included in one of the Phase 3 trial for dose exploration and to provide additional safety information.

The pharmacokinetics and tolerability of pirfenidone were evaluated in healthy older (50 to 79 years) subjects following the administration of single dose of 801 mg pirfenidone. Food and antacid effects upon the single dose pirfenidone PK were also evaluated. The pharmacokinetics and tolerability were also evaluated in healthy older (50 to 79 years) subjects with repeated dose up to 4005 mg/d (1335 mg TID) for 3 days with a dose titration scheme. The pharmacokinetics of pirfenidone was evaluated in IPF patents in the pivotal Phase 3 trial, PIPF-004, which included two dosing regimens (801 mg TID and 399 mg TID).

No mass balance study in human was performed. The influence of renal and hepatic impairment on pirfenidone pharmacokinetics was assessed following a single 801 mg oral dose. The effect of CYP1A2 strong inhibitor fluvoxamine and smoking upon single dose pirfenidone PK was investigated.

The effect of therapeutic and supratherapeutic doses of pirfenidone on ECG parameters, was investigated in healthy subjects following repeated three-time daily doses of 801 and 1335 mg. This thorough QT study design and analysis was conducted according to ICH-E14 guidance.

2.2.2 What is the basis for selecting the response endpoints, i.e., clinical or surrogate endpoints, or biomarkers (collectively called pharmacodynamics, PD) and how are they measured in clinical pharmacology and clinical studies?

The sponsor stated due to the challenge that few large, placebo-controlled clinical trials have been conducted in patients with IPF, the endpoint selection remains a daunting issue and is a matter of ongoing discussion in the clinical community. Consensus guidelines published for the management of patients with IPF[2], was based upon expert opinion rather than rigorously collected evidence and did not specifically address the issue of endpoint selection or design of clinical trials. Details related to this matter was presented, thoroughly discussed, and debated at Pulmonary-Allergy Drugs Advisory Committee (PADAC) Meeting for pirfenidone on March 9, 2010.

A brief summary in regard to the basis for selecting the clinical endpoints is provided by the sponsor. The primary efficacy endpoint was absolute change in percent predicted forced vital capacity (FVC) from Baseline to Week 72. According to the sponsor, the rationale for choosing percent change of FVC was based upon the followings:

- FVC is a measure of lung volume, and progressive loss of lung function is a hallmark of IPF
- FVC is widely used and accepted as a clinical meaningful measure of IPF disease status
- Accruing data from multiple studies showed that the change in FVC is a strong independent prognosticator of mortality in patients with IPF.
- FVC is a comparable measure to vital capacity (VC), the endpoint in the Shionogi trials, in the setting of a restrictive lung disease without significant obstructive airway disease.

The secondary efficacy endpoints included categorical percent FVC, progression-free survival, 6-minute walk test distance (6MWT), lowest SpO_2 during 6MWT, mean change from baseline in percent predicted DLco, dyspnea (UCSD SOBQ), and time to IPF worsening, all measured at Week 72. Death was an exploratory endpoint. Survival was examined on-treatment (up to 28 days after treatment discontinuation) and at the end of the entire study period (vital status assessment).

2.2.3 Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships? (if yes, refer to 2.6 Analytical section. If not, describe the reason)

The parent compound, pirfenidone, is the active moiety. Pirfenidone concentrations in plasma and urine were measured by high performance liquid chromatography with mass spectrometric detection (LC-MS/MS) method. For details, see Section 2.6.1.

2.2.4 Dose-response

Dose-response was conducted and submitted by the sponsor and reanalyzed by the Biostatistics reviewer at FDA. For details, see Briefing Packages published for the PADAC Meeting on March 9, 2010.[1] A brief summary of the findings is presented below.

Dose-Efficacy Relationship

There are two pivotal Phase 3 trials in this submission: PIPF-004 and PIPF-006. Both trials were randomized, double-blind, placebo-controlled, clinical trials to assess the efficacy and safety of pirfenidone for the treatment of patients with IPF to reduce the decline in lung function. The duration of the trials was 72 weeks. Both trials were similar in design with a few key differences. PIPF-004 included two active treatment groups 2403 mg/day and 1197 mg/day and randomization was 2:2:1 for the 2403 mg/day:placebo:1197 mg/day groups, respectively, PIPF-006 randomization was 1:1 to 2403 mg/day or placebo. The pirfenidone 1197 mg/day group was included in PIPF-004 only to explore a dose-response relationship. It was not adequately powered to demonstrate efficacy.

The primary efficacy results are shown in Table 2. The results for the primary endpoint in PIPF-004 are statistically significant, Trial PIPF-006 showed lack of treatment effect.

Table 2 Primary Efficacy Endpoint Results from PIPF-004 and -006.

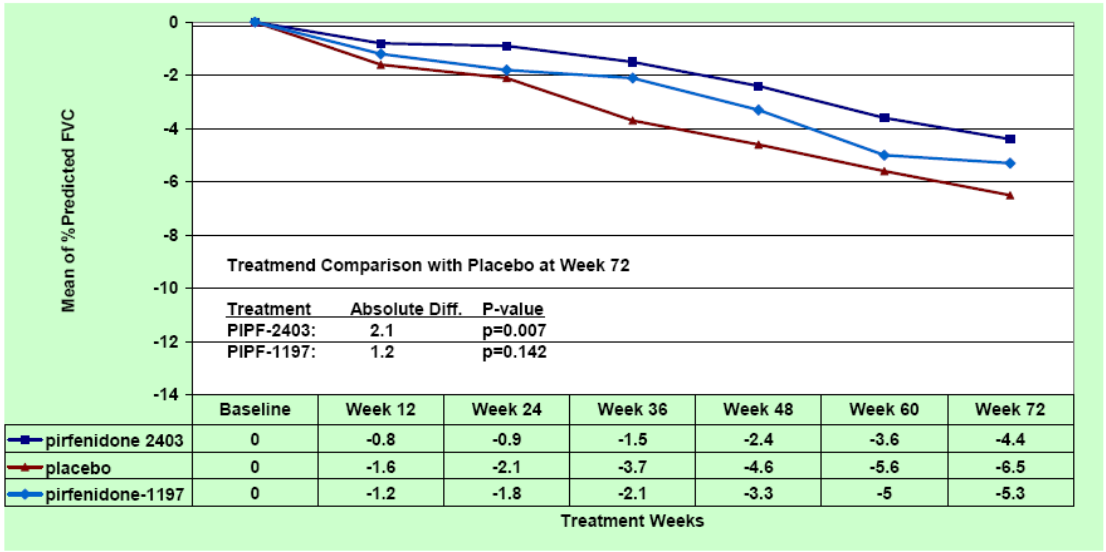
	Pirfenidone 1197mg/day	Pirfenidone 2403mg/day	Placebo	Difference from Placebo (p value)†
PIPF-004	-9.9 (n=87)	-8.0 (n=174)	-12.4 (n=174)	4.4 (p < 0.001)
PIPF-006		-9.0 (n=171)	-9.6 (n=173)	0.6 (p=0.501)

* Missing data imputed: if patient died, then 0 imputed; if patient alive imputation by the sum of squared differences method (SSD)
† comparison for pirfenidone 2403mg/day group; rank ANCOVA with imputation of missing data

Source: Adapted from FDA biostatistics summary for PADAC Meeting, March 9, 2010

Exploration of dose-response relationship of pirfenidone in the treatment of patients with IPF showed that there was a numerical reduction in the mean decline from baseline in percent predicted FVC in patients receiving pirfenidone 1197 mg/day compared with those receiving placebo at Week 72 (p=0.172, rank ANCOVA). The treatment effect of pirfenidone 1197 mg/day appeared to be intermediate to that of pirfenidone 2403 mg/day and placebo in the primary efficacy analysis (Figure 2).

Figure 2 Dose Response in Mean Change from Baseline in Percent Predicted FVC (ranked ANCOVA, no imputation)



Source: Adapted from FDA Biostatistics Summary for PADAC Meeting, March 9, 2010

Dose-Safety Relationship

The safety analysis was focused on treatment emergent adverse events using pooled data from the two pivotal Phase 3 trials. For details, see FDA Clinical Briefing Document published for PADAC Meeting on March 9, 2010.[1]

Death

Overall, the percentage of deaths was lower in the pirfenidone 2403 mg/day group compared with the placebo and pirfenidone 1197 mg/day group (19 patients, 5.5%; 29 patients, 8.4%; and 8 patients, 9.2%, respectively). However, in PIPF-004, where two doses of pirfenidone were explored, no numerical dose

response was demonstrated. It should be noted that death was not adjudicated but rather was based upon investigators' judgment. Therefore, these data should be interpreted carefully.

Serious Adverse Events (SAE)

No dose response was noted in this category. The overall occurrence of treatment-emergent SAEs was equally distributed across treatment groups (31.4% to 32.8%).

Dropouts and/or Discontinuations

Numerically, the percentage of patients discontinued treatment due to an AE were trending higher with the increase of doses (8.6%, 10.3%, and 14.8% in placebo, 1197 mg/day, and 2403 mg/day, respectively), the numbers of patients discontinuing secondary to any particular AE were small.

Significant Adverse Events

Numerically, the percentage of patients having their doses reduced or treatment interrupted due to an AE were trending higher with the increase of dose (18.4%, 42.5%, and 46.4% in placebo, 1197 mg/day, and 2403 mg/day, respectively). However, the difference between 2403 mg/day and 1197 mg/day were small (~4.0%). The common AEs ($\geq$ 4% of patients) that led to dose interruption or reduction that were reported more frequently by patients treated with pirfenidone than placebo included rash, gastrointestinal disorders (nausea, vomiting, and diarrhea), photosensitivity reaction, and fatigue.

Does this drug prolong the QT or QTc interval?

Effects of multiple doses of proposed therapeutic (801 mg TID) and supratherapeutic dose (1335 mg TID) of pirfenidone upon QT prolongation were studied in 80 healthy subjects and compared to placebo and moxifloxacin. Details see the Interdisciplinary Review Team's (IRT) review dated July 31, 2008 in the appendix.

The results from this thorough QT (TQT) study are inconclusive. Overall, TQT study failed to demonstrate the positive control's anticipated effect. First, assay sensitivity cannot be established because the moxifloxacin QTc-time profile is highly variable and does not follow the expected time-course based on the known pharmacokinetics. There are three peaks of similar magnitude in the $\Delta\Delta$QTcI-time profile corresponding to somewhat to the three dosing events on Day 10 (0800h, 1200h, and 1800h) (Figure 3). Secondly, the mean effect of moxifloxacin on the QTc is less than 5 ms as evidence by the largest adjusted lower bound of 90% CIs being 3.8 ms, using the most conservative Bonferroni adjustment (adjusted by 4 time points) (Table 3). In addition, the supratherapeutic dose only obtained a 1.6-fold increase in exposure, which did not cover maximum pirfenidone exposure increase with co-administration of fluvoxamine, a strong CYP1A2 inhibitor.

It should be noted that the sponsor performed QTc analysis using QTcI. IRT review analysis found that results were consistent between QTcF and QTcI analysis. Therefore, results of QTcI were presented.

Figure 3 Mean (90% CI) ΔΔQTcI by Time for Moxifloxacin

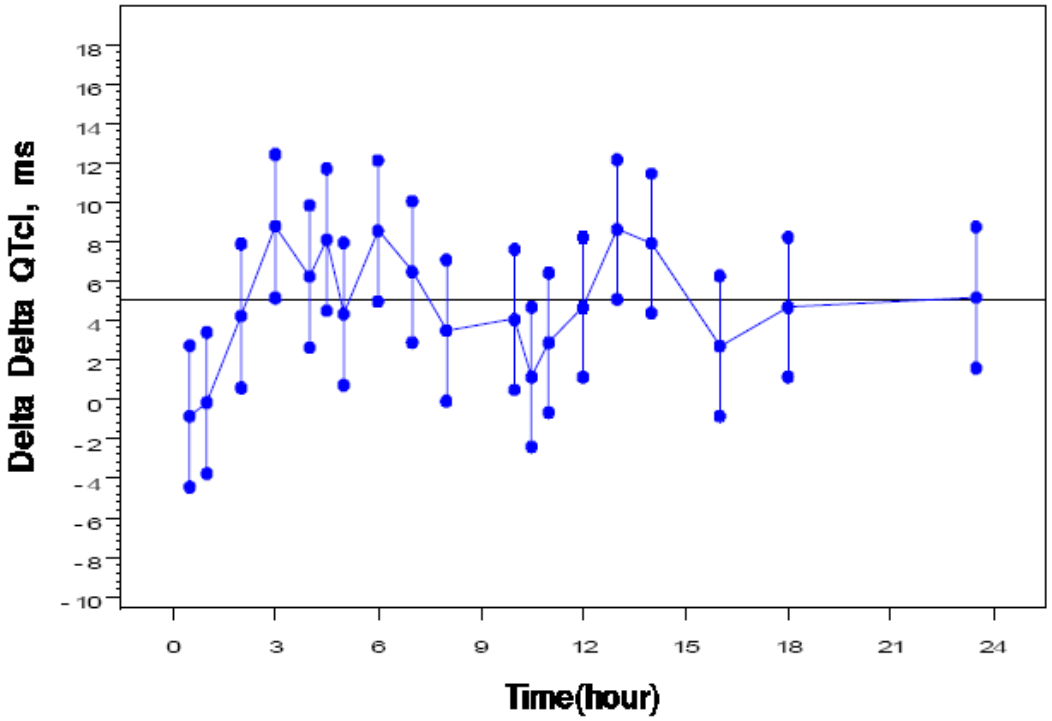


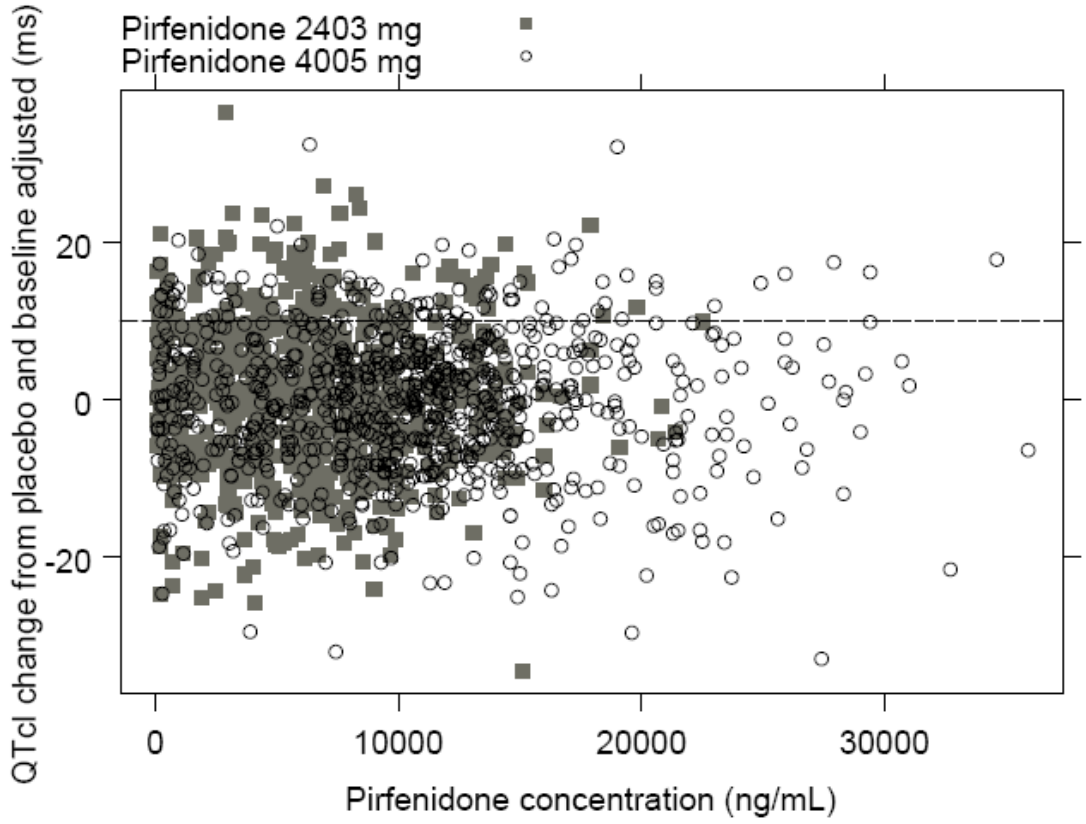
Table 3 Analysis Results of ΔΔQTcI between Moxifloxacin and Placebo Group

	Moxifloxacin		Placebo		ΔΔQTcI		
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI	Adjusted 90% CI
0.5	-4.1	1.5	-3.2	1.5	-0.9	(-4.4, 2.7)	(-5.7, 4.0)
1	-2.0	1.5	-1.8	1.5	-0.2	(-3.7, 3.4)	(-5.0, 4.7)
2	3.6	1.6	-0.6	1.6	4.2	(0.6, 7.9)	(-0.7, 9.2)
3	7.8	1.6	-1.0	1.6	8.8	(5.2, 12.4)	(3.8, 13.7)

Visual inspection on relationship between ΔΔQTcI and pirfenidone concentration revealed no evident exposure-response relationship (Figure 4).

Categorical analysis showed no subjects observed a QTcI > 480 ms or a change from baseline QTcI > 60 ms.

Figure 4 ΔΔQTcI vs. Pirfenidone Plasma Concentrations



Reviewer's Comments:

The clinical findings with respect to QT prolongation in the Phase 3 program are of particular relevance, because of the failed positive control cohort in this TQT study. Analysis of the ECGs collected during the Phase 3 trials PIPF-004 and PIPF-006 showed no clear evidence of a pirfenidone-related effect on heart rate, cardiac depolarization, or QT prolongation.[1] Thus, repeating TQT study is not warranted. It should be noted that effect of pirfenidone at exposure greater than 1.6-fold of the therapeutic concentrations upon QT prolongation is unknown. Concomitant use of pirfenidone with medications expected to increase pirfenidone exposure should be cautious. Therefore, it is recommended in the label that co-administration of pirfenidone and drugs that will inhibit pirfenidone metabolism should be cautious.

2.2.5 What are the PK characteristics of the drug and its major metabolite?

2.2.5.1 What are the single dose and multiple dose PK parameters?

Single Dose

The sponsor recommends that pirfenidone should be taken with food to reduce the incidence of nausea and dizziness. Therefore, PK parameters presented below were estimated under fed condition. For PK parameters estimated under fasted condition, see Section 2.5.3.

Following single oral dose administration of pirfenidone with food, it is absorbed at a moderate rate (medium T_{max} ~3.50 hr). The mean peak plasma concentration of pirfenidone is 7.87 mg/L.

The plasma pharmacokinetics of pirfenidone and its metabolite 5-carboxy-pirfenidone were characterized following single oral dose administration of 801 mg (three 267-mg capsules) dose of pirfenidone to healthy older subjects (50 to 79 years) in Study PIPF-005 (Table 4). There is only one single dose level (801 mg) studied in the entire clinical pharmacology program. The pharmacokinetics of pirfenidone and 5-carboxy-pirfenidone in healthy subjects from other clinical pharmacology studies are summarized in Table 4.

Table 4 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone Following Single Oral Dose of 801 mg in Healthy Subjects

Pirfenidone PK Parameters	PIPF-005*,†	PIPF-009	PIPF-010	PIPF-011
N	16	6	25	12
AUC_{last} (hr×mg/L)	58.8 (22.2)	42.1 (17.4)	46.1 (11.8)	55.4 (27.2)
$AUC_{0\text{-}inf}$ (hr×mg/L)	59.2 (22.3)	42.4 (17.5)	46.3 (11.8)	55.8 (27.5)
C_{max} (mg/mL)	7.87 (2.30)	9.93 (3.45)	8.82 (1.56)	11.9 (3.53)
T_{max} (hr)[a]	3.50 [1.00 – 6.00]	1.50 [0.500 – 2.00]	3.00 [1.00 – 4.00]	1.00 [0.500 – 4.00]
$T_{1/2}$ (hr)	3.16 (0.960)	2.59 (0.551)	2.80 (0.588)	3.15 (1.28)
CL/F (L/hr)	15.9 (7.87)	23.1 (13.3)	18.4 (4.49)	19.0 (11.2)
Vz/F (L)	65.4 (15.8)	80.0 (29.8)	72.2 (17.0)	69.6 (15.9)
M:P ratio	0.566 (0.208)	0.673 (0.314)	0.644 (0.245)	0.615 (0.354)

[a] median [range]
* High fat meal was given, while other three trials, standard meals were given.
† Data from Treatment C group only

Table 5 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma 5-Carboxy-Pirfenidone Following Single Oral Dose of 801 mg in Healthy Subjects

Pirfenidone PK Parameters	PIPF-005*,†	PIPF-009	PIPF-010	PIPF-011
N	16	6	26	12
AUC_{last} (hr×mg/L)	34.3 (7.03)	28.2 (4.85)	25.1 (5.74)	30.5 (4.69)
$AUC_{0\text{-}inf}$ (hr×mg/L)	34.6 (7.04)	28.4 (4.88)	25.3 (5.73)	30.8 (4.70)
C_{max} (mg/mL)	4.62 (1.13)	6.16 (1.27)	7.43 (1.89)	6.18 (2.76)
T_{max} (hr)[a]	4.00 [1.00 – 6.00]	2.00 [0.500 – 3.00]	2.00 [1.00 – 4.00]	1.00 [0.500 – 4.00]
$T_{1/2}$ (hr)	3.27 (1.00)	2.65 (0.663)	1.69 (0.46)	3.26 (1.29)

[a] median [range]
* High fat meal was given, while other three trials, standard meals were given.
† Data from Treatment C group only

Pirfenidone and its metabolites 5-carboxy, 5-hydroxymethyl, and 4-hydrox- pirfenidone urinary pharmacokinetics following single dose of 801 mg pirfenidone were evaluated. 4-Hydrox-pirfenidone urine concentrations were not detectable. Urine parameter estimates for pirfenidone, 5-carboxy-pirfenidone, and 5-hydroxymethy-pirfenidone are listed in Table 6.

Overall, close to 80% of the dose of pirfenidone was excreted in the urine as parent drug or one of the four metabolites. In urine, the majority of pirfenidone was excreted as the 5-carboxy-pirfenidone metabolite (~99.6% of that recovered) with less than 1% occurring as unchanged drug. It should be noted that 1-O-acyl-glucuronide was also present in urine. However, a validated GLP assay is not available. It is reported that the nonvalidated assay demonstrated that this glucuronide accounted for ~1 – 5% of the excreted dose in the urine.

Table 6 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Urine Pirfenidone, 5-Carboxy-Pirfenidone, 5-Hydroxymethyl-Pirfendione Following Single Oral Dose of 801 mg in Healthy Subjects

	Pirfenidone	5-Carboxy-Pirfenidone	5-Hydroxymethyl-Pirfenidone	Total
N	16	16	16	16
Ae (mg)	2.96 (1.41)	723 (140)	0.0570 (0.0257)	726
Ae%	0.370 (0.176)	77.8 (15.0)	0.0065 (0.0030)	78.2 (15.1)
CLr (L/hr)	0.0532 (0.0219)	22.0 (6.56)	0.0011 (0.0010)	n.a.

Multiple Doses

Two studies contained pirfenidone plasma PK characteristics following multiple doses, PIPF-005 and PIPF-007.

Not optimal for assessing dose linearity due to the study design, the results from PIPF-005 suggested that in the dose range from 801 mg/day to 4005 mg/day, pirfenidone AUC_{last} and C_{max} increase in a dose-linear manner. For details, see Section 2.2.5.8. No changes in T_{max} and $T_{1/2}$ were observed across the dose groups indicating pirfenidone PK is dose-independent. The Plasma PK parameter estimates of pirfenidone and metabolite 5-carboxy-pirfenidone following multiple doses administration are presented in Table 7 and Table 8, respectively.

Table 7 Arithmetic Mean (SD) of Multiple-Dose Pharmacokinetic Parameters for Plasma Pirfenidone in Study PIPF-005

Dose Level	267 mg TID	534 mg TID	801 mg TID	1068 mg TID	1135 mg TID
N	9	9	8	9	9
AUC_{last} (hr×mg/L)	18.3 (7.65)	31.6 (11.3)	57.7 (20.6)	65.8 (15.4)	93.5 (40.8)
C_{max} (mg/L)	3.10 (1.47)	5.46 (1.05)	9.03 (1.99)	11.0 (2.56)	16.8 (5.06)
T_{max} (hr) [a]	3.00 [0.500– 4.00]	2.00 [1.00 – 4.00]	2.00 [2.00 – 4.00]	3.00 [2.00 – 4.00]	2.00 [0.500 – 4.00]
$T_{1/2}$ (hr)	3.18 (0.731)	2.87 (0.661)	3.05 (0.781)	2.52 (0.453)	3.13 (0.641)
CL/F (L/hr)	16.1 (5.75)	18.0 (5.23)	15.0 (4.77)	16.6 (3.24)	16.7 (10.9)
Vz/F (L)	69.1 (13.9)	70.8 (12.7)	62.2 (12.3)	58.7 (7.52)	70.1 (39.2)
M:P ratio	0.551 (0.154)	0.660 (0.188)	0.583 (0.191)	0.603 (0.138)	0.564 (0.242)

[a] median [range]

Table 8 Arithmetic Mean (SD) of Multiple-Dose Pharmacokinetic Parameters for Plasma 5-Carboxy-Pirfenidone in Study PIPF-005

Dose Level	267 mg TID	534 mg TID	801 mg TID	1068 mg TID	1135 mg TID
N	9	9	8	9	9
AUC_{last} (hr×mg/L)**	10.6 (2.95)	23.0 (6.27)	36.3 (9.43)	45.0 (8.01)	54.9 (23.1)
C_{max} (mg/L)	1.85 (0.710)	3.99 (0.961)	5.63 (1.74)	7.12 (1.28)	9.23 (4.00)
T_{max} (hr) [a]	3.00 [0.500 - 4.00]	2.00 [1.00 – 4.00]	2.50 [2.00 – 4.00]	3.00 [2.00 – 4.00]	3.00 [0.500 – 4.00]
$T_{1/2}$ (hr)	3.06 (0.803)	2.92 (0.707)	3.42 (0.795)	2.74 (0.468)	3.26 (0.716)

[a] median [range]

In study PIPF-007, the multiple doses were administered through dose titration schemes listed below:

- Pirfenidone therapeutic dose arm: 801 mg TID for 2 days, then 1602 mg TID for 2 days, then 2403 mg TID for 6 days.

- Pirfenidone supratherapeutic dose arm: 801 mg TID for 2 days, then 1602 mg TID for 2 days, then 2403 mg TID for 2 days, then 3204 mg for 2 days, then 4005 mg TID for 2 days.

PK samples were collected and analyzed on Day 10 when subjects continued to received pirfenidone doses (total three doses were given), a key difference from Study PIPF-005. The estimated pharmacokinetic parameters of pirfenidone and 5-carboxy-pirfenidone are summarized in Table 9 and Table 10, respectively.

Mean systemic exposure (C_{max} and AUC_{0-24h}) increases dose-proportionally as a result of dose increase from 2403 mg/day to 4005 mg/day. No change in T_{max} and $T_{1/2}$ was observed between the two dose groups.

Table 9 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone in Study PIPF-007

Pirfenidone PK Parameters	Pirfenidone Dose Escalated to 2403 mg/day	Pirfenidone Dose Escalated to 4005 mg/day
N	40	40
AUC_{0-24} (hr×mg/L)	55.9 (26.2)	92.9 (40.8)
C_{max} (mg/L)	12.3 (3.80)	19.8 (6.45)
T_{max} (hr)*	1.49 (0.92)	1.80 (0.84)
CL/F (L/hr)	16.7 (7.40)	16.8 (8.20)
$T_{1/2}$ (hr)	2.39 (0.54)	2.39 (0.52)

* Time to maximum plasma concentration in the first dose interval.

Table 10 Arithmetic Mean (SD) of Pharmacokinetic Parameters for plasma 5-Carboxy-Pirfenidone in Study PIPF-007

5-Carboxy-Pirfenidone PK Parameters	Pirfenidone Dose Escalated to 2403 mg/day	Pirfenidone Dose Escalated to 4005 mg/day
N	40	40
AUC_{0-24} (hr×mg/L)	34.5 (7.28)	57.2 (15.4)
C_{max} (mg/L)	7.34 (1.50)	11.1 (2.63)
T_{max} (hr)*	1.58 (0.94)	1.69 (0.85)
$T_{1/2}$ (hr)	2.82 (0.82)	2.92 (0.77)

* Time to maximum plasma concentration in the first dose interval.

2.2.5.2 How does the PK of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Population PK analysis indicated that clearance of pirfenidone and its metabolite 5-carboxy-pirfenidone in IPF patients are similar to those in age-matched healthy volunteers. For details, see Pharmacometric Review in Section 4.2.1..

2.2.5.3 What are the characteristics of drug absorption?

The absolute oral bioavailability study has not been conducted in humans, owing to lack of IV formulation.

Upon oral administration of a single 801 mg dose (3 of 267 mg capsules) under fasted condition, pirfenidone is absorbed at a fast rate. The median T_{max} [range] is 0.500 [0.500 – 4.00] hours. Mean pirfenidone C_{max} and AUC_{0-inf} are 15.7 mg/L and 68.1 hr×mg/L, respectively. Food decreases the rate of absorption. A high fat meal decreases single dose pirfenidone C_{max} and AUC_{0-inf} by ~49% and 16%, respectively. Median T_{max} is shifted from 0.500 to 3.50 hours. For details, see Section 2.5.3.

In vitro study showed that pH has no effect on pirfenidone solubility (Table 11). However, sponsor did examine the effect of antacid (Mylanta® Maximum Strength Liquid 20 mL) upon single dose pirfenidone PK because it had been administered accompanied with an antacid to lessen possible gastrointestinal side effects based on anecdotal information.

Table 11 pH Solubility of Pirfenidone

pH	Buffer System (25 mM)	Solubility at 25°C (mg/mL)[a]		
		2 hours	24 hours	48 hours
1	Deionized water, pH adjusted with HCl	NT	20.5[b]	NT
2	Potassium phosphate monobasic and phosphoric acid	21	20	19
3		20	19	19
4	Sodium acetate and acetic acid	21	20	21
5		22	19	19
6	Potassium phosphate monobasic and sodium hydroxide	21	19	19
7		20	19	19
8		20	19	19
9	Boric acid and sodium hydroxide	21	19	20
10		21	19	19

NT = not tested
[a] Lot PIRFA00502 unless noted.
[b] Lot PIRFA00106.

The antacid preparation Mylanta® Maximum Strength Liquid did not affect the absorption of pirfenidone (Table 12), nor did it affect pirfenidone PK profile under fed condition.

Table 12 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone and 5-Carboxy-Pirfenidone Following Single Oral Dose of 801 mg in Healthy Subjects with and without Administration of Antacid

Parameters	Pirfenidone		5-Carboxy-Pirfenidone	
	Fed	Fed+Antacid	Fed	Fed+Antacid
N	16	16	16	16
AUC_{last} (hr×mg/L)	58.8 (22.2)	56.7 (19.3)	34.3 (7.03)	34.3 (7.44)
$AUC_{0\text{-}inf}$ (hr×mg/L)	59.2 (22.3)	57.1 (19.3)	34.6 (7.04)	34.7 (7.47)
C_{max} (mg/mL)	7.87 (2.30)	7.83 (1.77)	4.62 (1.13)	4.61 (1.41)
T_{max} (hr) [a]	3.50 [1.00 – 6.00]	3.00 [0.500 – 4.00]	4.00 [1.00 – 6.00]	3.00 [1.00 – 4.00]
$T_{1/2}$ (hr)	3.16 (0.960)	3.08 (0.915)	3.27 (1.00)	3.21 (0.979)
CL/F (L/hr)	15.9 (7.87)	16.1 (7.37)	n.a.	n.a.
Vz/F (L)	65.4 (15.8)	64.9 (13.5)	n.a.	n.a.
M:P ratio	0.566 (0.208)	0.586 (0.236)	n.a.	n.a.

[a] median [range]
n.a. not applicable

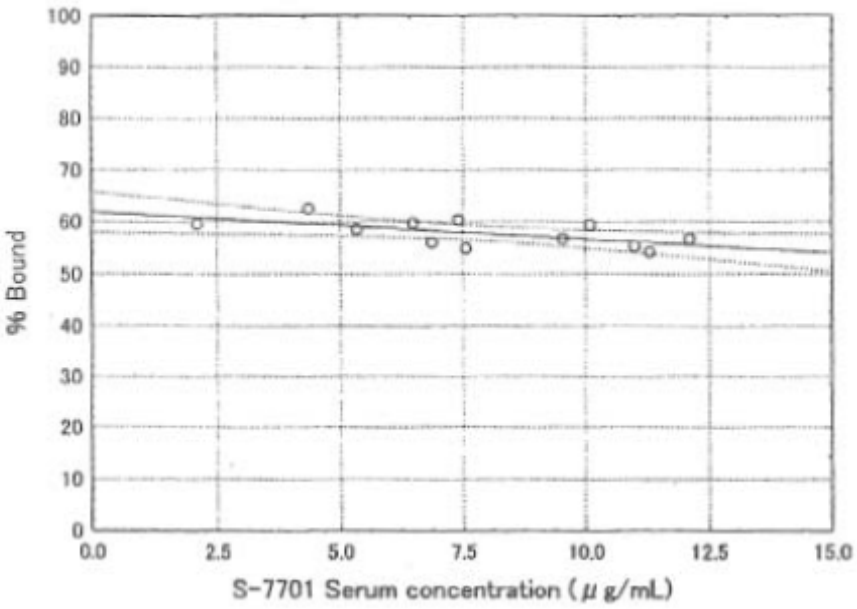
Table 13 Summary Statistical Analysis of Pirfenidone Exposure with or without Antacid under Fed Status

Parameter·	Geometric Mean (Fed+Antacid, Test)	Geometric Mean (Fed, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
$AUC_{0\text{-}inf}$ (hr×mg/L)	53.8	55.0	97.8	91.2	105
C_{max} (mg/L)	7.63	7.58	101	89.1	114

2.2.5.4 What are the characteristics of drug distribution?

Two *in vitro* studies are conducted to characterize the extent of serum protein binding of pirfenidone. Pirfenidone serum protein binding rates in single oral administration of 600 mg drug in healthy male Japanese subjects were measured in the range of 54 to 62%. It should be noted that the binding appears to be higher when the pirfenidone concentration was lower (Figure 5).

Figure 5 Linear Regression Analysis of Pirfenidone Serum Concentration and Percent Protein Bound.



% Bound = 61.892 – 0.5205 * Serum concentration
Correlation: r = -0.6219

In vitro serum protein binding of [^{14}C]-pirfenidone was also investigated in human tissue obtained from healthy Japanese volunteers at concentrations of 1, 10, and 100 µg/mL. The binding ratios are 57.95, 58.10 and 49.67% in human serum, respectively. The binding ratio can be considered constant over the therapeutic concentration range of 1 to 10 µg /mL.

The *in vitro* protein bindings of [^{14}C]-pirfenidone in purified human sera protein solution indicated that albumin is the major binding protein.

The mean volume of distribution for pirfenidone following multiple doses administration ranged from approximately 59 L to 71 L (Table 7) indicating pirfenidone distributes into tissue.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study was conducted in this submission. However, the sponsor conducted full renal impairment study and reduced hepatic impairment study. For details, see Sections 2.3.5 (renal impairment) and 2.3.6 (hepatic impairment), respectively.

2.2.5.6 What are the characteristics of drug metabolism?

Pirfenidone is converted to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone in NADPH-fortified human liver microsomes. The results of experiments with human recombinant CYP enzymes implicated several CYP enzymes such as CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1 and 2J2 in the metabolism of pirfenidone. In incubations of pirfenidone at 100 µM, 5-carboxy-pirfenidone was formed above the limit of quantification by rCYP1A2 and rCYP3A4. In incubations of pirfenidone at 1000 µM, 5-carboxy-pirfenidone was formed above the limit of quantification by rCYP3A4. 5-hydroxmethyl-pirfenidone was formed above the limit of quantification by rCYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1 and 2J2.

The conversion of pirfenidone (100 and 1,000 µM) to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone by human liver microsomes was inhibited by monoclonal antibody against CYP1A2 (by 44% and 48%, respectively). Weak inhibition was also observed with antibody against CYP2C8 (7%) at 100 µM pirfenidone and by antibodies against CYP2C8 and CYP2D6 (13 and 11%, respectively) at 1,000-µM pirfenidone. Formation of 5-carboxy-pirfenidone was completely inhibited by monoclonal antibody against CYP1A2. No other antibody tested inhibited 5-carboxy-pirfenidone formation.

Pirfenidone (100 µM) was incubated with a bank of 16 samples of human liver microsomes to determine the inter-individual differences in metabolite formation. The sample-to-sample variation in the rate of formation of 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone both correlated highly with CYP1A2 activity ($r = 0.851$ and 0.934, respectively).

The overall results indicate CYP1A2 is the major CYP involved in the metabolism, however, other CYP enzymes participate in the overall metabolism of pirfenidone.

2.2.5.7 What are the characteristics of drug excretion?

Approximately 80% of the dose of pirfenidone is excreted in the urine as parent drug or one of the four metabolites (Table 6). In urine, the majority of pirfenidone is excreted as the 5-carboxy metabolite (~99.6% of that recovered) with less than 1% occurring as unchanged drug or as the 4-hydroxy or 5-hydroxymethyl metabolites (Table 6).

2.2.5.8 Based on PK parameters, what is the degree of linearity or nonlinearity in the dose-concentration relationship?

Single dose PK parameters were estimated only in one dose level, 801 mg, hence, the dose-linearity is not assessable.

Multiple doses levels were studied ranging from 801 mg/d (267 mg TID) to 4005 mg/d (1335 mg TID) in Study PIPF-005. Not designed for assessing dose linearity, the results suggested that in the dose range from 801 mg/day to 4005 mg/day, pirfenidone AUC_{last} and C_{max} increase in a dose-linear manner (Figure 6 and Figure 7).

Figure 6 Individual and Geometric Mean of Dose Normalized AUC_{last} by Dose Group (Open Square Represents Individual Values, Filled Circle Represents Geometric Mean)

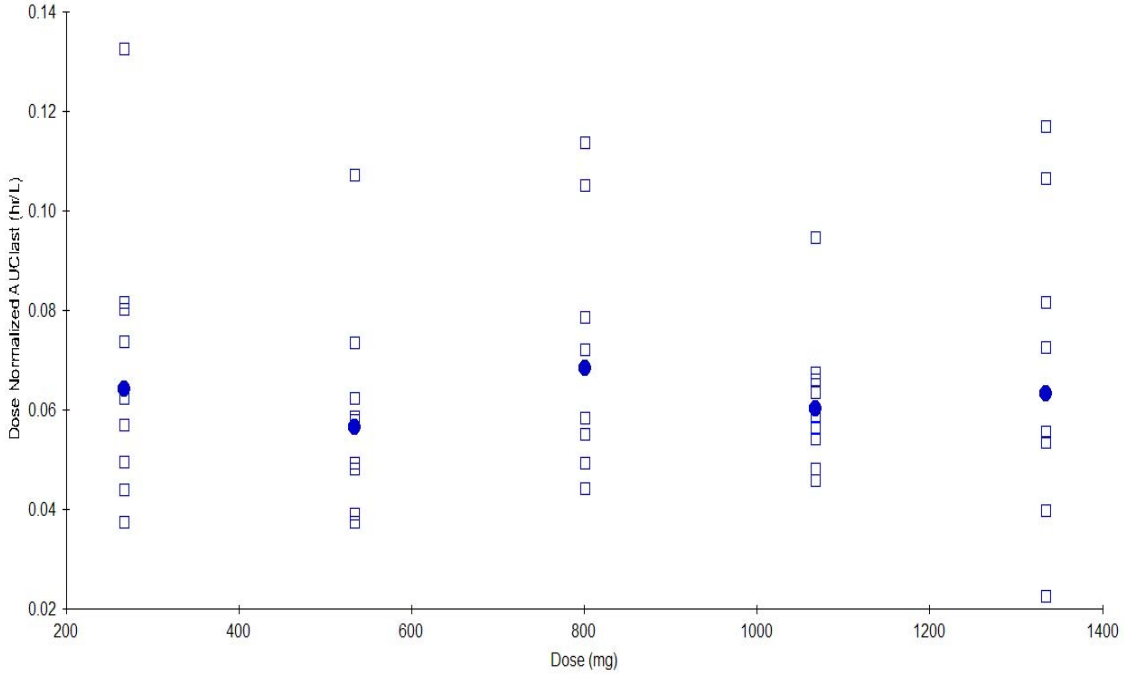
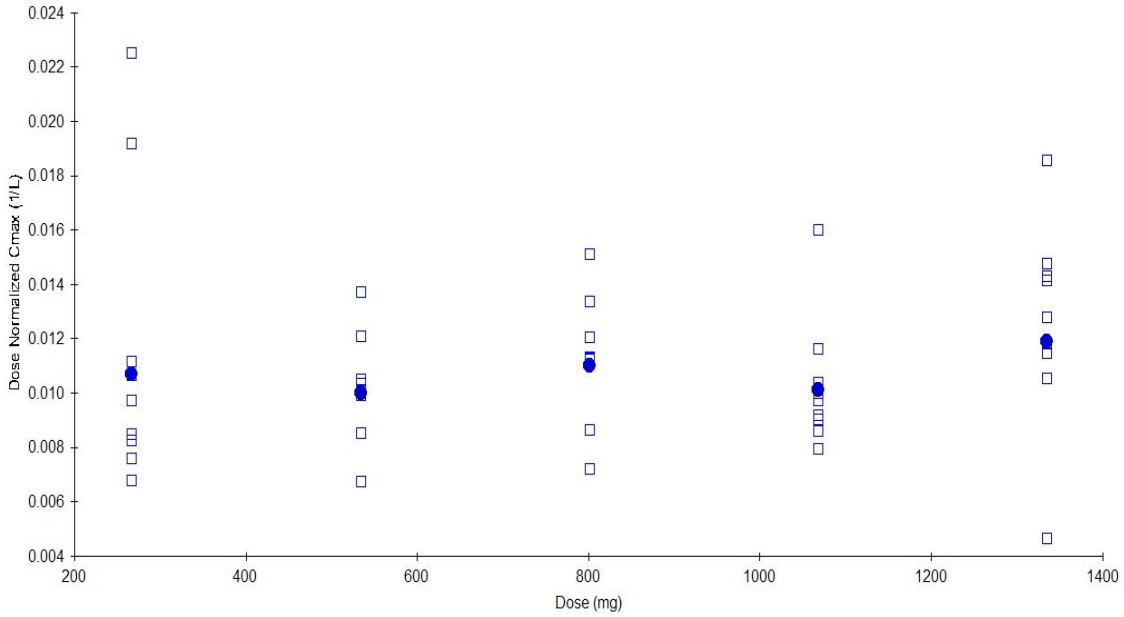


Figure 7 Individual and Geometric Mean of Dose Normalized C_{max} by Dose Group (Open Square Represents Individual Values, Filled Circle Represents Geometric Mean)



Pirfenidone systemic exposure (AUC_{0-24h} and C_{max}) increases with dose after repeated doses of 2403 mg/day and 4005 mg/day in a dose-proportional manner.

2.2.5.9 How do the PK parameters change with time following chronic dosing?

Due to the limitation of study design in multiple doses study (Clinical Study PIPF-005), evaluation of the effect of multiple-dosing upon PK parameters were limited. However, study results suggested that at therapeutic dose of 801 mg TID, pirfenidone shows time-independent pharmacokinetics. The $T_{1/2}$, CL/F, and T_{max} derived from single dose cohort are similar to those from multiple doses cohort.

2.2.5.10 What is the inter- and intra-subject variability of PK parameters patients?

The inter-subject variability in clearance of pirfenidone and 5-carboxy pirfenidone is 40 and 35% respectively. The intra-subject (or interoccasion) variability is large. For details, see Pharmacometric Review in Section 4.2.1.

2.3 Intrinsic Factors

2.3.1 Elderly

Population PK analysis showed that clearance of pirfenidone decreased with increase in age. However, renal function was not evaluated as a covariate since approximately 80% of the dose is excreted in the urine as parent drug or one of the four metabolites. For details, see Pharmacometric Review Section 4.2.1.

2.3.2 Pediatric patients; also- what is the status of pediatric studies and/or any pediatric plan for study.

Waiver of conducting pediatric studies was granted at the End of Phase 2 meeting in 2004 because IPF does not occur in pediatric patient population.

2.3.3 Gender

Population PK analysis showed that clearance of pirfenidone are similar between males and females. For details, see Pharmacometric Review Section 4.2.1.

2.3.4 Race, in particular differences in exposure and/or response in Caucasians, African-Americans and/or Asians

Population PK analysis showed that clearance of pirfenidone are similar between Caucasians and African Americans. For details, see Pharmacometric Review in Section 4.2.1.

2.3.5 Renal impairment

The geometric mean of systemic exposure (AUC_{0-inf}) to pirfenidone increased ~1.4, 1.5, and 1.2-fold in subjects with mild, moderate and severe renal impairment, respectively. The effect of dialysis on pirfenidone PK has not been evaluated in this submission.

The C_{max} of 5-carboxy-pirfenidone increased 1.8 to 3-fold in subjects with moderate and severe renal impairment, respectively. The AUC_{0-inf} increased 1.7, 3.4, and 5.6-fold in mild, moderate, and severe renal impairment, respectively. The renal clearance of 5-carboxy-pirfendone decreased significantly.

The summary statistical analysis on plasma PK parameters of pirfenidone and 5-carboxy-pirfendione is listed in Table 14 and Table 15, respectively. Relationship between pirfenidone and 5-carboxy-pirfenidone systemic exposure (AUC_{0-inf}) and degrees of renal impairment is presented in Figure 8 and Figure 9.

Table 14 Summary Statistical Analysis of Pharmacokinetic Parameters of Pirfenidone in Healthy and Renal Impaired Subjects

Parameters	Renal Function	Geometric Mean (mg/L) (Renal Group, Test)	Geometric Mean (Healthy Group, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	Mild	10.1	9.31	108	71.0	164
	Moderate	10.0	9.31	108	70.8	164
	Severe	10.8	9.31	116	76.1	176
AUC_{last} (hr×mg/L)	Mild	55.2	38.5	144	98.2	210
	Moderate	57.3	38.5	149	102	218
	Severe	44.5	38.5	116	79.1	169
AUC_{0-inf} (hr×mg/L)	Mild	55.7	38.7	144	98.4	211
	Moderate	57.6	38.7	149	102	218
	Severe	44.7	38.7	115	78.9	169
$T_{1/2}$ (hr)	Mild	3.34	2.55	131	102	168
	Moderate	3.58	2.55	141	110	180
	Severe	2.52	2.55	99.1	77.4	127

Table 15 Summary Statistical Analysis of Pharmacokinetic Parameters of 5-Carboxy-Pirfenidone in Healthy and Renal Impaired Subjects

Parameters	Renal Function	Geometric Mean (mg/L) (Renal Group, Test)	Geometric Mean (Healthy Group, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	Mild	6.59	6.04	109	84.5	141
	Moderate	10.8	6.04	180	139	232
	Severe	17.9	6.04	296	229	382
AUC_{last} (hr×mg/L)	Mild	46.5	27.8	167	125	224
	Moderate	95.0	27.8	342	255	458
	Severe	154	27.8	555	414	745
AUC_{0-inf} (hr×mg/L)	Mild	47.3	28.1	168	125	227
	Moderate	95.8	28.1	341	253	460
	Severe	155	28.1	553	411	745
$T_{1/2}$ (hr)	Mild	3.66	2.59	142	105	190
	Moderate	4.21	2.59	162	121	219
	Severe	3.57	2.59	138	102	186
CLr (L/hr)	Mild	19.4	27.7	70.1	48.0	103
	Moderate	9.63	27.7	34.8	23.8	50.9
	Severe	4.62	27.7	16.7	11.4	24.4

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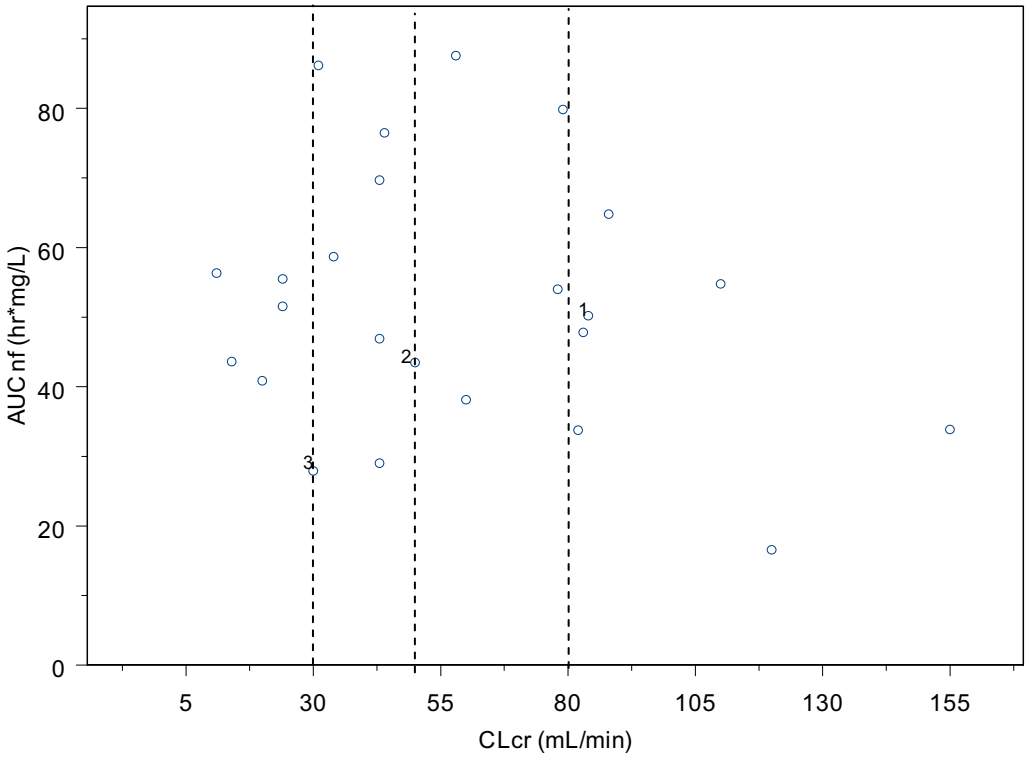
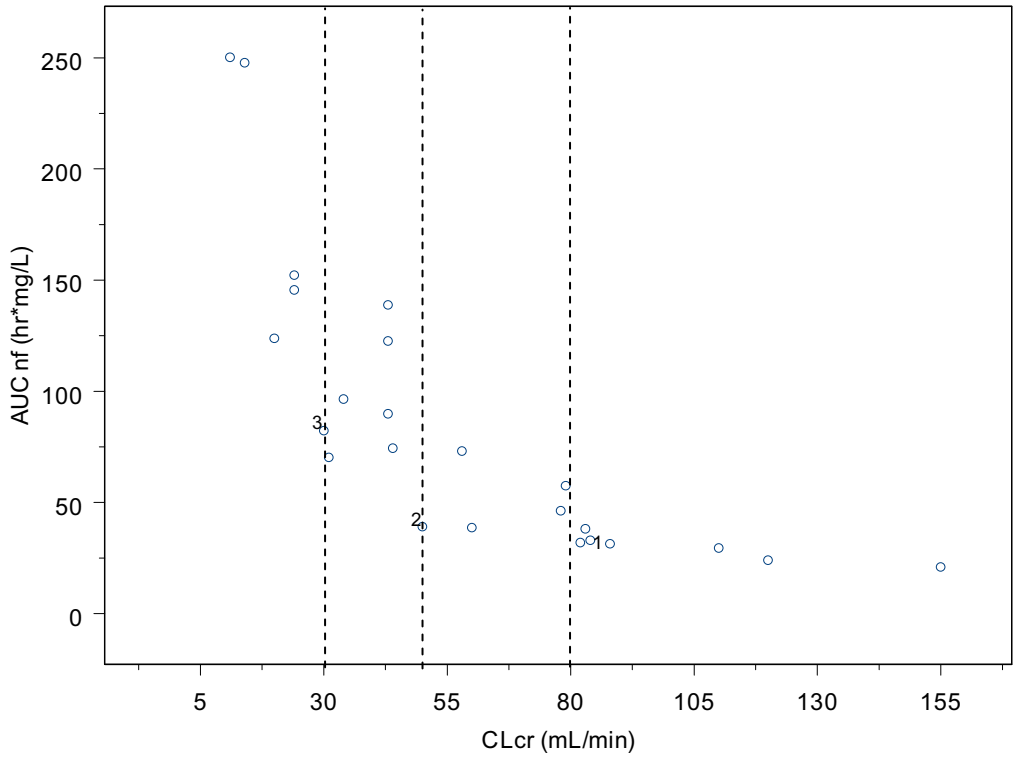
Figure 8 Pirfenidone Plasma Exposure Versus Pre-dose (Day -1) Serum Creatinine Clearance (Vertical Dashed Lines Represent the Creatinine Clearance Cuttoffs for the Four Groups)



[1] Mild renal impairment; [2] Moderate renal impairment; [3] Severe renal impairment

Figure 9 5-Carboxy-Pirfenidone Plasma Exposure Versus Pre-dose (Day -1) Serum Creatinine Clearance (Vertical Dashed Lines Represent the Creatinine Clearance Cuttoffs for the Four Groups)



[1] Mild renal impairment; [2] Moderate renal impairment;[3] Severe renal impairment

2.3.6 Hepatic impairment

Twelve moderate hepatic impaired subjects based on their Child-Pugh scores (7 smokers and 5 non-smokers) and 12 matched healthy subjects (7 smokers and 5 non-smokers) received a single dose 801 mg dose with food. The effect of smoking status upon pirfenidone pharmacokinetics was not statistically significant in this study probably due to small sample size. Therefore, only the group effect (hepatic status) upon pirfenidone pharmacokinetics was investigated and results are presented below. The effect of smoking status upon pirfenidone pharmacokinetics is discussed more in detail in Section 2.4.1.

The systemic exposure (C_{max} and $AUC_{0\text{-}inf}$) to pirfenidone increased ~1.4 to 1.6-fold in subjects with moderate hepatic impairment compared to 12 demographically matched healthy subjects. No difference in AUC to 5-carboxy-pirfenidone was found between the two groups. The effect of mild or severe hepatic impairment on pirfenidone PK has not been studied.

The summary statistical analysis on plasma pharmacokinetic parameters of pirfenidone and its metabolite 5-carboxy-pirfenidone is listed in Table 16 and Table 17.

Table 16 Summary Statistical Analysis of Pharmacokinetic Parameters of Pirfenidone in Healthy and Hepatic Impaired Subjects

Parameter	Geometric Mean (Hepatic Group, Test)	Geometric Mean (Healthy Group, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	16.1	11.4	141	115	173
AUC_{last} (hr×mg/L)	77.0	48.5	159	109	230
$AUC_{0\text{-}inf}$ (hr×mg/L)	78.9	48.9	161	110	237
$T_{1/2}$ (hr)	4.28	2.88	149	108	205

Table 17 Summary Statistical Analysis of Pharmacokinetic Parameters of 5-Carboxy-Pirfenidone in Healthy and Hepatic Impaired Subjects

Parameter	Geometric Mean (Hepatic Group, Test)	Geometric Mean (Healthy Group, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	4.45	5.62	79.1	53.6	117
AUC_{last} (hr×mg/L)	29.9	30.2	99.3	83.0	119
$AUC_{0\text{-}inf}$ (hr×mg/L)	31.1	30.4	102	86.3	121
$T_{1/2}$ (hr)	4.60	3.00	153	110	214
CLr (L/hr)	18.8	20.8	90.6	68.9	119

2.3.7 What pharmacogenetics information is there in the application?

There is no pharmacogenetics information related to clinical pharmacology in the application.

2.3.8 What pregnancy and lactation use information is there in the application

There are no adequate and well-controlled studies of pirfenidone in pregnant women or nursing mothers.

2.3.9 What dosage regimen adjustments, if any, are recommended for each of these groups?

No dose adjustment is needed for age, gender, race, or body weight based upon the findings from covariates analysis in population PK (Section 4.2).

No dose adjustment is needed in patients with mild, moderate, or severe renal impairment eventhough there were ~40 to 50% increase in pirfenidone exposure. In the two pivotal Phase 3 trials, greater than 75% of patients had some degrees of renal insufficiency. Full doses of pirfenidone were administered to these patients for up to 72 Weeks while no apparent relationship between degree of renal insufficiency and incidence of AEs has been reported. However, patients with renal impairment taking pirfenidone should follow dose modification plan proposed by the sponsor. Detail dose modification plan is outlined in the Label.

Use of pirfenidone in patients with end-stage renal disease requiring dialysis is not recommended since the study to assess effect of dialysis upon pirfenidone PK and safety has not been performed.

No dose adjustment is needed in patients with mild (Child Pugh Class A) or moderate (Child Pugh Class B) hepatic impairment. The magnitude of elevation in pirfenidone exposure in subjects with moderate hepatic impairment is similar to those with renal impairment. Based upon the exposure to pirfenidone, no dose adjustment is required. However, it should be noted that patients with underline liver diseases were excluded from the two Phase 3 trials. The long term safety for patients with underline liver diseases taking pirfenidone is unknown. Patients with mild and moderate hepatic impairment should follow the dose modification plan presented in the Label closely. Dose adjustments should be made according to the Label if liver aminotransferase elevation is found.

Use of pirfenidone in patients with severe hepatic impairment (Child Pugh Class C) is not recommended since evaluation of PK and safety has not been conducted in patients with severe hepatic impairment.

2.4 Extrinsic Factors

2.4.1 What extrinsic factors (drugs herbal products, diet, smoking, and alcohol use) influence exposure?

Smoking, a CYP1A2 inducer, is identified as an extrinsic factor that influences the PK of pirfenidone.

Systemic exposure ($AUC_{0\text{-}inf}$ and C_{max}) to single dose pirfenidone is significantly lower in smokers comparing to nonsmokers. $AUC_{0\text{-}inf}$ and C_{max} of pirfenidone in smokers were 46% and 68% of those in nonsmokers, respectively (Table 18). Terminal elimination half-life is significantly shorter in smokers (Table 18).

Similarly, systemic exposure ($AUC_{0\text{-}inf}$) to metabolite 5-carboxy-pirfenidone is significantly lower in the smokers. However, the C_{max} was ~1.2-fold higher with the lower bound of 90% CI greater than 100 (Table 19).

Table 18 Summary Statistical Analysis of Pharmacokinetic Parameters of Pirfenidone in Smokers and Nonsmokers

Parameter	Geometric Mean (Smoker, Test)	Geometric Mean (Nonsmoker, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	5.88	8.68	67.7	59.2	77.5
AUC_{last} (hr×mg/L)	20.5	44.7	45.9	38.6	54.5
$AUC_{0\text{-}inf}$ (hr×mg/L)	20.7	44.9	46.1	38.8	54.7
$T_{1/2}$ (hr)	1.59	2.74	58.2	52.1	65.0
CLr (L/hr)	0.0592	0.0648	91.4	74.8	112

Table 19 Summary Statistical Analysis of Pharmacokinetic Parameters of 5-Carboxy-Pirfenidone in Smokers and Nonsmokers

Parameter	Geometric Mean (Smoker, Test)	Geometric Mean (Nonsmoker, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	7.19	5.79	124	108	143
AUC_{last} (hr×mg/L)	24.6	31.4	78.2	69.6	87.8
$AUC_{0\text{-}inf}$ (hr×mg/L)	24.7	31.7	78.0	69.6	87.5
$T_{1/2}$ (hr)	1.63	2.84	57.3	51.1	64.1
CLr (L/hr)	31.5	24.0	131	114	151

2.4.1 Based upon what are known about exposure-response relationships and their variability, what dosage regimen adjustments, if any, do you recommend for each of these factors?

Smoking should be avoided when using pirfenidone due to the potential for smoking to induce CYP1A2 metabolism resulting in decreased exposure to pirfenidone. Patients should be encouraged to stop smoking before treatment with pirfenidone.

2.4.2 Drug-drug interactions

2.4.2.1 Is the drug a substrate of CYP enzymes?

In vitro studies indicated that pirfenidone mainly metabolized by CYP1A2 (~48%). For details, see Section 2.2.5.6.

There is no study investigating the influences of genetics on metabolism in this submission.

2.4.2.2 Is the drug an inhibitor and/or an inducer of CYP enzymes?

Inhibition

The potential for pirfenidone to inhibit CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A4 was investigated using human liver microsomes in three *in vitro* studies. The IC_{50} was greater than 1000 μM for pirfenidone for all the CYP enzymes evaluated. At 1000 μM, pirfenidone caused direct inhibition of CYP 1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4, of approximately 34%, 27%, 30.4%, 27.5%, 21%, 27%, and 9.6%, respectively. Assuming the observed steady-state mean C_{max} of 79 μM in human subjects receiving the proposed therapeutic dose of 2403 mg/day, as the sponsor stated, the estimated $[I]/IC_{50}$ ratio is ~0.08.

The potential inhibitory effect of pirfenidone upon CYP2C8 has not been evaluated *in vitro* or *in vivo*.

The potential for 5-carboxy-pirfenidone to inhibit CYP1A2, 2A6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5 was also investigated using human liver microsomes. At 500 μM, 5-carboxy-pirfenidone caused inhibition of CYP 1A, 2A6, 2C8/9, 2C19, 2D6, 2E1, and 3A4 of 1.9, -2.9, -8.6, -0.1, 7.6, 2.0, 0.1%. Assuming the observed steady-state mean C_{max} of 79 μM in human subjects receiving the proposed therapeutic dose of 2403 mg/day, as the sponsor stated, the corresponding C_{max} for 5-carboxy-pirfenidone is estimated to be

~44 μM based upon metabolite-to-parent ratio of 0.56. The estimated [I]/IC_{50} ratio is ~0.088. 5-carboxy-pirfenidone is unlikely to cause drug-drug interactions.

Reviewer's Comments:
In vivo drug-drug interaction studies to examine the inhibitory effect of pirfenidone upon CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, 3A4 are not warranted based upon the fact that [I]/IC_{50} calculations for these enzymes are less than 0.1.

There is no information about inhibitory effect of pirfenidone on CYP2C8 available in the submission. Identify in vitro pirfenidone IC_{50} values for this enzyme is recommended.

Concomitant use of pirfenidone with medications of CYP2C8 substrates with narrow therapeutic index is not recommended.

Induction

Pirfenidone is a weak inducer of CYP3A and CYP2C19 at concentrations (250 μM) ~3-fold of the mean maximum therapeutic concentration (C_{max}, 80 μM). Pirfenidone at 50 and 100 μM didn't show potential of CYP3A or CYP2C19 induction. Assuming steady-state C_{max} of 79 μM, it is unlikely that pirfenidone will cause CYP3A or CYP2C19 induction *in vivo* following administration of proposed therapeutic dose of 2403 mg/day.

Table 20 Fold Increases in Microsomal Cytochrome P450 (CYP) Enzyme Activity Following Treatment of Cultured Human Hepatocytes with Pirfenidone (S-7701), 5-Carboxyl-Pirfenidone, or Prototypical Inducers

Treatment	Concentration	7-Ethoxyresorufin *O*-dealkylation[a] (CYP1A2)	Diclofenac 4′-hydroxylation[a] (CYP2C9)	*S*-Mephenytoin 4′-hydroxylation[a] (CYP2C19)	Testosterone 6β-hydroxylation[a] (CYP3A4/5)
DMSO	0.1% (v/v)	1.00 ± 0.08[b]	1.00 ± 0.53[b]	1.00 ± 0.95[b]	1.00 ± 0.14[b]
S-7701	50 μM	1.01 ± 0.22	1.16 ± 0.13	1.07 ± 0.11	1.32 ± 0.21
S-7701	100 μM	1.36 ± 0.40	1.13 ± 0.13	0.830 ± 0.376	1.38 ± 0.34
S-7701	250 μM	1.45 ± 0.48	1.47 ± 0.46	2.20 ± 0.45†	1.87 ± 0.62†
5-carboxylic S-7701	50 μM	1.08 ± 0.23	1.06 ± 0.24	0.672 ± 0.162	0.955 ± 0.207
5-carboxylic S-7701	100 μM	1.07 ± 0.23	1.00 ± 0.16	0.871 ± 0.109	0.842 ± 0.184
5-carboxylic S-7701	250 μM	1.12 ± 0.27	1.02 ± 0.24	0.798 ± 0.236	0.874 ± 0.145
β-Naphthoflavone	33 μM	6.34 ± 1.48*§	1.46 ± 0.15§	2.22 ± 0.75§	0.580 ± 0.477
Rifampin	20 μM	2.11 ± 0.64§	3.02 ± 1.27*	7.01 ± 1.97§	2.96 ± 1.01*§

[a] Values are the mean ± standard deviation of fold increase (rounded to three significant figures) for three human hepatocyte preparations: H374, H376, H380.
[b] %CV = Rate standard deviation ÷ Mean Rate of like treatment samples, calculated instead of standard deviation to give a more realistic representation of variance between control samples.
Mean Fold Increase of like treatment samples = Average of Fold Increase of Average Rate.
Fold increase = Average Rate (pmol/mg/min) ÷ Average Rate (pmol/mg/min) of 0.1% DMSO of appropriate human.
* Significantly different from vehicle control (0.1% DMSO) according to Dunnett's test ($p < 0.05$).
§ Significantly different from vehicle control (0.1% DMSO) according to t-test ($p < 0.05$).
† Significantly different from vehicle control (0.1% DMSO) according to Dunnett's test without prototypical inducers ($p < 0.05$).
DMSO: Dimethyl sulfoxide

A concentration-dependent increase in testosterone 6-beta-hydroxylase activity (up to 1.9 fold in hepatocytes treated with 250 μM pirfenidone) was observed. Pirfenidone appears to be a weak CYP3A4 inducer. At 250 μM, the fold change was greater than 40% (~45%) of the positive control. Pirfenidone at 50 and 100 μM didn't show potential of CYP3A4 induction. Assuming steady-state C_{max} of 79 μM, it is unlikely that pirfenidone will cause CYP3A4 induction *in vivo* following administration of proposed therapeutic dose of 2403 mg/day.

A 2.2-fold increase in *S*-mephenytoin 4'-hydroxylase activity with pirfenidone (250 μM) treatment was reported. Pirfenidone, at 250 μM, is a weak inducer of CYP2C19 with a fold change greater than 40% of the positive control. Pirfenidone at 50 and 100 μM didn't show potential of CYP2C19 induction. Assuming steady-state C_{max} of 80 μM, it is unlikely that pirfenidone will cause CYP2C19 induction *in vivo* following administration of proposed therapeutic dose of 2403 mg/day.

5-Carboxy-pirfenidone, at concentration of 250 µM, does not appear to be an inducer of CYP1A2, 2C9, 2C19 or 3A4/5.

2.4.2.3 Is the drug a substrate and/or an inhibitor of P-glycoprotein transport processes?

Due to the high passive permeability of the pirfenidone (Table 21), a conclusion regarding potential transport by P-gp cannot be drawn. The polarization ratio of approximately 1 could indicate either lack of test article transport by P-gp, or the masking of such transport by the high passive permeability.

It is unlikely that pirfenidone to be a P-gp substrate based upon the finding that the mean net flux ratios ($Permeability_{app, B A}$/$Permeability_{app, A B}$) were 1.1, 1.2, and 1.2 at pirfenidone concentrations of 10, 100, 1000 µM pirfenidone test systems, respectively (Table 21).

Table 21 Permeability Results of [^{14}C]-Pirfenidone

Test article ID	Nominal conc [uM]	Observed conc [uM]	Incubation time [min]	Papp [cm/sec] A to B				Papp [cm/sec] B to A				Polarization Ratio [B-A/A-B]
							mean				mean	
pirfenidone	10	9.4	90	3.4E-05	3.2E-05	3.0E-05	3.2E-05	3.1E-05	3.6E-05	3.5E-05	3.4E-05	**1.1**
pirfenidone	100	98	90	3.0E-05	2.9E-05	2.8E-05	2.9E-05	3.1E-05	3.5E-05	3.6E-05	3.4E-05	**1.2**
pirfenidone	1000	994	90	2.8E-05	2.7E-05	2.7E-05	2.7E-05	3.0E-05	3.4E-05	3.5E-05	3.3E-05	**1.2**
Positive Controls / Comparators												
digoxin	5		90	1.2E-06	1.4E-06	1.4E-06	1.4E-06	1.3E-05	1.3E-05	1.6E-05	1.4E-05	**10.4**
propranolol	50		90	8.8E-06	8.8E-06	1.0E-05	9.2E-06	-	-	-	-	-
mannitol	50		90	3.4E-07	3.6E-07	3.4E-07	3.5E-07	-	-	-	-	-

The potential for pirfenidone to inhibit P-gp mediated transport of digoxin (5.0 µM) was evaluated in the absence and presence of pirfenidone at concentrations ranging from 1 to 1000 µM. Pirfenidone showed weak inhibition (10 to 30%) of P-gp facilitated digoxin B-A efflux at concentrations of 100 µM and above (Table 22). The IC_{50} value was estimated to be greater than 1000 µM. The estimated $[I_2]/IC_{50}$ is ~17.3, exceeding the value of 10.[3] Therefore, the potential of pirfenidone to interact with P-gp substrate *in vivo* can not be ruled out.

Reviewer's Comments:

Identifying pirfenidone IC_{50} values for P-gp inhibition is recommended. Concomitant use of pirfenidone with medications known to P-gp substrates (e.g. digoxin) with narrow therapeutic index should be cautious.

Table 22 Inhibition of Digoxin Efflux by Pirfenidone

Test article ID	Nominal conc [uM]	Incubation time [min]	Papp [cm/sec] A to B			Papp [cm/sec] B to A			Efflux Ratio [B-A/A-B]	% Inhibtion
digoxin 5 uM	5.0	90	1.3E-06	1.4E-06	1.4E-06	1.2E-05	1.3E-05	1.3E-05	9.2	
dig5 + ketoconazole 25 uM	5.0	90	4.3E-06	4.6E-06	6.5E-06	5.2E-06	6.1E-06	6.9E-06	1.0	100%
dig5 + cyclosporine 10 uM	5.0	90	4.3E-06	7.0E-06	5.4E-06	5.3E-06	5.5E-06	6.7E-06	1.1	98%
dig5 + pirfenidone 1 uM	5.0	90	1.4E-06	1.5E-06	1.5E-06	1.2E-05	1.3E-05	1.3E-05	8.6	7%
dig5 + pirfenidone 3 uM	5.0	90	1.4E-06	1.4E-06	1.4E-06	1.3E-05	1.3E-05	1.4E-05	9.5	-4%
dig5 + pirfenidone 10 uM	5.0	90	1.3E-06	1.4E-06	1.4E-06	1.3E-05	1.3E-05	1.4E-05	9.7	-7%
dig5 + pirfenidone 30 uM	5.0	90	1.5E-06	1.4E-06	1.5E-06	1.4E-05	1.4E-05	1.4E-05	9.7	-6%
dig5 + pirfenidone 100 uM	5.0	90	1.6E-06	1.5E-06	1.5E-06	1.1E-05	1.2E-05	1.3E-05	7.7	18%
dig5 + pirfenidone 300 uM	5.0	90	1.5E-06	1.4E-06	1.5E-06	1.3E-05	1.2E-05	1.2E-05	8.3	10%
dig5 + pirfenidone 1000 uM	5.0	90	1.8E-06	1.9E-06	1.9E-06	1.3E-05	1.2E-05	1.3E-05	6.8	29%
Permeability Comparators										
Propranolol (50 uM)	50	90	8.5E-06	9.1E-06	9.0E-06					
Mannitol (50 uM)	50	90	5.9E-07	m.s.	6.5E-07					

m.s. - missing sample (data point censored, suspected experimental error)

2.4.2.4 Are there any *in vivo* drug-drug interaction studies that indicate that exposure are different when drugs are co-administered?

Effect of fluvoxamine on pirfenidone

Following repeated oral doses (10 day) of fluvoxamine (50 mg qhs for 3 days; 50 bid for 3 days, and 50 qam and 100 mg qhs for 4 days), a strong CYP1A2 inhibitor, systemic exposure (C_{max} and $AUC_{0\text{-}inf}$) to pirfenidone increased significantly (1.7 and 4-fold, respectively) in healthy nonsmoking subjects (Table 23). The C_{max} of 5-carboxy-pirfenidone was significantly decreased without significant change in AUC in healthy nonsmoking subjects (Table 24). The mean metabolite-to-parent ratio was decreased from 0.64 to 0.17 following the fluvoxamine treatment, indicating that the increase in exposure to pirfenidone is a result of fluvoxamine inhibition on pirfenidone metabolism. For details, see Section 4.4.3.

Larger fold change in systemic exposure was observed in smokers following the fluvoxamine treatment. Systemic exposure (C_{max} and $AUC_{0\text{-}inf}$) to pirfenidone increased significantly (2.4 and 7-fold, respectively) in smokers (Table 25). However, it should be noted that the greater fold changes in systemic exposure observed in smoker is primarily due to the decreased baseline (pre-fluvoxamine treatment) exposure of C_{max} and AUC. Following the treatment, the absolute values of C_{max} and AUC of pirfenidone between smokers and nonsmokers were similar. C_{max} of 5-carboxy-pirfenidone was significantly decreased without significant change in AUC following fluvoxamine treatment (Table 26). The mean metabolite-to-parent ratio was decreased from 1.14 to 0.17, indicating that the increase in exposure to pirfenidone in smokers is a result of fluvoxamine inhibition on pirfenidone metabolism. For details, see Section 4.4.3.

Table 23 Summary Statistical Analysis of Pirfenidone Exposure in the Presence and Absence of Fluvoxamine in Nonsmokers

Parameter	Geometric Mean (Post-Fluvoxamine, Test)	Geometric Mean (Pre-fluvoxamine, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	14.7	8.68	170	156	184
AUC_{last} (hr×mg/L)	167	44.7	374	336	416
$AUC_{0\text{-}inf}$ (hr×mg/L)	180	44.9	400	359	446

Table 24 Summary Statistical Analysis of 5-Carboxy-Pirfenidone Exposure in the Presence and Absence of Fluvoxamine in Nonsmokers

Parameter	Geometric Mean (Post-Fluvoxamine, Test)	Geometric Mean (Pre-fluvoxamine, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	2.37	5.79	41.0	35.4	47.4
AUC_{last} (hr×mg/L)	30.4	31.4	97.0	84.7	111
$AUC_{0\text{-}inf}$ (hr×mg/L)	33.5	31.7	106	92.3	121

Table 25 Summary Statistical Analysis of Pirfenidone Exposure in the Presence and Absence of Fluvoxamine in Smokers

Parameter	Geometric Mean (Post-Fluvoxamine, Test)	Geometric Mean (Pre-fluvoxamine, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	13.8	5.88	235	207	268
AUC_{last} (hr×mg/L)	141	20.5	688	576	821
$AUC_{0\text{-}inf}$ (hr×mg/L)	148	20.7	717	597	860

Table 26 Summary Statistical Analysis of 5-Carboxy-Pirfenidone Exposure in the Presence and Absence of Fluvoxamine in Smokers

Parameter	Geometric Mean (Post-Fluvoxamine, Test)	Geometric Mean (Pre-fluvoxamine, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	2.28	7.19	31.7	28.3	35.6
AUC_{last} (hr×mg/L)	26.0	24.6	106	95.8	117
$AUC_{0\text{-}inf}$ (hr×mg/L)	27.6	24.7	112	101	124

Reviewer's comments: Fluvoxamine inhibits not only CYP1A2, but also inhibits other CYP enzymes. Fluvoxamine is not recommended in co-administration with pirfenidone based upon the fact that a 4-fold increase in systemic exposure and there is not enough safety data to provide the safety margin with this magnitude of increase in exposure. Other weak, moderate, strong CYP1A2 inhibitors should be use with caution because the PK and safety has not been studied under these circumstances.

2.5 General Biopharmaceutics

2.5.1 Based on BCS principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Pirfenidone is a high permeable (Table 21) and high soluble (Table 27) compound, which puts it into BCS class I.

Permeability of pirfenidone

The *in vitro* permeability of pirfenidone was determined using Caco-2 cells. Apical to basal (A to B) transport of [^{14}C]-pirfenidone was studied at 10, 100, 1000 µM. The apparent permeability of pirfenidone was 3.2E-05, 2.9E-05, and 2.7E-05 at concentration 10, 100, and 1000 µM, respectively (Table 21). At all three concentrations, the A to B permeability of pirfenidone was greater than that of the high permeability comparator propranolol. Pirfenidone is therefore classified as a high permeability compound.

Solubility of Pirfenidone

Over a pH range of 1 – 10, pirfenidone has a consistent solubility profile in the range of 19-22 mg/mL (Table 11). It is more soluble in methanol, ethyl alcohol, acetone and chloroform than in water and 1.0 N HCl. The solubility of pirfenidone in various solvent is presented in Table 27.

Table 27 Solubility of Pirfenidone in Various Solvent

Parameter	Results
Solubility at 25°C	
Acetone, acetonitrile, chloroform, dimethoxyethane, dimethylformamide, dimethylsulfoxide, ethanol, ethyl acetate, isopropyl alcohol, methanol, toluene	77 to 100 mg/mL (at 48 h)
Triethylamine	5 mg/mL
Water	19 mg/mL

Dissolution of Pirfenidone

The dissolution parameters of pirfenidone are shown in Table 28 and Table 29.

Table 28 Dissolution Parameters

Dissolution Apparatus	USP Apparatus II (Paddle)
Media	Deionized water
Media Volume	1000 mL
Media Temperature	37.0°C ± 0.5°C
Paddle Speed	50 RPM
Detection Method	
UV cell	2.0 mm path length
Wavelength	318 nm

mL = milliliter; mm = millimeter; nm = nanometer; RPM = rotations per minute; UV = ultraviolet;
°C = degree Celsius (centigrade)
[a] Dissolution is conducted using a sinker

Table 29 Dissolution Profiles of 267-mg Pirfenidone Capsules in (b) (4) and Deionzed Water (b) (4)) Media

Time (minutes)	% Pirfenidone Dissolved[a]	
	(b) (4)	DI Water (b) (4) (b) (4)
5		
10		
20		
30		
60		

DI = deionized
[a] Batch 0801545.

2.5.2 What is the relative bioavailability of the proposed to-be-marketed formulation to the pivotal clinical trials?

The proposed to-be-marketed formulation of pirfenidone is same as that used in the pivotal clinical trials.

2.5.3 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

The effect of food on PK of pirfenidone was evaluated following a single oral dose of 801 mg pirfenidone in 16 healthy older adult volunteers (50-79 years of age). Administration with high fat breakfast resulted

in a ~49% decrease in pirfenidone C_{max} and a ~16% reduction in $AUC_{0\text{-}inf}$ (Table 31). The rate of pirfenidone absorption slowed with food, as indicated by increased median T_{max} (range) from 0.500 (0.500 to 4.00) hour to 3.50 (1.00 to 6.00) hours (Table 30). Since taking pirfenidone with food reduces the incidence of nausea and dizziness based upon sponsor's analysis, and the Phase 3 clinical trials were conducted with pirfenidone administrated with food, pirfenidone should be given with meals.

Table 30 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone and 5-Carboxy-Pirfenidone Following Single Oral Dose of 801 mg in Healthy Subjects

Pirfenidone PK Parameters	Pirfenidone		5-Carboxy-Pirfenidone	
	Fed	Fasted	Fed	Fasted
N	16	16	16	16
AUC_{last} (hr×mg/L)**	58.8 (22.2)	67.5 (20.4)	34.3 (7.03)	35.9 (7.53)
$AUC_{0\text{-}inf}$ (hr×mg/L)	59.2 (22.3)	68.1 (20.5)	34.6 (7.04)	36.4 (7.43)
C_{max} (mg/mL)	7.87 (2.30)	15.7 (4.80)	4.62 (1.13)	7.22 (3.39)
T_{max} (hr) [a]	3.50 [1.00 – 6.00]	0.5 [0.5 – 4.00]	4.00 [1.00 – 6.00]	1.00 [0.5 – 4.00]
$T_{1/2}$ (hr)	3.16 (0.960)	3.03 (0.996)	3.27 (1.00)	3.26 (1.04)
CL/F (L/hr)	15.9 (7.87)	12.9 (4.52)	n.a.	n.a.
Vz/F (L)	65.4 (15.8)	52.6 (12.4)	n.a.	n.a.
M:P ratio	0.566 (0.208)	0.494 (0.154)	n.a.	n.a.

[a] median [range]
n.a. not applicable

Table 31 Summary Statistical Analysis of Pirfenidone Exposure under Fasted and Fed Status Following Single Oral Dose of 801 mg Pirfenidone

Parameter	Geometric Mean (Fed, Test)	Geometric Mean (Fasted, Reference)	Ratio of Geometric Mean (%) (Test/Reference)	90% CI, Lower	90% CI, Upper
N	16	16	16	16	16
$AUC_{0\text{-}inf}$ (hr×mg/L)	55.0	65.1	84.5	77.3	99.2
C_{max} (mg/L)	7.58	14.9	50.9	41.9	61.7

2.6 Analytical Section

2.6.1 What bioanalytical methods are used to assess concentrations?

Pirfenidone, 5-carboxy-pirfenidone, 5-hydroxymethyl-pirfenidone, and 4'-hydroxy-pirfenidone in human plasma and urine was analyzed by a validated liquid chromatography-mass spectrometry/mass spectrometry (LC-MS/MS) method developed and qualified by (b) (4) Identical LC-MS/MS methods were used for all pharmacokinetic studies.

The results are acceptable as evidenced by QC sample precision and accuracy within ± 15%.

Bioanalytical methods, matrices, and analytes evaluated in pharmacokinetic studies are shown in Table 32. Summary of plasma and urine bioanalytical validation methods are listed in Table 33 and Table 34. The results of sample analyses in individual studies are provided in Table 35 and Table 36.

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Table 32 Bioanalytical Methods, Matrices, and Analytes Evaluated in Pharmacokinetic Studies

Clinical Study Number	Study Title	Sample Matrix	Analytes	Bioanalytical Method (Bioanalytical Method Validation Report)
PIPF-004	A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-Arm Study of the Safety and Efficacy of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis	Plasma	Pirfenidone 5-Carboxy-pirfenidone	**Plasma**: Study: AA20773-01: Bioanalytical method for the determination of pirfenidone, 5-Hydroxymethyl-pirfenidone, 5-carboxy-pirfenidone and 4′-hydroxy-pirfenidone in human EDTA plasma Study: AA20773-01: Validation of an LC-MS/MS Method for the Determination of Pirfenidone, 5-Hydroxymethyl-pirfenidone, 5-Carboxy-pirfenidone, and 4′-Hydroxy-pirfenidone in Human Plasma [EDTA] **Urine**: Study: AA20773-02: Bioanalytical method for the determination of pirfenidone, 5-Hydroxymethyl-pirfenidone, 5-carboxy-pirfenidone, and 4′-hydroxy-pirfenidone in human urine Study: AA20773-02: Validation of an LC-MS/MS Method for the Determination of Pirfenidone, 5-Hydroxymethyl-pirfenidone, 5-Carboxy-pirfenidone, and 4′-Hydroxy-pirfenidone in Human Urine
PIPF-005	The Pharmacokinetics of Oral Pirfenidone in Healthy Older Adults, Including Effects of Multiple-Dosing, Dose-Ranging, Food and Antacids	Plasma and Urine	Pirfenidone 5-Hydroxymethyl-pirfenidone 5-Carboxy-pirfenidone 4′-Hydroxy-pirfenidone	
PIPF-007	A Double-Blind, Randomized, Parallel Study to Define the Electrocardiographic Effects of Oral Pirfenidone using a Clinical and Supratherapeutic Dose Compared to Placebo and Moxifloxacin (an Open-Label Positive Control) in Healthy Volunteers			
PIPF-009	An Open-Label Phase 1 Study to Determine the Pharmacokinetics and Safety of Pirfenidone in Subjects with Renal Insufficiency		Pirfenidone 5-Carboxy-pirfenidone	
PIPF-010	An Open-Label Phase 1 Study to Determine the Impacts of a Strong CYP1A2 Inhibitor and a CYP1A2 Inducer on the Pharmacokinetics and Safety of Pirfenidone in Healthy Subjects			
PIPF-011	An Open-Label Phase 1 Study to Determine the Pharmacokinetics and Safety of Pirfenidone in Subjects with Hepatic Insufficiency			

Table 33 Plasma Bioanalytical Method Validation Summary

Attribute	Pirfenidone	5-Hydroxymethyl-Pirfenidone	5-Carboxy-Pirfenidone	4'-Hydroxy-Pirfenidone
Standard Concentrations (ng/mL)	30.0, 60.0, 150, 300, 600, 1800, 2700, 3000	15.0, 30.0, 75.0, 150, 300, 900, 1350, 1500	30.0, 60.0, 150, 300, 600, 1800, 2700, 3000	10.0, 20.0, 50.0, 100, 200, 600, 900, 1000
Linear Range (ng/mL)	30.0–3000	15.0–1500	30.0–3000	10.0–1000
Correlation Coefficient (r)	>0.999	>0.997	>0.998	>0.995
Accuracy Across Standard Curve Concentrations (%)	99.3–101	96.0–102	98.2–101	98.0–104
Recovery (%)	30 ng/mL: 81 300 ng/mL: 80 3000 ng/mL: 72 Internal standard: 72	15.0 ng/mL: 88 150 ng/mL: 84 1500 ng/mL: 86 Internal standard: 77	30 ng/mL: 90 300 ng/mL: 87 3000 ng/mL: 89 Internal standard: 81	10.0 ng/mL: 94 100 ng/mL: 89 1000 ng/mL: 93 Internal standard: 79
LLOQ (ng/mL)	30.0	15.0	30.0	10.0
Intra-Batch Precision (%CV) at LLOQ	2.2–8.0	1.7–6.7	2.7–6.2	5.0–9.5
Inter-Batch Precision (%CV) at LLOQ	4.7	5.6	5.3	8.4
Intra-Batch Accuracy (% of nominal) at LLOQ	99.0–105	94.7–105	95.3–103	96.1–106
Inter-Batch Accuracy (% of nominal) at LLOQ	101	101	99.0	101
QC Concentrations (ng/mL)	90.0, 1000, 2250	45.0, 500, 1130	90.0, 1000, 2250	30, 250, 750
Intra-Batch Precision (%CV) of Quality Control Samples at Low, Medium, and High	Low: 1.6–3.8 Medium: 1.7–2.9 High: 1.5–3.8	Low: 1.7–7.1 Medium: 2.8–4.3 High: 1.6–3.5	Low: 2.1–3.0 Medium: 1.8–2.6 High: 1.2–4.0	Low: 3.7–6.1 Medium: 2.3–8.2 High: 3.1–6.7
Inter-Batch Precision (%CV) of Quality Control Samples at Low, Medium, and High	Low: 3.8 Medium: 2.4 High: 3.2	Low: 4.7 Medium: 4.6 High: 6.1	Low: 4.8 Medium: 3.9 High: 5.1	Low: 5.3 Medium: 6.7 High: 5.1
Intra-Batch Accuracy (% of nominal) of Quality Control Samples at Low, Medium, and High	Low: 95.9–105 Medium: 99.5–103 High: 98.2–104	Low: 100–106 Medium: 95.2–103 High: 92.9–109	Low: 94.3–105 Medium: 94.2–103 High: 95.6–108	Low: 98.3–106 Medium: 90.8–103 High: 92.1–100

Attribute	Pirfenidone	5-Hydroxymethyl-Pirfenidone	5-Carboxy-Pirfenidone	4'-Hydroxy-Pirfenidone
Inter-Batch Accuracy (% of nominal) of Quality Control Samples at Low, Medium, and High	Low: 102 Medium: 102 High: 101	Low: 102 Medium: 98.4 High: 100	Low: 101 Medium: 100 High: 103	Low: 101 Medium: 96.4 High: 97.6
Selectivity (fluvoxamine concentration of 300 ng/mL), % Recovery (%CV)	90 ng/mL: 97.1 (8.3) 2250 ng/mL: 96.9 (2.2)	Not Tested	90 ng/mL: 97.2 (7.0) 2250 ng/mL: 94.2 (3.6)	Not Tested

Table 34 Urine Bioanalytical Method Validation Summary

Attribute	Pirfenidone	5-Hydroxymethyl-Pirfenidone[a]	5-Carboxy-Pirfenidone	4'-Hydroxy-Pirfenidone
Standard Concentrations (ng/mL)	0.250, 0.500, 1.00, 2.00, 5.0, 10.0, 40.0, 50.0	25.0, 50.0, 100, 200, 500, 1000, 4000, 5000	25.0, 50.0, 100, 200, 500, 1000, 4000, 5000	12.5, 25.0, 50.0, 100, 250, 500, 2000, 2500
Linear Range (ng/mL)	0.250–50.0	25.0–5000	25.0–5000	12.5–2500
Correlation Coefficient (r)	>0.997	>0.998	>0.997	>0.994
Accuracy Across Standard Curve Concentrations (%)	97.5–102	98.4–101	97.5–103	96.4–104
Recovery (%)	0.250 ng/mL: 85 5.00 ng/mL: 83 50.0 ng/mL: 86 Internal standard: 80	25.0 ng/mL: 77 500 ng/mL: 68 5000 ng/mL: 69 Internal standard: 69	25.0 ng/mL: 83 500 ng/mL: 82 5000 ng/mL: 87 Internal standard: 83	12.5 ng/mL: 92 250 ng/mL: 87 2500 ng/mL: 90 Internal standard: 87
LLOQ (ng/mL)	0.250	25.0	25.0	12.5
Intra-Batch Precision (%CV) at LLOQ	5.6–14.5	2.4–5.2	2.0–8.3	4.1–12.5
Inter-Batch Precision (%CV) at LLOQ	12.3	5.4	5.6	9.4
Intra-Batch Accuracy (% of nominal) at LLOQ	94.0–115	92.4–104	99.2–106	93.6–106
Inter-Batch Accuracy (% of nominal) at LLOQ	106	99.2	102	101
QC Concentrations (ng/mL)	0.750, 7.50, 37.5	75.0, 750, 3750	75.0, 750, 3750	37.5, 375, 1880
Intra-Batch Precision (%CV) of Quality Control Samples at Low, Medium, and High	Low: 2.3–4.2 Medium: 2.0–5.4 High: 2.7–5.0	Low: 2.5–4.8 Medium: 1.9–4.1 High: 1.1–4.3	Low: 1.7–4.6 Medium: 2.1–5.0 High: 2.2–5.9	Low: 1.4–8.6 Medium: 3.0–6.0 High: 2.8–7.3
Inter-Batch Precision (%CV) of Quality Control Samples at Low, Medium, and High	Low: 4.2 Medium: 4.9 High: 3.7	Low: 4.0 Medium: 3.7 High: 2.5	Low: 4.0 Medium: 4.4 High: 4.4	Low: 6.0 Medium: 6.1 High: 5.9
Intra-Batch Accuracy (% of nominal) of Quality Control Samples at Low, Medium, and High	Low: 97.2–105 Medium: 96.0–105 High: 95.5–99.7	Low: 97.5–102 Medium: 96.9–103 High: 96.3–98.7	Low: 97.9–106 Medium: 96.3–103 High: 96.3–102	Low: 94.7–103 Medium: 94.7–106 High: 93.1–105
Inter-Batch Accuracy (% of nominal) of Quality Control Samples at Low, Medium, and High	Low: 100 Medium: 99.2 High: 97.9	Low: 99.6 Medium: 99.2 High: 97.3	Low: 101 Medium: 99.7 High: 98.7	Low: 99.5 Medium: 99.5 High: 98.4
Selectivity (fluvoxamine concentration of 4.00 µg/mL), % Recovery (%CV)	0.750 ng/mL; 105 (2.7) 37.5 ng/mL: 100 (1.6)	Not Tested	75.0 ng/mL: 105 (3.9) 3750 ng/mL: 98.1 (4.1)	Not Tested

Table 35 Plasma and Urine Assay Parameters for Pirfenidone and 5-Carboxy-Pirfenidone by Studies

Biometrics	**Plasma**		**Urine**	
Parameters	Pirfenidone	5-Carboxy-Pirfenidone	Pirfenidone	5-Carboxy-Pirfenidone
PIPF-005				
Lower Limit of Quantitation (ng/mL)	30.0	30.0	0.250	25.0
Assay Range (ng/mL)	30.0 to 3000	30.0 to 3000	0.250 to 50.0	25.0 to 5000
Linearity (correlation coefficient)	≥0.9937	≥0.9862	≥0.9914	≥0.9948
Precision (%CV)	3.6 to 6.5	3.4 to 4.9	4.8 to 8.6	4.2 to 8.5
Accuracy (% difference from theoretical)	-0.4 to 5.4	1.0 to 3.0	-1.1 to 2.4	-0.5 to 3.5
PIPF-007				
Lower Limit of Quantitation (ng/mL)	30.0	30.0	n.a.	n.a.
Assay Range (ng/mL)	30.0 to 3000	30.0 to 3000	n.a.	n.a.
Linearity (correlation coefficient)	≥0.9958	≥0.9933	n.a.	n.a.
Precision (%CV)	2.9 to 5.5	3.6 to 4.6	n.a.	n.a.
Accuracy (% difference from theoretical)	-0.4 to 2.0	-0.4 to 5.2	n.a.	n.a.
PIPF-009				
Lower Limit of Quantitation (ng/mL)	30.0	30.0	0.250	25.0
Assay Range (ng/mL)	30.0 to 3000	30.0 to 3000	0.250 to 50.0	25.0 to 5000
Linearity (correlation coefficient)	≥0.9976	≥0.9907	≥0.9923	≥0.9893
Precision (%CV)	1.2 to 3.7	3.4 to 4.7	2.3 to 4.6	3.9 to 11.8
Accuracy (% difference from theoretical)	-1.8 to 3.0	-2.2 to 3.4	-2.4 to 7.5	-4.5 to 11.5
PIPF-010				
Lower Limit of Quantitation (ng/mL)	30.0	30.0	0.250	25.0
Assay Range (ng/mL)	30.0 to 3000	30.0 to 3000	0.250 to 50.0	25.0 to 5000
Linearity (correlation coefficient)	≥0.9963	≥0.9929	≥0.9917	≥0.9887
Precision (%CV)	1.7 to 2.3	3.0 to 4.3	2.8 to 4.3	3.4 to 5.1
Accuracy (%	-1.8 to 2.0	-0.4 to 1.6	1.9 to 4.3	-5.9 to 6.1

difference from theoretical)				
PIPF-011				
Lower Limit of Quantitation (ng/mL)	30.0	30.0	0.250	25.0
Assay Range (ng/mL)	30.0 to 3000	30.0 to 3000	0.250 to 50.0	25.0 to 5000
Linearity (correlation coefficient)	≥0.9946	≥0.9922	≥0.9967	≥0.9884
Precision (%CV)	2.2 to 2.5	2.7 to 4.4	2.0 to 4.5	2.5 to 3.6
Accuracy (% difference from theoretical)	-1.8 to 3.1	-1.8 to 2.1	-0.3 to 4.4	-4.5 to 7.6

n.a. Not applicable

Table 36 Plasma and Urine Assay Parameters for 4'-Hydroxy-Pirfenidone and 5-Hydroxymethyl-Pirfenidone in Study PIPF-005

Biometrics	**Plasma**		**Urine**	
Parameters	4'-Hydroxy-Pirfenidone	5-Hydroxymethyl-Pirfenidone	4'-Hydroxy-Pirfenidone	5-Hydroxymethyl-Pirfenidone
PIPF-005				
Lower Limit of Quantitation (ng/mL)	10.0	15.0	12.5	25.0
Assay Range (ng/mL)	10.0 to 1000	15.0 to 1500	12.5 to 2500	25.0 to 5000
Linearity (correlation coefficient)	≥0.9916	≥0.9944	≥0.9922	≥0.9960
Precision (%CV)	5.8 to 6.6	3.8 to 5.3	7.2 to 11.1	4.2 to 4.9
Accuracy (% difference from theoretical)	2.8 to 6.3	-0.8 to 2.0	-2.1 to 2.7	-2.1 to 0.7

2.7 References

1 **Pulmonary-Allergy Drugs Advisory Committee Briefing Package. Web site. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PulmonaryAllergyDrugsAdvisoryCommittee/UCM206398.pdf. Accessed March 30, 2010.**

2 **American Thoracic Society: Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment International Consensus Statement. Am J Respir Crit Care Med 161:646–664, 2000**

3 **FDA Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, and Implications for Dosing and Labeling. September 11, 2006**

3 Detailed Labeling Recommendations

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

4 Appendix

4.1 Cover Sheet and OCPB Filing/Review Form

18 Pages Have Been Withheld As A Duplicate Copy Of The "OCPB Filing Review Form" dated December 31, 2009 Which Is Located In This Clinical Pharmacology Review Section Of This NDA Approval Package.

4.2 Consult Reviews

4.2.1 Pharmacometric Review

OFFICE OF CLINICAL PHARMACOLOGY:
PHARMACOMETRIC REVIEW

1 SUMMARY OF FINDINGS

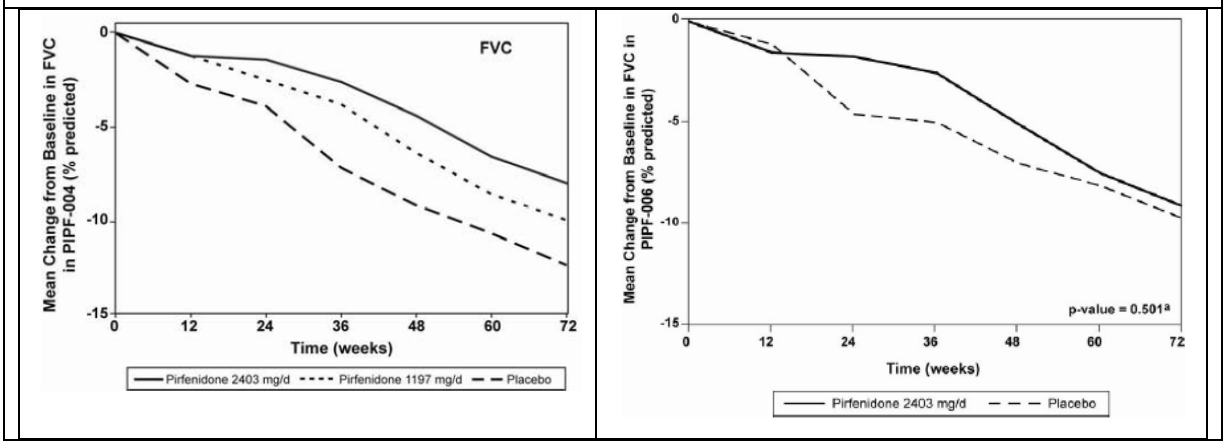
1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1 Is there a relationship between dose/exposure and benefit?

The primary outcome variable in study PIPF-004, PIPF-006 was change in lung function, measured by percent predicted FVC (Forced Vital Capacity) as shown in Figure 1. PIPF-004 showed that 2403 mg/day has greater efficacy than 1197 mg/day. However in PIPF-006, there was no difference between placebo and 2403 mg/day.

Figure 1. (A) **Mean Change from Baseline in Percent Predicted FVC in PIPF-004 (B) Mean Change from Baseline in Percent Predicted FVC in PIPF-006.**



The sponsor's exposure-efficacy analyses showed conflicting results on two different efficacy endpoints (FVC and PFS(Progression-Free Survival)). Sponsor attributed these results to sampling bias, patient self-selection, and the smaller sample size. The reviewer did not derive any conclusions from the relationship between AUC, Cmin of pirfenidone and efficacy measures since pharmacokinetics of pirfenidone was only characterized in a subset of patients in Study PIPF-004 (88 out of 261 patients in pirfendione arms).

1.1.2 Is there a relationship between dose/exposure and risk?

Table 1 shows the dose dependency of treatment-emergent adverse events (gastrointestinal side effects, photosensitivity reaction or rash) in study PIPF-004 (Placebo, 1197 and 2403 mg/day). Given the obvious dose-response relationship, the relationship between pharmacokinetic exposure of pirfenidone and safety measures was not explored.

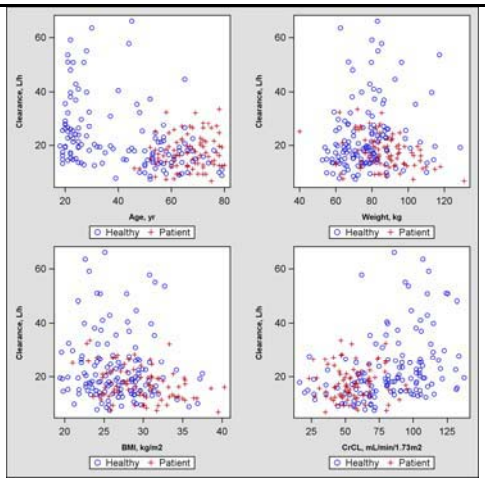
Table 1. Treatment-Emergent Adverse Events Reported in ≥5% of Patients in Any Treatment Group (All Randomized Patients)

	Number of Patients, n (%)		
System Organ Class Preferred Term	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 174)	Placebo (N = 174)
Skin and Subcutaneous Tissue Disorders	45 (51.7%)	105 (60.3%)	62 (35.6%)
Rash	15 (17.2%)	53 (30.5%)	18 (10.3%)
Photosensitivity reaction	6 (6.9%)	25 (14.4%)	2 (1.1%)
Gastrointestinal Disorders	59 (67.8%)	137 (78.7%)	104 (59.8%)
Nausea	22 (25.3%)	60 (34.5%)	32 (18.4%)
Diarrhoea	22 (25.3%)	43 (24.7%)	30 (17.2%)
Dyspepsia	12 (13.8%)	30 (17.2%)	16 (9.2%)
GERD	11 (12.6%)	26 (14.9%)	14 (8.0%)
Vomiting	11 (12.6%)	24 (13.8%)	7 (4.0%)
Constipation	9 (10.3%)	16 (9.2%)	13 (7.5%)
Abdominal pain	6 (6.9%)	16 (9.2%)	7 (4.0%)
Abdominal pain upper	9 (10.3%)	15 (8.6%)	15 (8.6%)
Abdominal distension	3 (3.4%)	15 (8.6%)	12 (6.9%)
Stomach discomfort	4 (4.6%)	14 (8.0%)	4 (2.3%)
Flatulence	8 (9.2%)	9 (5.2%)	8 (4.6%)

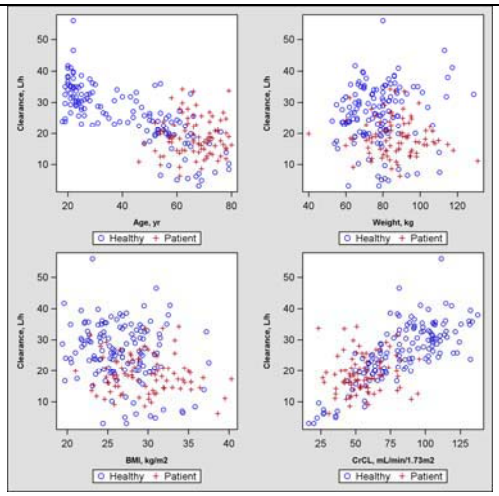
1.1.3 Are there differences in pharmacokinetics between healthy subjects and patients with idiopathic pulmonary fibrosis(IPF)?

No. Figure 2 shows the relationship between clearance of pirfenidone, metabolite (5-carboxy pirfenidone) and age, body weight, bmi, renal function (CrCL). The clearance of pirfenidone and 5-carboxy pirfenidone in age matched group of healthy and patients with IPF is similar.

Figure 2. (A) Relationship between clearance of pirfenidone and age, weight, body mass index (BMI) and Creatinine clearance (CrCL) (B) Relationship between clearance of 5-carboxy pirfenidone and age, weight, body mass index (BMI) and Creatinine clearance (CrCL).



(A)



(B)

1.2 Recommendations

NA

1.3 Label Statements

Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

Please refer to the review by Dr Elizabeth Shang for labeling language.

2 PERTINENT REGULATORY BACKGROUND

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is being developed as a treatment for patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function. The mechanism of action of pirfenidone has not been fully established; however, data from in vitro and animal models suggest pirfenidone has both anti-inflammatory and antifibrotic activity, mediated through TNF-α and TGF-β, respectively. The proposed to-be-marketed dose of pirfenidone is 2403 mg/d, administered orally as 3 immediate-release 267-mg hard gelatin capsules 3 times daily. Sponsor conducted population pharmacokinetic analysis of the data using S-ADAPT®. The population for this analysis consisted of pirfenidone-treated subjects from four Phase 1 studies (PIPF-005, PIPF-007, PIPF-009, and PIPF-010) and one Phase 3 study (PIPF-004) in patients with IPF.

3 RESULTS OF SPONSOR'S ANALYSIS

The summary of the Phase 1 and Phase 3 studies in which pharmacokinetics of pirfenidone and 5-carboxy pirfenidone was characterized is shown in Table 2 below.

Table 2. Summary of Phase 1 and Phase 3 Studies in which pharmacokinetics for Pirfenidone and 5-carboxy pirfenidone were assessed.

Study No.	Title	Subject Description[a]	Doses Administered	Sampling Schedule[b]
PIPF-005	The Pharmacokinetics of Oral Pirfenidone in Healthy Older Adults, Including Effects of Multiple-Dosing, Dose-Ranging, Food and Antacids	Healthy adults aged 50 to 66 years; n = 16 in single dose, n = 24 in multiple dose	Single dose: 801 mg Multiple dose: 801 – 4005 mg/day	Single dose: Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 hours postdose Multiple dose: 21 samples per dose; sampled on 2 of the 5 doses (randomly assigned)
PIPF-007	A Double-Blind, Randomized, Parallel Study to Define the Electrocardiographic Effects of Oral Pirfenidone Using a Clinical and a Supra-therapeutic Dose Compared to Placebo and Moxifloxacin (an Open-Label Positive Control) in Healthy Volunteers	Healthy adults aged 18 to 45 years (n = 80)	Therapeutic: 2403 mg/day Supra-therapeutic: 4005 mg/day	Predose, 0.5, 1, 2, 3, 4, 4.5, 5, 6, 7, 8, 10, 10.5, 11, 12, 13, 14, 16, 18, 23.5 hours postdose
PIPF-009	An Open-Label Phase 1 Study to Determine the Pharmacokinetics and Safety of Pirfenidone in Subjects with Renal Insufficiency	Age 40-80 years (n = 24); normal, mild, moderate, and severe renal impairment	Single dose: 801 mg	Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 32 hours postdose
PIPF-010	An Open-Label Phase 1 Study to Determine the Impacts of a Strong CYP1A2 Inhibitor and a CYP1A2 Inducer on the Pharmacokinetics and Safety of Pirfenidone in Healthy Subjects	Age 18-75 years (n = 54); smokers and nonsmokers	Two single doses: 801 mg (with and without fluvoxamine)	Predose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 32 hours postdose (with and without fluvoxamine)

[a]Includes planned numbers of subjects enrolled
[b]All samples were assayed for both pirfenidone and 5-carboxy-pirfenidone

Protocol Number	Title	Subject Description	Doses Administered	Sampling Schedule
PIPF-004	A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-Arm Study of the Safety and Efficacy of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis	Patients with IPF	399 or 801 mg TID	Predose, 0.5, 1, 2, and 4 hours postdose, and 6 hours postdose

The summary of continuous and categorical demographic and disease characteristics are shown in Table 3.

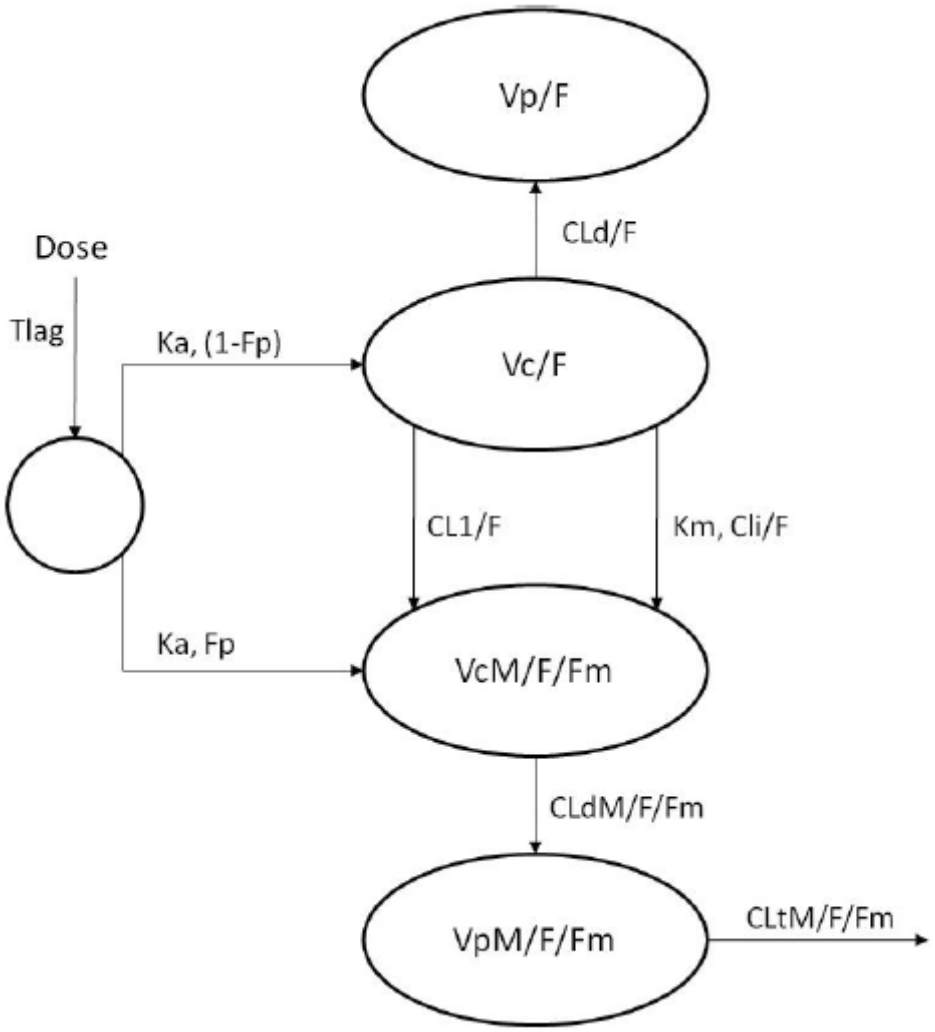
Table 3. Summary of continuous and categorical subject demographic and disease characteristics of the pharmacokinetics analysis population.

Variable	Phase 1 Studies (n = 194)		Phase 3 Study (n = 88)		All Subjects	
	Mean (CV%)	Median (Min. – Max.)	Mean (CV%)	Median (Min. – Max.)	Mean (CV%)	Median (Min. – Max.)
Age (yr)	38.6 (44.6)	33.5 (18.0 – 79.0)	66.5 (12.0)	67.0 (46.0 – 80.0)	47.3 (41.9)	51.0 (18.0 – 80.0)
Weight (kg)	77.0 (17.4)	78.0 (52.6 – 129)	86.8 (16.2)	86.8 (40.0 – 131)	80.1 (17.9)	80.0 (40.0 – 131)
Height (cm)	170 (5.40)	168 (151 – 201)	171 (5.42)	173 (138 – 191)	170 (5.41)	170 (138 – 201)
IBW (kg)	63.9 (15.6)	61.6 (45.5 – 93.7)	65.7 (14.6)	68.4 (45.5 – 84.5)	64.5 (15.3)	64.0 (45.5 – 93.7)
BSA (m^2)	1.92 (10.4)	1.92 (1.55 – 2.60)	2.05 (9.76)	2.04 (1.26 – 2.60)	1.96 (10.7)	1.96 (1.26 – 2.60)
BMI (kg/m^2)	26.5 (13.5)	26.1 (19.4 – 37.5)	29.6 (13.7)	29.7 (21.0 – 40.3)	27.5 (14.5)	27.1 (19.4 – 40.3)
CLcr ($mL/min/1.73m^2$)	84.2 (28.9)	85.9 (16.3 – 137)	55.4 (27.4)	53.5 (23.3 – 95.5)	75.2 (34.0)	73.5 (16.3 – 137)
Albumin (g/dL)	4.29 (6.29)	4.20 (3.70 – 5.20)	3.97 (6.80)	4.00 (3.30 – 4.60)	4.19 (7.40)	4.20 (3.30 – 5.20)

Variable		Phase 1 N (%)	Phase 3 N (%)	All Subjects N (%)
Sex	Male	99 (51.0)	62 (70.5)	161 (57.1)
	Female	95 (49.0)	26 (29.6)	121 (42.9)
Race	White	163 (84.0)	86 (97.7)	249 (88.3)
	Black	20 (10.3)	2 (2.27)	22 (7.80)
	Asian	4 (2.06)	—	4 (1.42)
	American Indian/Alaska Native	4 (2.06)	—	4 (1.42)
	Native Hawaiian or Pacific Islander	1 (0.520)	—	1 (0.350)
	Multiple	2 (1.03)	—	2 (0.710)
Smoking Status	Nonsmoker	168 (86.6)	86 (97.7)	254 (90.1)
	Current Smoker	26 (13.4)	2 (2.27)	28 (9.93)

Figure 3 below shows the pharmacokinetic model used to describe the concentrations of pirfenidone and 5-carboxy pirfenidone simultaneously.

Figure 3. Schematic of base structural model used for population PK analysis.



Due to the high degree of random variability in PK between sampling windows (termed occasions) in PIPF-004 (as shown in Figure 4), it was not feasible to co-model data for all occasions for each patient. The population pharmacokinetic analysis was conducted separately for each occasion.

Figure 4. Representative plots of individual pirfenidone and 5-carboxy pirfenidone concentrations versus time since previous dose for PIPF-004,stratified by sampling occasion.

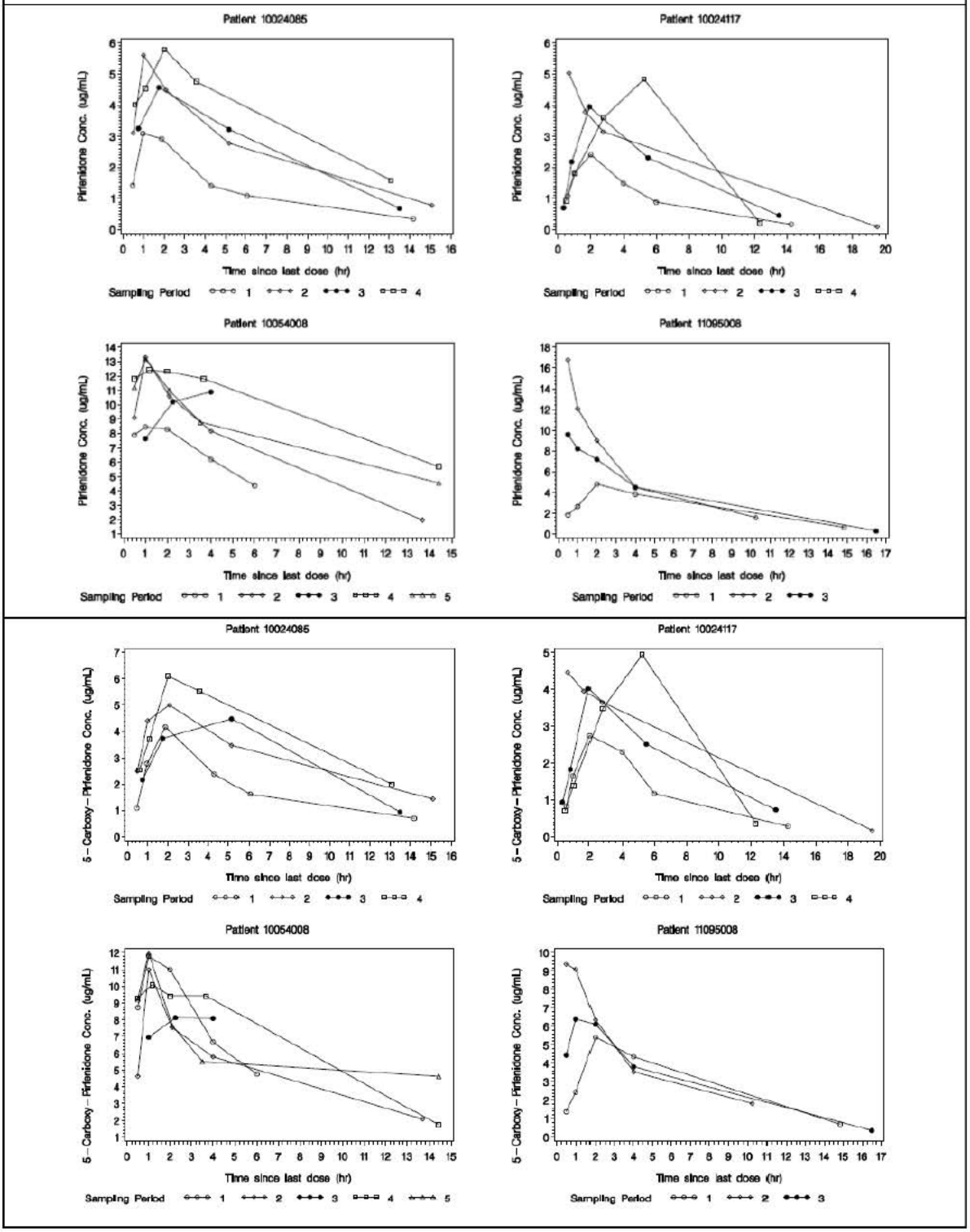


Table 4 shows the estimates of pharmacokinetic parameters of pirfenidone and 5-carboxy pirfenidone by occasion.

Table 4. Summary statistics of the pharmacokinetic parameter estimates by occasion.

Variable	Occasion 1 (n = 282)		Occasion 2 (n = 65)		Occasion 3 (n = 43)		Occasion 4 (n = 20)		Occasion 5 (n = 6)	
	Mean (CV%)	Median (Min. – Max.)	Mean (CV%)	Median (Min. – Max.)	Mean (CV%)	Median (Min. – Max.)	Mean (CV%)	Median (Min. – Max.)	Mean (CV%)	Median (Min. – Max.)
Lag Time (hr)	0.419 (116)	0.311 (0.0210–6.01)	0.238 (180)	0.109 (0.0104–3.25)	0.213 (90.1)	0.170 (0.0205–0.876)	0.327 (105)	0.208 (0.0199–1.26)	0.143 (126)	0.0868 (0.0106–0.500)
Ka (1/hr)	0.840 (38.3)	0.764 (0.284–2.04)	1.06 (42.2)	0.978 (0.311–2.06)	0.804 (56.1)	0.631 (0.326–1.91)	0.773 (38.2)	0.879 (0.313–1.29)	0.819 (57.4)	0.630 (0.367–1.62)
Vc/F-Pirfenidone (L)	46.2 (56.4)	43.3 (6.44–208)	32.0 (61.8)	24.0 (5.71–120)	32.2 (45.9)	29.8 (9.48–62.0)	29.2 (59.7)	28.9 (6.88–60.5)	24.1 (58.3)	23.0 (8.47–46.9)
Vp/F-Pirfenidone (L)	24.1 (80.9)	18.2 (3.43–145)	34.6 (57.5)	32.7 (2.81–76.3)	33.2 (83.3)	25.7 (1.16–146)	34.7 (88.3)	21.5 (3.21–111)	27.9 (92.5)	18.9 (6.20–72.7)
CLd/F-Pirfenidone (L/h)	18.4 (275)	5.38 (0.237–681)	29.4 (104)	18.5 (0.275–138)	38.5 (169)	12.1 (0.0576–296)	32.2 (134)	8.34 (0.112–140)	27.6 (139)	11.5 (0.427–99.7)
CL1/F-Pirfenidone (L/h)	0.0810 (95.2)	0.059 (0.00426–0.617)	0.104 (112)	0.0593 (0.00596–0.545)	0.0540 (134)	0.0285 (0.00234–0.436)	0.218 (120)	0.0981 (0.0239–0.959)	0.280 (76.3)	0.226 (0.0785–0.595)
CLi/F-Pirfenidone (L/h)	23.5 (43.1)	21.5 (8.54–75.4)	18.9 (33.5)	18.5 (6.03–37.6)	17.1 (34.4)	16.2 (6.55–31.4)	16.4 (40.6)	14.9 (6.75–36.0)	13.3 (17.9)	13.1 (10.7–16.2)
Km-Pirfenidone (µg/mL)	75.0 (103)	46.4 (3.40–637)	238 (225)	37.9 (2.89–3080)	367 (145)	146 (8.13–2320)	110 (92.8)	78.0 (10.7–375)	35.0 (77.6)	22.7 (14.7–85.1)
First-Pass Fraction	0.0310 (132)	0.0180 (0.000399–0.263)	0.0504 (122)	0.0319 (0.00312–0.357)	0.0757 (117)	0.0523 (0.0108–0.514)	0.0277 (97.3)	0.0216 (0.00520–0.126)	0.0317 (68.5)	0.0385 (0.00312–0.0544)

Variable	Occasion 1 (n = 282)		Occasion 2 (n = 65)		Occasion 3 (n = 43)		Occasion 4 (n = 20)		Occasion 5 (n = 6)	
	Mean (CV%)	Median (Min. – Max.)	Mean (CV%)	Median (Min. – Max.)	Mean (CV%)	Median (Min. – Max.)	Mean (CV%)	Median (Min. – Max.)	Mean (CV%)	Median (Min. – Max.)
Vc/F/Fm-5-Carboxy (L)	1.95 (145)	1.10 (0.0140–23.0)	4.42 (38.5)	4.09 (1.64–11.8)	7.50 (109)	5.02 (0.568–33.5)	1.15 (110)	0.606 (0.0922–4.79)	0.937 (82.2)	0.771 (0.152–2.31)
Vp/F/Fm-5-Carboxy (L)	3.83 (37.8)	3.53 (1.24–13.9)	2.53 (102)	1.67 (0.218–13.0)	4.89 (36.2)	4.50 (2.32–10.3)	6.08 (50.5)	5.43 (2.14–14.5)	6.97 (41.0)	6.42 (3.25–11.7)
CLd/F/Fm-5-Carboxy (L/h)	52.6 (471)	4.46 (0.000464–3400)	82.4 (377)	0.733 (9.45E-05–2340)	2403 (289)	180 (0.163–32800)	108 (205)	18.0 (1.43–927)	39.8 (142)	7.42 (1.26–138)
CLt/F/Fm-5-Carboxy (L/h)	32.0 (44.0)	30.9 (3.89–146)	21.2 (34.6)	20.1 (8.09–48.8)	22.2 (41.7)	21.0 (7.93–50.8)	19.7 (34.1)	20.3 (8.78–31.3)	14.6 (29.1)	13.1 (9.28–20.4)
Slope of CLt/F/Fm-CLcr Relationship	0.409 (—)	0.409 (—)	0.405 (—)	0.405 (—)	0.399 (—)	0.399 (—)	0.403 (—)	0.403 (—)	0.404 (—)	0.404 (—)

Reviewer's Comments: The reviewer re-analyzed the data using NONMEM® to evaluate differences in pharmacokinetics of pirfenidone and 5-carboxy pirfenidone between healthy subjects and patients with IPF. The reviewer conducted separate analysis for pirfenidone and 5-carboxy pirfenidone concentrations (from doses upto 2403 mg/day) using two compartment models.

4 REVIEWER'S ANALYSIS

The plasma concentrations of pirfenidone and its metabolite (5-carboxy pirfenidone) obtained after doses upto 2403 mg/day were analyzed separately using two compartment models.

4.1 Introduction

NA

4.2 Objectives

Analysis objectives are:

1. To check for differences in pharmacokinetics of pirfenidone and 5-carboxy pirfenidone between healthy subjects and patients with IPF.

4.3 Methods

4.3.1 Data Sets

Data sets used are summarized in Table 5.

Table 5. Analysis Data Sets

Study Number	Name	Link to EDR
PIPF-004	pkallFp1.csv,pkallFp2.csv pkallFp3.csv, pkallFp4.csv pkallFp5.csv	\\Cdsesub1\evsprod\NDA022535\0000\m5\53-clin-stud-rep\533-rep-human-pk-stud\5335-popul-pk-stud-rep\pipf-ord1

4.3.2 Software

NONMEM(Version VI)®, SAS(Ver 9.2)®.

4.3.3 Models

Two compartment models were used to analyze the plasma concentrations of pirfenidone and 5-carboxy pirfenidone. The dosing regimen for pirfenidone was used to model the data for 5-carboxy pirfenidone.

4.4 Results

Base Model (No Covariates)

Figure 5 and Figure 6 show that a two compartment model adequately describes the data of pirfenidone and 5-carboxy pirfenidone.

Figure 7 and Figure 8 show the observed and model fitted pirfenidone and 5-carboxy pirfenidone concentration data in a few healthy subjects.

The estimated pharmacokinetic parameters for pirfenidone are shown in Table 6.

Table 6. Estimates of pirfenidone pharmacokinetic parameters by occasion

Occasion	Lag Time (h)	Ka (/h)	Vc (L)	Vp (L)	CLD (L/h)	CL (L/h)
1	0.17	1.35	69.4	10.9	0.96	19.1
2	0.11	1.21	64.0	9.59	2.26	19.1
3	0.15	1.26	68.2	10.5	0.88	19.7
4	0.16	1.25	67.5	10.8	0.94	19.4
5	0.16	1.29	69.3	10.5	0.91	19.1

Ka- Absorption rate constant, Vc-Volume of distribution of central compartment, Vp-Volume of distribution of peripheral compartment, CLD- Intercompartment clearance, CL- Clearance from central compartment.

The estimates of inter-subject variability of pirfenidone pharmacokinetic parameters are shown in Table 7.

Table 7. Estimates of inter-subject variability (%CV) in pharmacokinetic parameters by occasion

Occasion	Lag Time	Ka	Vc	Vp	CLD	CL
1	266	88	32	140	349	51
2	524	85	32	186	220	54
3	344	82	32	156	378	54
4	309	86	32	147	437	53
5	317	83	31	140	393	51

Ka- Absorption rate constant, Vc-Volume of distribution of central compartment, Vp-Volume of distribution of peripheral compartment, CLD- Intercompartment clearance, CL- Clearance from central compartment.

The estimate of intra-subject variability for pirfenidone is shown in Table 8.

Table 8. Estimates of intra-subject (unexplained) variability by occasion

Occasion	%CV
1	15
2	16
3	16
4	15
5	15

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The estimated pharmacokinetic parameters for 5-carboxy pirfenidone are shown in Table 9.

Table 9. Estimates of 5-carboxy pirfenidone pharmacokinetic parameters by occasion

Occasion	Lag Time (h)	Ka (/h)	Vc (L)	Vp (L)	CLD (L/h)	CL (L/h)
1	0[#]	1.15	86.2	19.5	1.79	22.6
2	0.12	0.97	79.5	19.3	1.94	20.7
3	0.13	0.87	79.7	18.5	1.87	21.8
4	0.17	0.20	21.5	6.72	0.52	17.0
5	0.18	0.97	87.7	20.1	2.08	23.0

Fixed, Ka- Absorption rate constant, Vc-Volume of distribution of central compartment, Vp- Volume of distribution of peripheral compartment, CLD- Intercompartment clearance, CL- Clearance from central compartment.

The estimates of inter-subject variability of 5-carboxy pirfenidone pharmacokinetic parameters are shown in Table 10.

Table 10. Estimates of inter-subject variability (%CV) in 5-carboxy pirfenidone pharmacokinetic parameters by occasion

Occasion	Lag Time	Ka	Vc	Vp	CLD	CL
1	-	90	45	327	296	87
2	377	75	45	292	276	78
3	325	59	41	290	261	84
4	282	27	86	364	248	65
5	181	72	45	284	302	82

- Not Estimated, Ka- Absorption rate constant, Vc-Volume of distribution of central compartment, Vp- Volume of distribution of peripheral compartment, CLD- Intercompartment clearance, CL- Clearance from central compartment.

The estimate of intra-subject variability for 5-carboxy pirfenidone is shown in Table 11.

Table 11. Estimates of intra-subject (unexplained) variability by occasion

Occasion	%CV
1	28
2	22
3	25
4	19
5	23

Figure 5. Goodness of fit plots for pirfenidone in healthy subjects and patients with IPF.

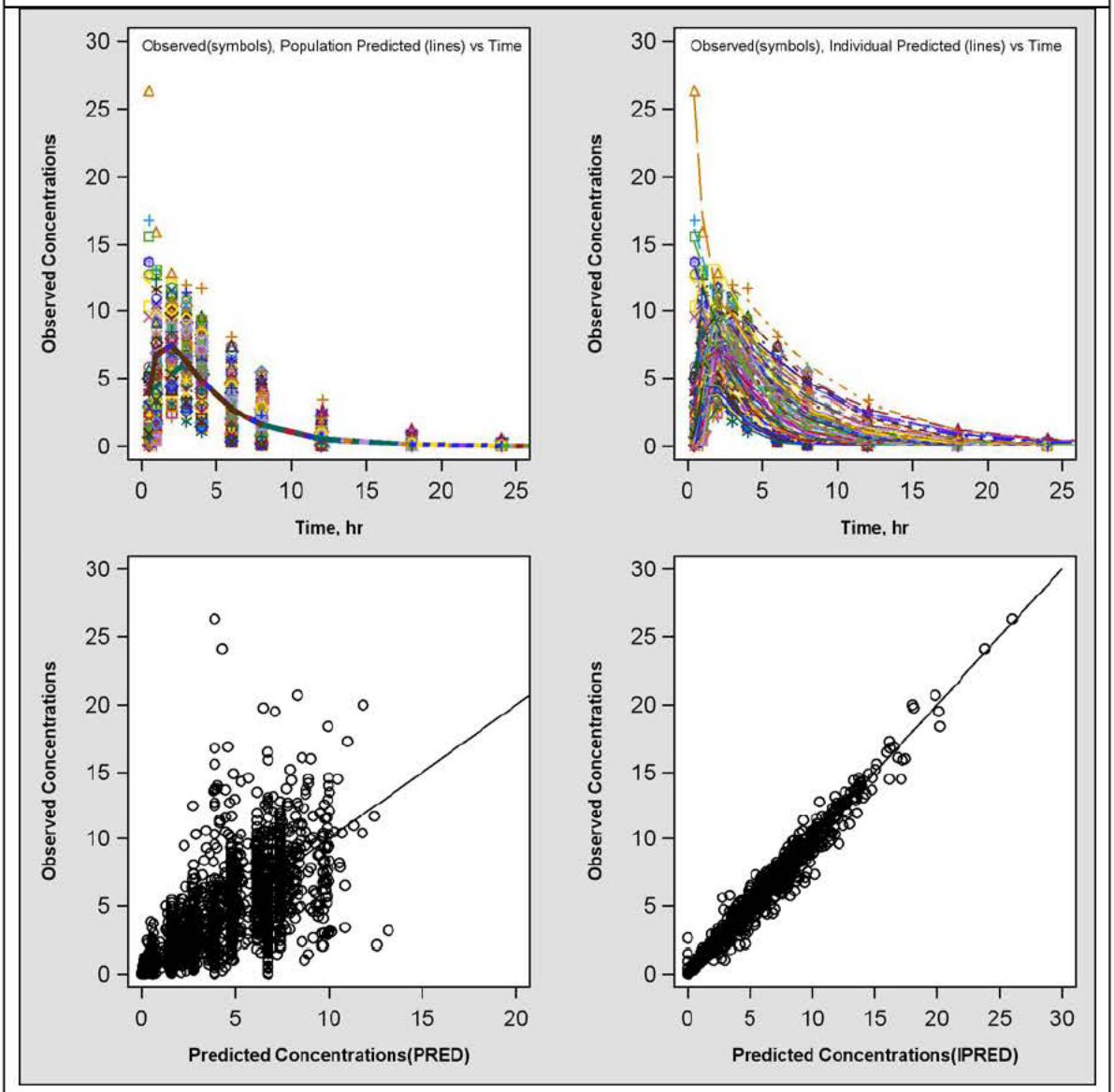


Figure 6. Goodness of fit plots for 5-carboxy pirfenidone in healthy subjects and patients with IPF.

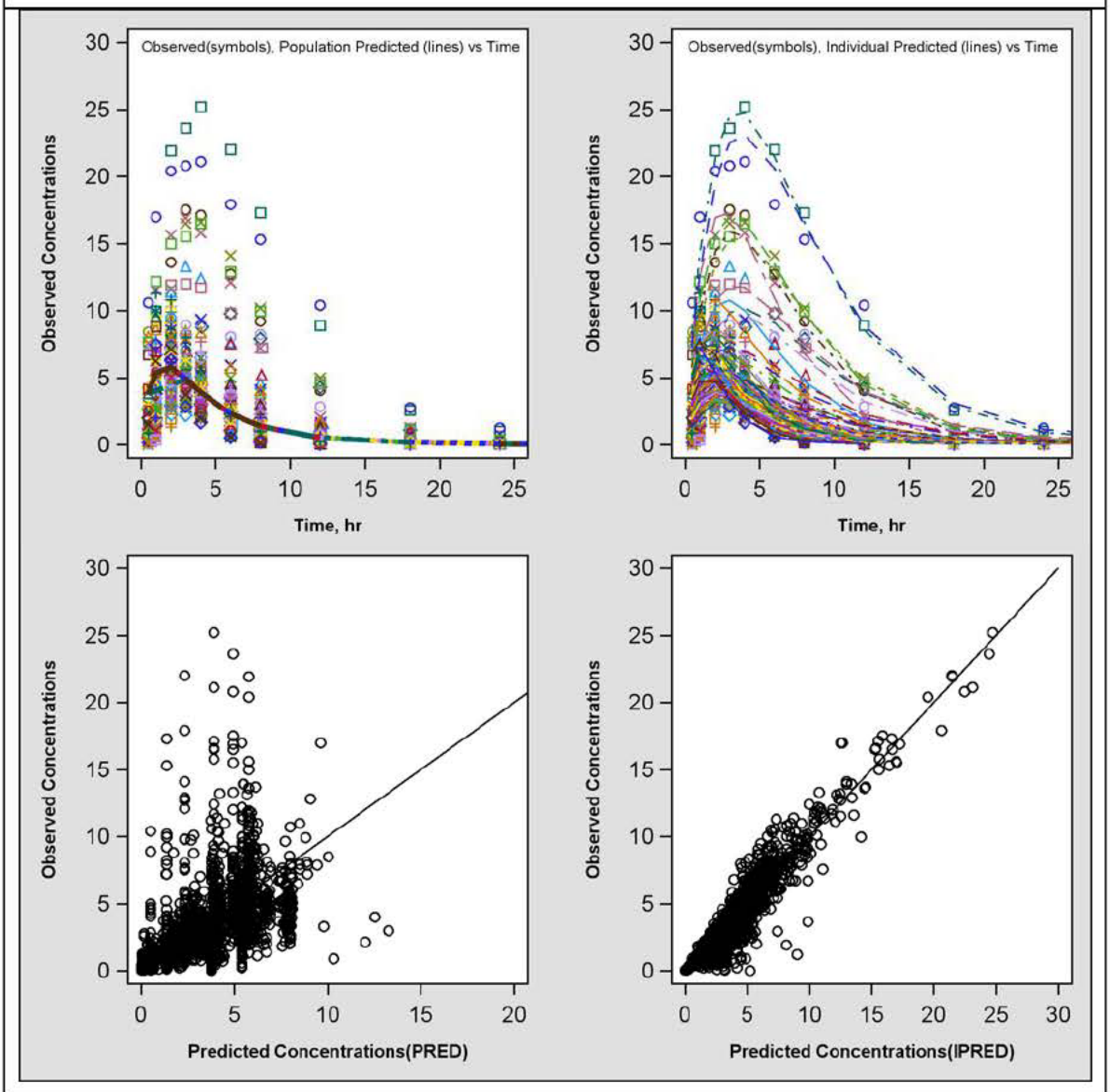


Figure 7. Observed and fitted (individual predicted) pirfenidone concentrations based on two compartment model in healthy subjects.

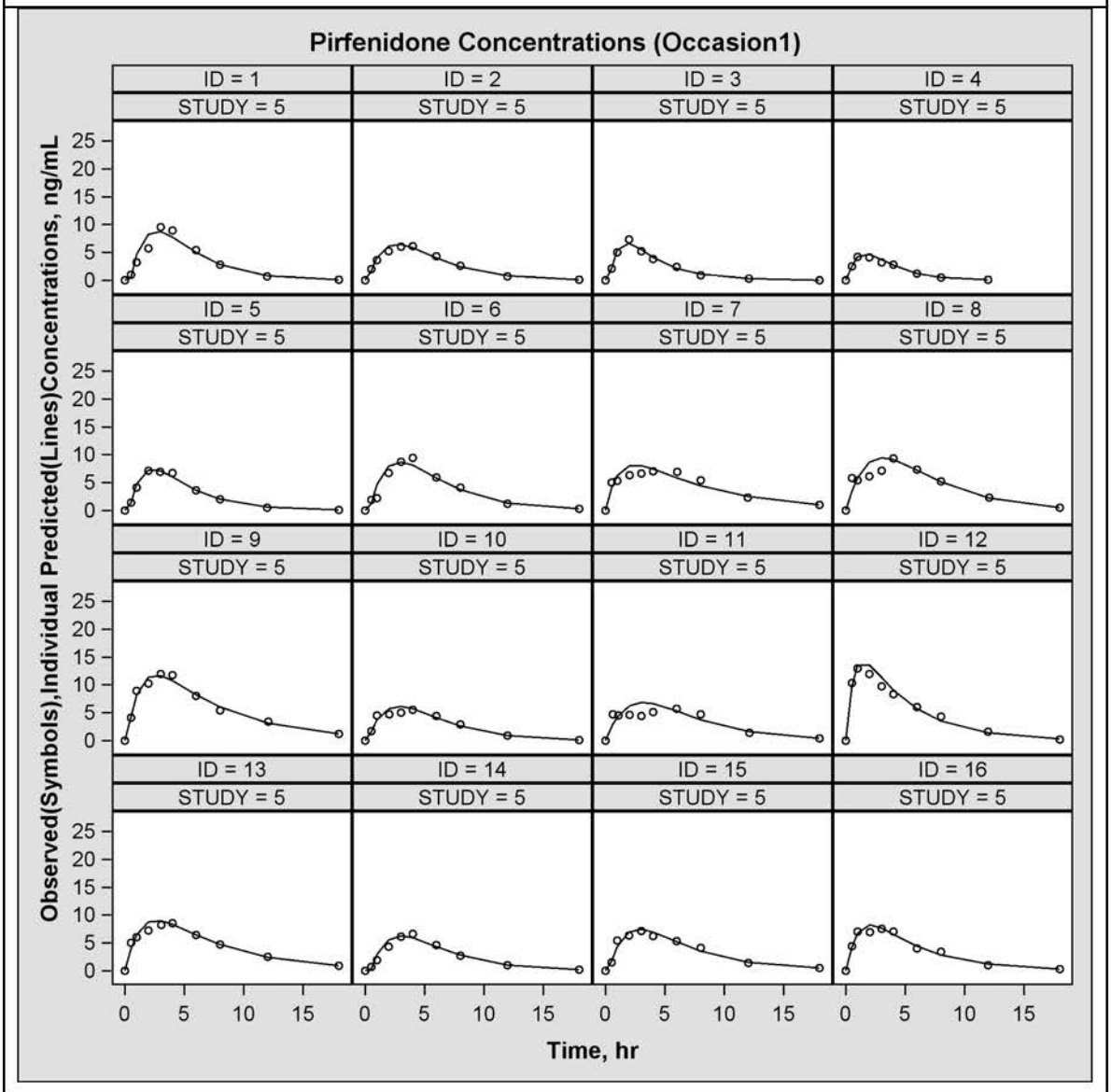
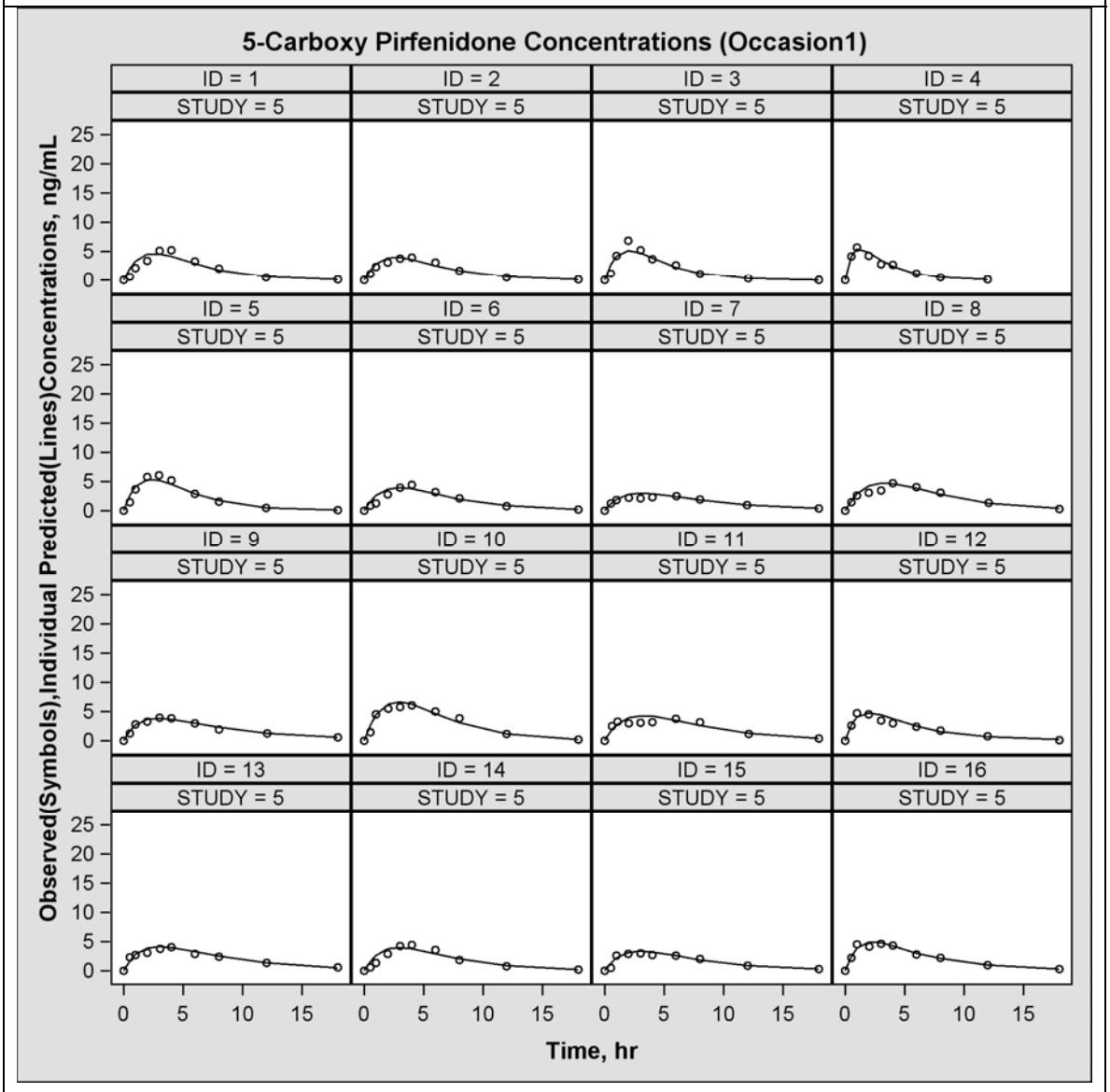


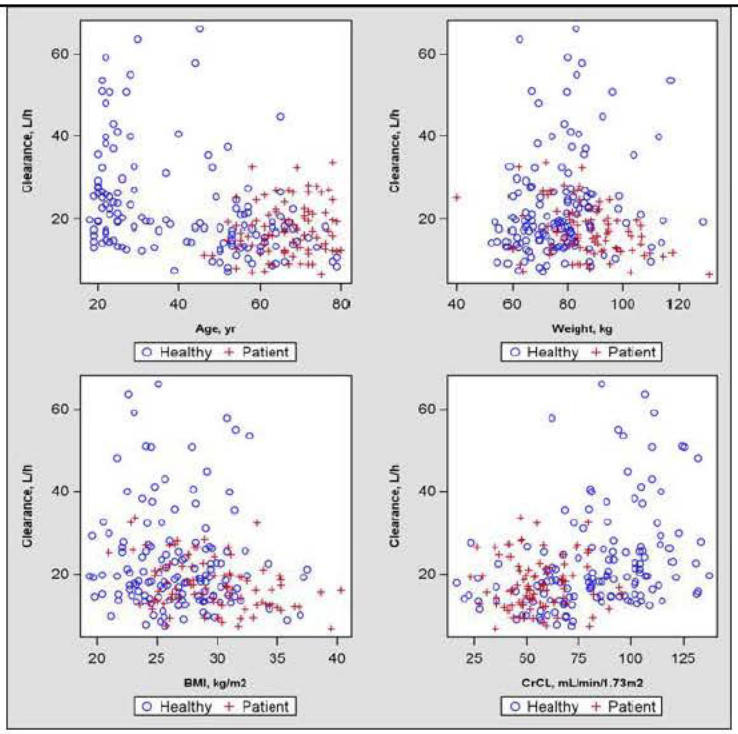
Figure 8. Observed and fitted (individual predicted) 5-carboxy pirfenidone concentrations based on two compartment model in healthy subjects.



Effect of covariates on pharmacokinetics of pirfenidone and 5-carboxy pirfenidone

Figure 9,Figure 10 show the relationship between clearance, volume of distribution (central compartment) and covariates such as age, renal function, body weight, body mass index (BMI) on the clearance of pirfenidone and 5-carboxy pirfenidone in healthy subjects and patients with IPF.

Figure 9. Relationship between pirfenidone clearance, volume of distribution and covariates (age, renal function (CrCL), body weight, BMI)



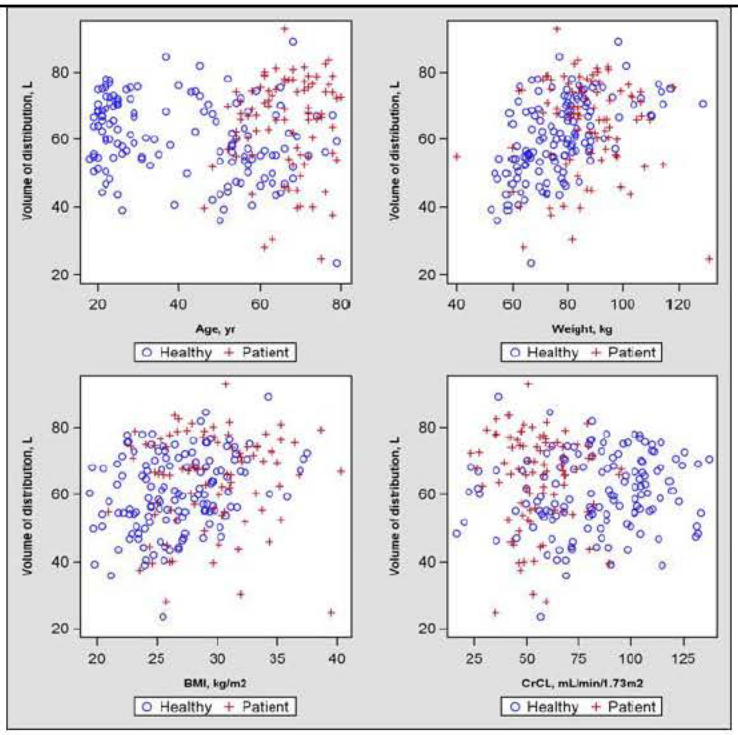
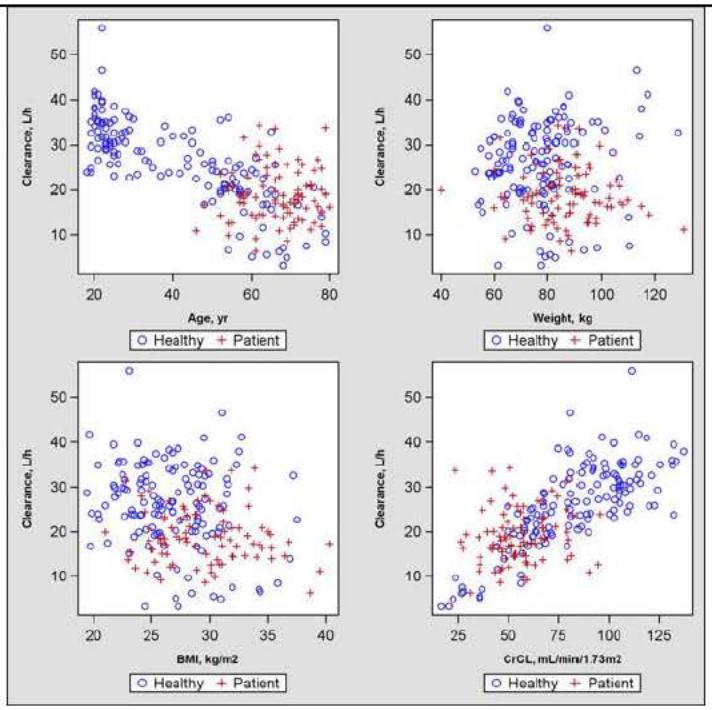
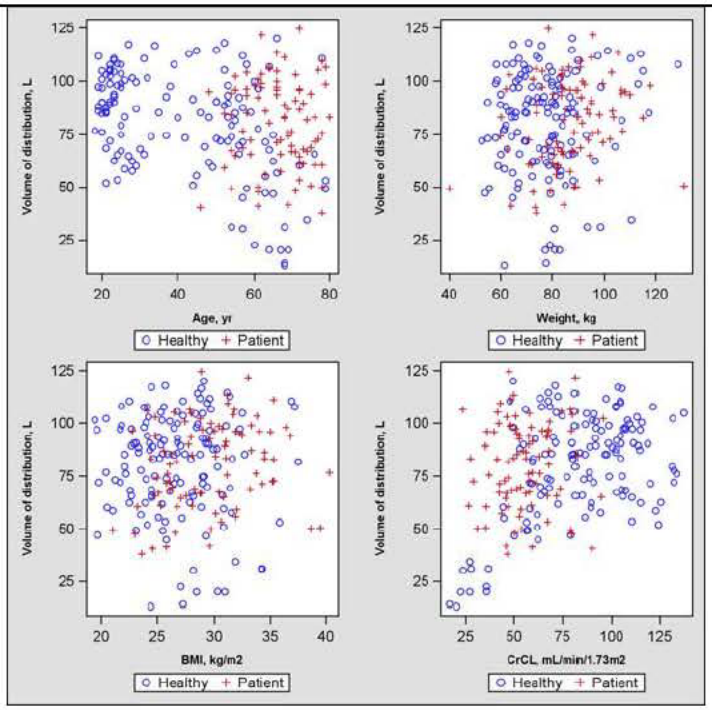


Figure 10. Relationship between 5-carboxy pirfenidone clearance, volume of distribution and covariates (age, renal function (CrCL), body weight, BMI)





Covariate Model for Pirfenidone

The reviewer analyzed the influence of covariates such as smoking, age, disease status, gender, body weight, race on the clearance of pirfenidone and 5-carboxy pirfenidone. The inter-subject variability for pirfenidone clearance decreased from 51% to 40% after including the covariates. The inter-subject variability for 5-carboxy pirfenidone clearance decreased from 87% to 35% after including the covariates. Table 12 and Table 13 show the pirfenidone and 5-carboxy pirfenidone pharmacokinetic parameters from full and reduced model using data from healthy subjects and patients with IPF (first occasion only).

Table 12. Pirfenidone pharmacokinetic parameters and standard error from full model and reduced model

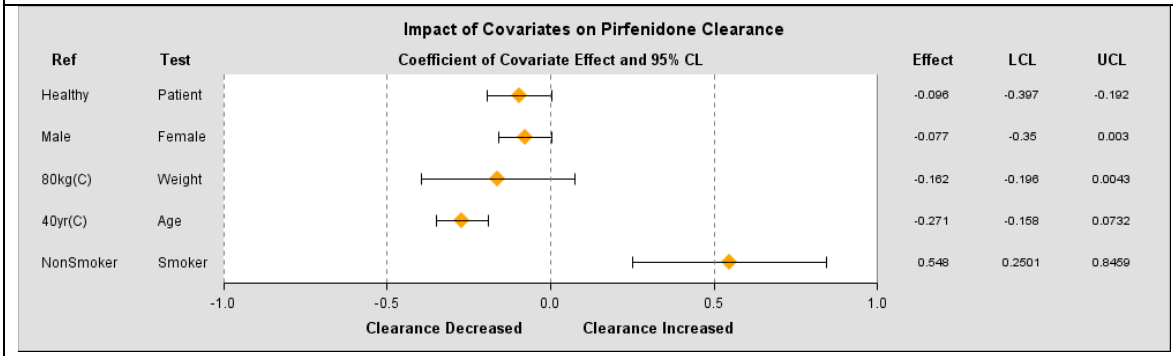
Parameter	Estimate (Standard Error)
Lag Time (h)	0.162 (0.05)
Absorption rate constant (Ka; h)	1.32 (0.076)
Volume of distribution of central compartment (Vc; L)	69.0 (1.73)
Volume of distribution of peripheral compartment (Vp; L)	5.88 (0.95)
Intercompartment clearance (CLD; L/h)	0.73 (0.14)
Clearance from central compartment (CL; L/h) Full Model	$155 \bullet (1 + 0.72 \bullet Smoking) \bullet (1 - 0.00483 \bullet Age) \bullet (1 - 0.130 \bullet Disease\ Status) \bullet (1 - 0.10 \bullet Sex) \bullet \left(\frac{Weight}{80}\right)^{-0.304} \bullet (0.125 \bullet Race_{other} + 0.172 \bullet Race_{White} + 0.149 \bullet Race_{African-American})$
Clearance from central compartment (CL; L/h) Reduced Model	$20.7 \bullet (1 + 0.55 \bullet Smoking) \bullet \left(1 - 0.27 \bullet \left(\frac{Age - 40}{40}\right)\right) \bullet (1 - 0.0959 \bullet Disease\ Status) \bullet (1 - 0.077 \bullet Sex) \bullet \left(1 - 0.16 \bullet \left(\frac{Weight - 80}{80}\right)\right)$

Table 13. 5-carboxy pirfenidone pharmacokinetic parameters and standard error from full model and reduced model

Parameter	Estimate (Standard Error)
Lag Time (h)	$0^{\#}$
Absorption rate constant (Ka; h)	1.39 (0.09)
Volume of distribution of central compartment (Vc; L)	81.4 (3.61)
Volume of distribution of peripheral compartment (Vp; L)	13.1 (2.86)
Intercompartment clearance (CLD; L/h)	1.46 (0.35)
Clearance from central compartment (CL; L/h) Full Model	$15.5 \bullet (1 + 0.33 \bullet Smoking) \bullet \left(1 + 0.93 \bullet \left(\frac{CrCL - 60}{60}\right)\right) \bullet$ $(1 - 0.083 \bullet Disease\ Status) \bullet (1 + 0.019 \bullet Sex) \bullet$ $\left(1 - 0.05 \bullet \left(\frac{Weight - 80}{80}\right)\right) \bullet (1.04 \bullet Race_{other} + 1.21 \bullet Race_{White} + Race_{African-American})$
Clearance from central compartment (CL; L/h) Reduced Model	$18.5 \bullet (1 + 0.29 \bullet Smoking) \bullet \left(1 + 0.95 \bullet \left(\frac{CrCL - 60}{60}\right)\right) \bullet$ $(1 - 0.075 \bullet Disease\ Status) \bullet (1 + 0.03 \bullet Sex) \bullet$ $\left(1 - 0.02 \bullet \left(\frac{Weight - 80}{80}\right)\right)$

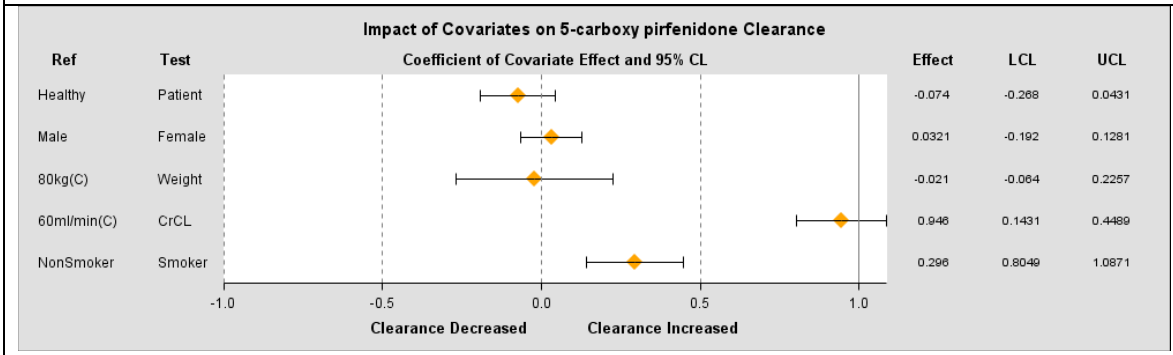
Figure 11 and Figure 12 shows the influence of covariates on pirfenidone and 5-carboxy pirfenidone clearance along with 95% confidence intervals. For example, in Figure 11, a value of 0.548 for smoker implies that clearance of pirfenidone increases by 54.8% when compared to non-smokers.

Figure 11. Impact of covariates on pirfenidone clearance. If zero is included in the confidence interval, it suggests lack of significant effect of the covariate (when compared to reference) on clearance of pirfenidone.



80kg(C) and 40yr(C) reflect centering of covariates around 80kg and 40 yr respectively.

Figure 12. Impact of covariates on 5-carboxy pirfenidone clearance. If zero is included in the confidence interval, it suggests lack of significant effect of the covariate (when compared to reference) on clearance of 5-carboxy pirfenidone.



80kg(C) and 60 mL/min(C) reflect centering of covariates around 80kg and 60 mL/min respectively.

The following conclusions on clearance of pirfenidone are derived

- No differences in clearance between white and african-american population.
- No differences in clearance between healthy subjects and patients with IPF when comparing similar age groups (Age>45 years).

- Decrease in clearance with increasing age. Renal function was not evaluated as a covariate since approximately 80% of the dose is excreted in the urine as parent drug or one of the four metabolites. The majority of dose was excreted as the 5-carboxy metabolite (>95% of that recovered).
- No differences in clearance between male and female subjects.
- Smokers have faster clearance that non-smokers.

The following conclusions on clearance of 5-carboxy pirfenidone are derived

- No differences in clearance between white and african-american population.
- No differences in clearance between healthy subjects and patients with IPF when comparing similar age groups (Age>45 years).
- No differences in clearance between male and female subjects.
- Decrease in clearance with poor renal function. Renal function was evaluated as a covariate since approximately 80% of the dose is excreted in the urine as parent drug or one of the four metabolites. The majority of dose was excreted as the 5-carboxy metabolite (>95% of that recovered).
- Smokers have faster clearance (30%) that non-smokers.

5 LISTING OF ANALYSES CODES AND OUTPUT FILES

File Name	Description	Location in \\cdsnas\pharmacometrics\

4.2.2 Pharmacogenomic Review

NDA Number	22,535
Submission Date	11/4/2009
Generic Name	Pirfenidone
Applicant Name	Intermune, Inc.
Proposed Indication	Treatment of patients with idiopathic pulmonary fibrosis (IPF) to reduce decline in lung function
Primary Reviewer	Mike Pacanowski, Pharm.D., M.P.H.
Secondary Reviewer	Issam Zineh, Pharm.D., M.P.H.

Background

Intermune, Inc. submitted a New Drug Application on November 4, 2009. The proposed indication for pirfenidone is 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 mechanism of action of pirfenidone has not been fully established, but in experimental studies it has demonstrated anti-inflammatory and anti-fibrotic properties. Pirfenidone is administered orally and titrated over a two-week period as tolerated to a target dose of 2403 mg/day divided into three doses. The applicant's proposed labeling bears a contraindication for concurrent use with fluvoxamine, which is an inhibitor of CYP1A2 and other CYP450 enzymes. The purpose of this review is to evaluate the need for additional studies related to genetic variation in CYP1A2.

NDA Content Related to Genomics

In the pivotal studies, PIPF-004 and -006, DNA samples were collected at selected sites on voluntary basis with separate informed consent for genetic polymorphism analysis. DNA samples were collected at day 1 or week 12. Genomic studies were not included as part of the current submission given their exploratory nature.

In PIPF-005, a healthy volunteer PK study (food effect), biomarker samples were collected but consent for DNA studies was not obtained. No genetic or biomarker samples were collected in PIPF-010 (healthy, smoking/fluvoxamine drug interaction) or PIPF-007 (healthy, thorough QT study).

Key Questions and Summary of Findings

3.1 Are additional pharmacogenetic studies required at this time?

No, additional pharmacogenetic studies are not required at this time. The applicant may consider conducting exploratory pharmacogenetic studies using DNA samples collected in the Phase 3 trials to evaluate associations with variants in relevant genes (e.g., CYP1A2) and pirfenidone efficacy and toxicity (e.g., hepatic events). Pirfenidone is metabolized by CYP1A2. A drug interaction study with fluvoxamine, which inhibits multiple CYP450 enzymes including CYP1A2, demonstrated a significant increase in pirfenidone exposure. The applicant proposes to contraindicate the concomitant use of pirfenidone and fluvoxamine.

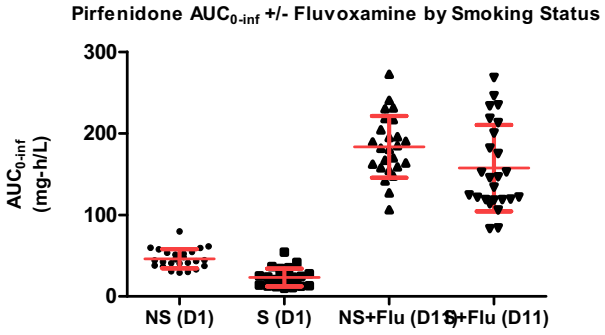
3.1.1 General clinical pharmacology attributes and CYP1A2-mediated drug interactions

Refer to the Clinical Pharmacology review for details on the pharmacokinetic and pharmacodynamic properties of pirfenidone. Pirfenidone pharmacokinetics was characterized in 6 clinical studies as follows: 5 Phase 1 studies (PIPF-005, PIPF-007, PIPF-009, PIPF-010, and PIPF-011) and 1 Phase 3 study (PIPF-004). Notable characteristics from a genomics standpoint are as follows: high oral bioavailability; pirfenidone is primarily metabolized by CYP1A2 *in vitro* (approximately 48%), with minor contributions from CYP1A1, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1 and 2J2 (each accounting for <13%); concurrent use of a CYP1A2 inhibitor with pirfenidone is contraindicated (as proposed by the sponsor);

approximately 80% of an orally administered dose of pirfenidone is cleared in the urine as 5-carboxy-pirfenidone.

CYP1A2 appears to be the major enzyme involved in the metabolism of pirfenidone based on incubations with recombinant CYP450 isoenzymes. In human hepatic microsomes, (study PDN-PIRF-111), metabolism of pirfenidone was highly correlated with CYP1A1/2 activity (n=16; hydroxymehyl-pirfenidone formation r=0.851, 5-carboxy-pirfenidone r=0.934). For both metabolites, FMO and CYP4A11 activities were also correlated (r>0.5) with metabolism. Pirfenidone metabolism was inhibited by anti-CYP1A2 antibodies.

A Phase 1, open-label, parallel-group study was conducted to investigate the impact of CYP1A2 inhibition (fluvoxamine, also a CYP2C9, 2C19, and 3A4 inhibitor) and induction (smoking) on the pharmacokinetics and safety of pirfenidone in healthy subjects. Fifty-one subjects were enrolled in two groups based on smoking status. Each subject was to receive a single 801-mg dose of pirfenidone on days 1 and 11. Fluvoxamine dosing was started on day 2 and titrated to the final dose of 50 mg in the morning and 100 mg at bedtime. Pirfenidone exposures are shown in the figure below. One smoker and one nonsmoker had pirfenidone exposures that were approximately 2 standard deviations from the mean following single-dose administration, but exposures were otherwise not markedly heterogeneous. Fluvoxamine administration significantly increased pirfenidone exposures in both smokers and non-smokers. Smoking status was associated with reduced pirfenidone exposure, which is consistent with CYP1A2 induction. Refer to primary Clinical Pharmacology review for detailed results.



Noncompartmental analysis; bars reflect mean and standard deviation; NS=nonsmoker, S=smoker, Flu=fluvoxamine; Data: \\CDSESUB1\EVSPROD\NDA022535\\0020\m5\53-clin-stud-rep\537-crf-ipl\datasets\pipf-nca-011\analysis\ncapar11.xpt

3.1.2 Design features of efficacy and safety trials for which DNA is available

The clinical efficacy and safety of pirfenidone in the treatment of IPF was evaluated in two Phase 3, randomized, double-blind, placebo-controlled, multicenter studies. PIPF-004 compared treatment with either pirfenidone 2403 mg/day (n=174) or pirfenidone 1197 mg/day (n=87) to placebo (n=174), while PIPF-006 compared pirfenidone 2403 mg/day (n=173) to placebo (n=174), each for a minimum of 72 weeks. The primary endpoint in both studies was the change from baseline to Week 72 in percent predicted forced vital capacity (FVC). Secondary outcomes included progression-free survival, categorical FVC change, 6-minute walk distance, Hgb-corrected DL_{CO}, and dyspnea.

For information related to pirfenidone's clinical efficacy and safety, refer to the Division of Pulmonary, Allergy, and Rheumatology Products clinical review. It is noted that PIPF-006 failed to meet its primary endpoint. From a safety standpoint, patients treated with pirfenidone 2403 mg/day in studies PIP-004 and -006 had a higher incidence of elevations in liver aminotransferases (serum ALT or AST >3X ULN) than placebo patients (14 of 345 [4.1%] vs. 2 of 347 [0.6%], respectively). Exposure/safety relationships were not formally evaluated. Pharmacogenetic analyses of efficacy and safety outcomes, specifically hepatic events, may be feasible provided the sample acquisition rates were high.

3.1.3 Candidate pharmacogenes

Since extrinsic factors that alter CYP1A2 activity have a significant effect on pirfenidone exposure (i.e., smoking and fluvoxamine), genetic variations in CYP1A2 might also be expected to have clinically relevant effects on pirfenidone exposure. The gene encoding CYP1A2 has numerous variants that affect inducibility of the enzyme and thus overall enzymatic activity. CYP1A2 alleles that alter the amino acid sequence or that have documented functional consequences are listed in the table below (many other alleles are known to exist). The most extensively studied polymorphisms are -3860G>A (CYP1A2*1C), -2467delT (*1D), -739T>G (*1E), and -163C>A located in intron 1 (*1F). The clinical implications of many of these variants have not been clearly established (see Zhou, et al. Drug Metab Rev 2009 [online] for a comprehensive review).

Allele	**Protein**	**Nucleotide changes, Gene***	**Effect**	**Enzyme activity**		**References**
				In vivo	***In vitro***	
*CYP1A2*1A*	CYP1A2.1	None		Normal	Normal	Ikeya et al, 1989 Quattrochi and Tukey, 1989
*CYP1A2*1C*	CYP1A2.1	**-3860G>A**		Decr		Nakajima et al, 1999
*CYP1A2*1F*	CYP1A2.1	-163C>A		Higher inducibility		Japanese patent 05719026 Sachse et al, 1999 Chida et al, 1999 Han et al., 2002
*CYP1A2*1K*	CYP1A2.1	-739T>G; **-729C>T**;-163C>A		Decr		Aklillu et al, 2003
*CYP1A2*2*	CYP1A2.2	63C>G	F21L			Huang et al, 1999
*CYP1A2*3*	CYP1A2.3	2116G>A; 5347T>C	D348N	Decr expr		Chevalier et al, 2001 Zhou et al., 2004
*CYP1A2*4*	CYP1A2.4	**2499A>T**	**I386F**	Decr expr		Chevalier et al, 2001 Zhou et al., 2004
*CYP1A2*5*	CYP1A2.5	3497G>A	C406Y			Chevalier et al, 2001
*CYP1A2*6*	CYP1A2.6	5090C>T	R431W	Decr expr		Chevalier et al, 2001 Zhou et al., 2004
*CYP1A2*7*		**3533G>A**	**Splicing defect**	Decr		Allorge et al, 2003
*CYP1A2*8*	CYP1A2.8	**5166G>A**; 5347T>C	**R456H**		Decr	Soyama et al., 2005 Saito et al., 2005
*CYP1A2*9*	CYP1A2.9	248C>T	T83M			Murayama et al, 2004
*CYP1A2*10*	CYP1A2.10	502G>C	E168Q			Murayama et al, 2004
*CYP1A2*11*	CYP1A2.11	**558C>A**	**F186L**		Decr	Murayama et al, 2004

Allele	Protein	Nucleotide changes, Gene*	Effect	Enzyme activity *In vivo*	*In vitro*	References
*CYP1A2*12*	CYP1A2.12	634A>T	S212C			Murayama et al, 2004
*CYP1A2*13*	CYP1A2.13	1514G>A	G299S			Murayama et al, 2004
*CYP1A2*14*	CYP1A2.14	5112C>T	T438I			Murayama et al, 2004
*CYP1A2*15*	CYP1A2.15	**125C>G; 5347T>C**	**P42R**		Decr	Soyama et al., 2005 Saito et al., 2005
*CYP1A2*16*	CYP1A2.16	**2473G>A; 5347T>C**	**R377Q**		Decr	Soyama et al., 2005 Saito et al., 2005
**Position 5347 should have a T instead of a C to be considered *1A.*						

http://www.cypalleles.ki.se/cyp1a2.htm

Comments

4.1 No genotype data were submitted as part of the current NDA submission. The applicant collected DNA as part of the clinical efficacy and safety trials of pirfenidone in the treatment of IPF, but not the Phase 1/2 clinical pharmacology studies. It is not known how many samples were collected.

4.2 Pirfenidone is extensively metabolized. The major enzyme appears to be CYP1A2. A drug interaction study with fluvoxamine, which inhibits multiple CYP450 enzymes, demonstrated a significant increase in pirfenidone exposure. The applicant proposes to contraindicate concurrent use of fluvoxamine and pirfenidone. Exposure/safety relationships have not been definitively established. It is noted that pirfenidone is titrated based on tolerability.

4.3 *Additional pharmacogenetic studies are not required at this time.* The applicant may consider conducting exploratory pharmacogenetic studies using DNA samples collected in the Phase 3 trials to evaluate the relationship between variants in the CYP1A2 gene, or other relevant candidate genes (e.g., other drug metabolism genes, HLA), and pirfenidone efficacy and toxicity (e.g., hepatic events).

Recommendations

The Office of Clinical Pharmacology Genomics Group has reviewed the priority NDA submission 22,535 for pirfenidone in the treatment of idiopathic pulmonary fibrosis. Additional pharmacogenetic studies are not required at this time.

LABEL Recommendations

None.

Associate Director, Genomics Group, OCP

_____
Michael A. Pacanowski, Pharm.D., M.P.H.
Reviewer, Genomics Group, OCP

_____
Issam Zineh, Pharm.D., M.P.H.

4.2.3 Interdisciplinary Review Team Review on Clinical Study PIPF-007

Interdisciplinary Review Team for QT Studies Consultation:
Thorough QT Study Review

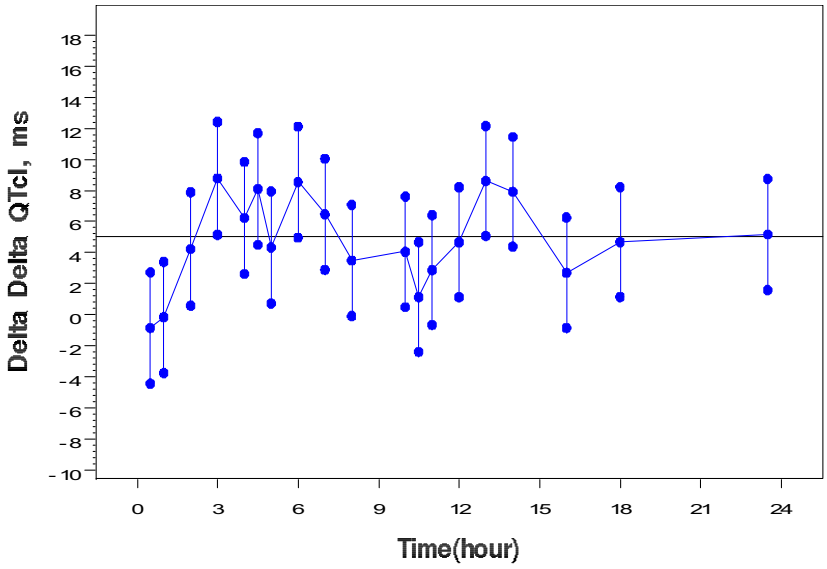
IND	67,284
Generic Name	Pirfenidone
Sponsor	InterMune, Inc.
Indication	Idiopathic Pulmonary Fibrosis
Dosage Form	Oral
Drug Class	Antifibrotic agent
Therapeutic Dosing Regimen	2403 mg/day (801 mg TID) with food
Duration of Therapeutic Use	Chronic
Maximum Tolerated Dose	4005 mg/day
Submission Number and Date	July 31, 2008, SDN 289
Clinical Division	DPAP / HFD 570

1 OVERALL SUMMARY OF FINDINGS

In thorough QT studies, it is important to have a high degree of confidence in the ability of the study as designed and conducted to detect small changes of around 5 ms in the QT/QTc interval. Failure to demonstrate the positive control's anticipated effect indicates that the study could not detect an effect of small magnitude for pirfenidone. When moxifloxacin is used as the positive control, we expect that (1) the ΔΔQTc-time profile follows the expected moxifloxacin concentration-time profile and (2) the mean effect on the QTc is greater than 5 ms (as evidence by the lower 90% confidence interval ≥ 5 ms) at one timepoint.

In our opinion, assay sensitivity cannot be established because the moxifloxacin QTc-time profile is highly variable and does not follow the expected time-course based on the known pharmacokinetics. As shown in Figure 1, there are three peaks of similar magnitude in the ΔΔQTc-time profile corresponding somewhat to the three dosing events on Day 10. Similar pattern is observed for the mean ΔQTc-time profile (Figure 6) and at the individual level (Appendix 6.3). Per the dosing schedule, subjects in the placebo-plus-moxifloxacin arm received one 400-mg tablet moxifloxacin plus 5 placebo capsules in the morning (0800 h) and only 5 placebo capsules in the afternoon (1200 h) and evening (1800 h). Blood samples were not analyzed for moxifloxacin concentrations to confirm the correct dosing schedule. However, the sponsor states that drug accountability was used to confirm correct dosing of all pirfenidone and moxifloxacin doses (Appendix 6.4).

Figure 1: Mean (90% Confidence Interval) ΔΔQTcI by Time for Moxifloxacin



In this double-blinded (except for moxifloxacin), randomized, 4-arm parallel study, 160 healthy subjects received either placebo, moxifloxacin (single-dose, 400 mg), or escalating doses of pirfenidone to reach the therapeutic dose (2403 mg/day) or supratherapeutic dose (4005 mg/day) by Day 10. Overall findings are summarized in Table 1.

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for pirfenidone (2403 mg/d and 4005 mg/d) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	ΔΔQTcI (ms)	90% CI (ms)
Pirfenidone 2403 mg/d	10	3.2	(-0.4, 6.7)
Pirfenidone 4005 mg/d	13	2.2	(-1.3, 5.8)
Moxifloxacin 400 mg*	3	8.8	(5.2, 12.4)

* Multiple endpoint adjustment is not applied. The largest lower bound after Bonferroni adjustment for 4 time points is below 5.0 ms

The sponsor used the maximum tolerated dose (4005 mg/d) as supratherapeutic dose, which is about 67% higher than the therapeutic dose. Because the drug is mainly eliminated through kidney (80%) as 5-carboxy-pirfenidone (> 95% of that recovered), one would expect that pirfenidone exposure will increase in patients with renal impairment or hepatic impairment. Coadministration of CYP1A2 inhibitor, such as fluvoxamine, can potentially affect pirfenidone exposure as well. However, the quantitative assessment of the exposure change under these conditions is unavailable (Appendix 6.1). Therefore, it is not feasible for us to determine whether the supratherapeutic dose can adequately cover the expected maximum exposure increase until the results of the renal, hepatic and drug interaction studies are complete.

2 PROPOSED LABEL

Not applicable.

3 BACKGROUND

3.1 MARKET APPROVAL STATUS

Pirfenidone is not approved for marketing in any country.

3.2 PRECLINICAL INFORMATION

From IB (4th edition)

> "In Study PCLN-PIRF-082, the IC_{50} for hERG channel was estimated to be approximately 932 µg/mL. This IC_{50} is approximately 100-fold greater than 11 µg/mL, the anticipated C_{max} of pirfenidone in patients given daily doses of 2403 mg/day (in divided doses of 801 mg, TID, taken with food).
>
> "An additional study with CHO cells transfected with hERG (Study PCLN-PIRF-081) investigated the potential for the 5-carboxylic acid metabolite to cause cardiac arrhythmias. The 5-carboxylic acid metabolite did not affect hERG channel polarization, even at the highest concentration tested, 215 µg/mL.
>
> "A series of *in vitro* experiments with guinea pig papillary muscle investigated possible effects of pirfenidone on cardiac action potential (Studies PCLN-PIRF-074, -075, and -076). These studies measured the action potential of electrically stimulated myocytes isolated from guinea pig right ventricle papillary muscle. The measurements consisted of resting membrane potential, action potential amplitude, maximum rising velocity, and action potential duration at 50% and 90% repolarization. Two of these studies examined pirfenidone (Studies PCLN-PIRF-074 and -076), and one examined the 5-carboxylic metabolite (Study PCLN-PIRF-075). The combined results of the three studies showed that neither pirfenidone nor its metabolite at concentrations ≤1,000 µM affects action potential parameters in isolated guinea pig papillary muscle. (1,000 µM corresponds to 185 and 215 µg/mL for pirfenidone and the 5-carboxylic metabolite, respectively).
>
> "Five safety pharmacology studies were performed in dogs. One of these, Study PCLN-PIRF-071, involved dose escalation in 4 conscious male beagle dogs configured with radiotelemetry devices. Single escalating oral doses of 0, 30, 100, and 300 mg/kg (C_{max}: 13.9, 46.3 and 139 µg/mL) were administered as capsules to dogs with cardiovascular (blood pressure, heart rate, electrocardiography) and respiratory (rate, blood gas) effects monitored for up to 24 h following each dose. There were no significant effects seen at a dose of 30 mg/kg (C_{max}: 13.9 µg/mL) and no remarkable effects upon blood pressure or respiratory parameters observed at any dose level. Dose-dependent and statistically significant increases in heart rate were identified 1 to 4 h following administration in dogs treated with doses ≥100 mg/kg (C_{max}: ≥46.3 µg/mL). At a dose of 100 mg/kg, prolongation of QT and QTc intervals were observed at 2, 12, and/or 24 h postdose; there was no change with regard to these parameters in this dose group at 4 h postdose. In contrast, at a dose of 300 mg/kg (C_{max}: 139 µg/mL), a shortening of these intervals was noted 1 to 2 h postdose and no effect on these intervals was seen at other time points. Definitive conclusions regarding the effects of pirfenidone upon QT intervals in this model cannot be drawn at this time based upon the lack of dose dependency and temporal inconsistencies seen in the data. As such, a follow-up study (PCLN-PIRF-109) was

undertaken in a conscious dog mode. The follow-up study in conscious dogs, Study PCLN-PIRF-109, involved single oral doses and intravenous infusions. Four male and four female dogs were dosed orally at escalating dose levels of 0, 30, and 100 mg/kg, and 1-h intravenous infusions were examined at 0, 8.8, 29.3, 58.3, and 88 mg/kg/h. Each intravenous infusion was preceded by a 5-min loading dose at respective dose levels of 0, 0.9, 3.1, 6.1 and 9.2 mg/kg. The objective of this intravenous dosing regimen was to emulate the plasma concentration time profile observed with oral dosing. Doses were administered twice per week, with a 3- to 4-day washout period between doses.

"Continuation study PCLN-PIRF-109: With oral doses of 30 and 100 mg/kg, slight, transient increases in heart rate and decreases in RR interval occurred, while only 100 mg/kg caused such decreases in the PR interval. Slight decreases in QT interval were observed but were transient in nature and within the normal range of variation, and were therefore not considered adverse. The NOAEL for cardiovascular parameters was determined to be at least 30 mg/kg (C_{max}: 13.9 μg/mL) with oral dosing because at 100 mg/kg, the amount of the dose discharged by emesis was unknown. Therefore, for cardiovascular endpoints, the NOAEL for intravenous dosing was determined to be the highest dose tested, 9.2 mg/kg bolus followed by 88 mg/kg/h. On the basis of toxicokinetics determinations for the next-lowest dose, the C_{max} for this cardiovascular NOAEL was > 62.4 μg/mL.

"Another dog safety pharmacology experiment (Study PCLN-PIRF-024) examined potential changes in blood pressure, cardiac rhythm, and respiration in pentobarbital anesthetized dogs administered pirfenidone by a continuous IV infusion. In four dogs administered pirfenidone at 3.0 and 4.0 mg/kg/min, pirfenidone did not affect blood pressure or heart rate, nor did it have any noticeable impact on respiration until the infused load reached 100 to 150 mg/kg with the 3.0 mg/kg/min regimen, and 150 to 200 mg/kg with the 4.0 mg/kg/min regimen. After reaching these threshold loads, the continued input of pirfenidone (via the ongoing infusions) caused gradual diminishment of blood pressure and respiration rate and depth. Death ensued at an average load of 400 mg/kg of pirfenidone, with respiratory failure being the precipitating cause of death.

"Electrocardiograms (Lead II) taken at the onset of the infusion, frequently during the infusion, and after the appearance of the respiratory inadequacy did not show evidence of any abnormal rhythms. QRS and PR intervals, QT values, and the character of the P and T tracings were normal in appearance and similar to control tracings taken before initiation of the infusions".

Reviewer's Comments: The IC_{50} for the parent compound to inhibit hERG channel currents was ~200-times the C_{max} unbound fraction of the proposed therapeutic dose. The metabolite did not affect hERG currents at concentrations up to 215 μg/ml. In the guinea pig myocyte model, neither pirfenidone nor its 5-carboxylic acid metabolite (at concentrations ≤185 μg/ml and 215μg/ml respectively) affected resting membrane potential, action potential amplitude, maximum rising velocity, or action potential duration at 50% and 90% repolarization. Study PCLN-PIRF-071performed in conscious telemetered dogs shows that pirfenidone, at doses 10-times the unbound C_{max} for the proposed therapeutic dose, increases heart rate and prolongs QTc. Study PCLN-PIRF-

109 evaluated orally and intravenously administered pirfenidone in conscious dogs. Oral and IV doses caused slight, transient increases in heart rate, the NOAEL for oral was 3-times the unbound C_{max} and for IV was 10-times the unbound C_{max}, in both cases based on a C_{max} exposure of a therapeutic dose of 2403 mg/day.

Taken together all these findings there are no preclinical evidences that pirfenidone may affect QTc.

3.3 PREVIOUS CLINICAL EXPERIENCE

From the IB

> "In Schmidt 1975, pirfenidone was administered orally to 20 healthy adults (18 males and 2 females). The doses were slowly increased from 300 to 2400 mg/subject/day for 3 days at each dose to examine tolerability. AEs were observed at 600 mg/subject/day or higher: one subject in the 1800 mg/subject/day group and 2 subjects in the 2400 mg/subject/day group required dose reductions.
>
> "PIPF-005, which studied oral pirfenidone in 35 healthy older adults, assessed the effects of multiple dosing, dose-ranging, food, and antacids. Subjects were divided into two groups, a Single-Dose Cohort and a Multiple-Dose Cohort. In the Single-Dose Cohort (801 mg total dose), there were no deaths, SAEs, or discontinuations due to AEs. The majority of subjects (75%) experienced mild to moderate AEs that were considered possibly or probably related to study treatment. The most frequent AEs were nausea (43.8%) and dizziness (37.5%).
>
> "No subjects had a postdose heart-rate adjusted QT-wave interval (Fridericia correction QTcF) greater than 500 ms or had a QTcF change from baseline greater than 60 ms.
>
> "In the Multiple-Dose Cohort, 22 subjects received all scheduled doses; the mean total cumulative dose of study drug received was 9345 (± 0) mg per patient. A total of 23 subjects (92%) experienced nonserious AEs. Most AEs were mild in severity and most were assessed as possibly or probably related to study treatment. The most common AEs were nausea (36%), somnolence (32%), headache (28%), dizziness (24%), constipation, dyspepsia, and flatulence (20% each). Of the AEs that increased in frequency with increasing dosages (headache, dyspepsia, nausea, back pain), most were apparent after treatment at the two highest dose levels (1068 and 1335 mg, TID).
>
> "Study PIPF-008, which was designed to determine the maximum tolerated dose of oral pirfenidone, was a double-blind, placebo-controlled study in 20 healthy younger adults. The subjects, 10 women and 10 men, between the ages of 19 and 38 years were. Of the 16 subjects who received pirfenidone, 14 subjects (87.5%) experienced nonserious AEs. The most common AEs in the pirfenidone group were headache (68.8%), nausea (50.0%), dyspepsia (50.0%), and vomiting (31.3%). Of the 8 women receiving pirfenidone, 3 (35%) discontinued treatment, 1 subject during the 4005-mg/day dose level and 2 during the 4806-mg/day dose level. No men discontinued the study secondary to AES. All 3 women discontinued due to a constellation of symptoms that included nausea and vomiting, and at least one of the three women experienced headache, dyspepsia,

dizziness, increased heart rate, and tremors. Therefore, based on the above-mentioned safety results from the study, the MTD was determined to be 4005 mg/day.

"The patient population enrolled in the seven completed IPF trials for which comprehensive data are available is consistent with the epidemiology in the United States of IPF patients with moderate impairment in lung function.

"The majority of patients enrolled in the seven studies were males in their early sixties (range: 28 to 81 years). Most patients had been diagnosed with IPF for more than one year before being treated with pirfenidone. The mean % predicted FVC at baseline ranged from 47.0% to 58.8%. Pirfenidone was generally well-tolerated at doses up to approximately 40 mg/kg/day for up to 2 years. The daily dose of pirfenidone ranged from 1200 to ≤3600 mg across the seven studies.

"As shown in Table 5 21, the most commonly reported AEs among patients treated with pirfenidone (206) or placebo (61) in the seven clinical IPF studies for which comprehensive data are available included nausea (72/206, 35% vs. 5/61, 8%), photosensitive rash (52/206, 25% vs. 2/61, 3%), fatigue (51/206, 25% vs. 6/61, 10%), anorexia (44/206, 21% vs. 4/61, 7%), cold syndrome (28/206, 14% vs. 0), γ-GTP elevation (23/206, 11% vs. 3/61, 5%), gastric discomfort (22/206, 11% vs. 3/61, 5%)."

Table 5–21 Pooled Adverse Events Occurring in ≥10% of Patients Treated with Pirfenidone[a] and at a Greater Rate than Control in the Seven Completed Studies

Adverse Event	Pirfenidone n = 206	Placebo n = 61	Prednisone n = 27
Nausea	72 (35%)	5 (8%)	3 (11%)
Rash (photosensitivity)	52 (25%)	2 (3%)	0
Fatigue	51 (25%)	6 (10%)	0
Anorexia	44 (21%)	4 (7%)	0
Cold syndrome	28 (14%)	0	0
γ-GTP elevation	23 (11%)	3 (5%)	0
Gastric discomfort	22 (11%)	3 (5%)	0

[a]AEs from six Marnac studies and the double-blind period of the Shionogi Phase 2 study (data on file, 2004).

Reviewer's Comments: The safety of pirfenidone in healthy subjects has been evaluated in four studies, ~70 subjects were exposed to pirfenidone either at single doses up to 801 mg or multiple doses up to 4000 mg/day. Approximately 250 patients were exposed to pirfenidone with daily doses up to 3600 mg/day. Similar rate of serious adverse events were reported in patients treated with drug or with placebo. Higher discontinuation rate due to AEs was seen in the pirfenidone group (14%) than in the placebo group (5%). No syncope, seizures, sudden death or ventricular tachy arrhythmias were reported in these studies. No changes in ECG parameters were reported.

3.4 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of pirfenidone's clinical pharmacology.

4 SPONSOR'S SUBMISSION

4.1 OVERVIEW

The sponsor submitted a thorough QT study report for pirfenidone including electronic datasets and waveforms to ECG warehouse. The QT-IRT had previously reviewed the protocol for this study and provided comments on December 4, 2006.

4.2 TQT STUDY

4.2.1 Title

A Double-Blind, Randomized, Parallel Study to Define the Electrocardiographic Effects of Oral Pirfenidone Using a Clinical and Supratherapeutic Dose Compared to Placebo and Moxifloxacin (an Open-Label Positive Control) in Healthy Volunteers

4.2.2 Protocol Number

PIPF-007

4.2.3 Study Dates

31 January 2007 (date first subject enrolled)

10 April 2007 (date last subject completed study)

4.2.4 Objectives

Primary Objectives (ECG Evaluation)

- To evaluate the impact of pirfenidone on the QT interval in healthy subjects
- To evaluate the impact of pirfenidone on other electrocardiogram (ECG) parameters

Secondary Objectives (Pharmacokinetic [PK] Evaluation)

- To evaluate the correlation between QTc change and the PK of pirfenidone and the major metabolite, 5-carboxy-pirfenidone

General Subject Safety Variables

- To evaluate the safety of escalating doses of oral pirfenidone

4.2.5 Study Description

4.2.5.1 Design

This is a double-blind, randomized, 4-arm, parallel study.

4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

4.2.5.3 Blinding

Moxifloxacin, positive control, was not blinded.

4.2.6 Treatment Regimen

4.2.6.1 Treatment Arms

A total of 160 healthy subjects (approximately 50% males, 50% females) were randomly assigned (1:1:1:1) to one of the following treatment groups:

Group 1 Pirfenidone 2403 mg/d (therapeutic dose)

Group 2 Pirfenidone 4005 mg/d (supratherapeutic dose)

Group 3 Positive control (placebo plus 400 mg/d oral moxifloxacin)

Group 4 Placebo

Table 2: Summary of the Dosing Schedule

Dosing Arms	Study Days											FU
	-1	1	2	3	4	5	6	7	8	9	10	11
Therapeutic												
Total daily dose of pirfenidone (mg)	0	801		1602		2403		2403		2403		0
No. of pirfenidone capsules TID		1		2		3		3		3		
No. of placebo capsules TID		0		0		0		1		2		
Total no. of capsules/day		3	3	6	6	9	9	12	12	15	15	
Supratherapeutic												
Total daily dose of pirfenidone (mg)	0	801		1602		2403		3204		4005		0
No. of pirfenidone capsules TID		1		2		3		4		5		
Total no. of capsules/day		3	3	6	6	9	9	12	12	15	15	
Positive Control												
No. of placebo capsules TID	0	1		2		3		4		5		0
No. of moxifloxacin tablets TID		0		0		0		0		0	1	
Total no. of capsules and tablets/day		3	3	6	6	9	9	12	12	15	15 + 1 Moxi.	
Placebo												
No. of placebo capsules TID	0	1		2		3		4		5		0
Total no. of capsules/day		3	3	6	6	9	9	12	12	15	15	

d = day; FU = follow-up; No. = number; TDD = total daily dose; TID = three times per day; Moxi. = moxifloxacin tablet.
Notes: All doses were to be taken TID with food at the following time points: ~0800, ~1200, and ~1800.

4.2.6.2 Sponsor's Justification for Doses

"This study used the same therapeutic dose of pirfenidone that is being used in the InterMune Phase 3 trials in patients with IPF: 2403 mg/d, given as 801 mg TID with food. The supratherapeutic dose used in this study was 4005 mg/d given as 1335 mg TID with food. This supratherapeutic dose was chosen based on results of the recently conducted MTD study (PIPF-008) in which 3 of the 8 (37.5%) female subjects receiving pirfenidone (1 at 4005 mg/d and 2 at 4806 mg/d) discontinued because of AEs including nausea, vomiting, shakiness, increased heart rate, headache, and tremor. Two of these 3 subjects experienced Grade 2 vomiting based on having 2 to 5 vomiting episodes during a 24-h period.

"Study PIPF-008 was stopped after dosing in the 4806-mg/d dosing level was completed. However, since the dose level of 4806 mg/d was considered to be intolerable due to the observed AEs and discontinuations, the next lower dose 4005 mg/d was designated as the MTD. Although this dose is less than 2 times the therapeutic dose, InterMune believes that, based on the discontinuations and AEs observed in Study PIPF-008, it would not have been possible to administer all the doses and conduct all the ECGs prescribed in the supratherapeutic dose

arm of this thorough QT/QTc study if a dose higher than 4005 mg/d had been used."

(Source: "Selection of Dose in the Study" from the clinical study report, P-38)

Reviewer's Comments:

1. *The selection of therapeutic dose of pirfenidone (i.e., 801 mg TID, total dose: 2403 mg/day) in this TQT study appears to be reasonable.*
2. *The sponsor used the maximum tolerated dose (4005 mg/d) as supra-therapeutic dose, which is about 67% higher than the therapeutic dose. Because the drug is mainly eliminated through kidney (80%) as 5-carboxy-pirfenidone (> 95% of that recovered), one would expect that pirfenidone exposure will increase in patients with renal impairment or hepatic impairment. Coadministration of CYP1A2 inhibitor, such as fluvoxamine, can potentially affect pirfenidone exposure as well. However, the quantitative assessment of the exposure change under these conditions is unavailable (Appendix 6.1: Highlights of Clinical Pharmacology). Therefore, it is not feasible for us to determine whether the supratherapeutic dose can adequately cover the expected maximum exposure increase until the results of the renal, hepatic and drug interactions studies are complete.*

4.2.6.3 Instructions with Regard to Meals

Doses were administered with food.

Reviewer's Comments: It appears that pirfenidone C_{max} is reduced by 50% in fed condition as compared to fast condition (Appendix 6.1: Table 2). GI disorder is one of the major adverse effects of pirfenidone (Appendix 6.1: Table 1). Taking pirfenidone with food might be able to increase the tolerability.

4.2.6.4 ECG and PK Assessments

Table 3: ECG and PK Assessment

Study Day	**0**	**6** [#4]	**10**
Intervention[#1]	No treatment (Baseline)	Multiple Dose (TID Dose)	Multiple Dose (TID Dose)
12-Lead ECGs [#3]	Record ECGs [#2]	Record ECGs [#2]	Record ECGs [#2]
PK Samples for drug	None collected	Collected [#2]	Collected [#2]

#1: The dosing schedule is summarized in Table 2.
#2: 0 (Predose), 0.5, 1, 2, 3, 4 (Predose), 4.5, 5, 6, 7, 8, 10 (Predose), 10.5, 11, 12, 13, 14, 16, 18, 23.5
#3: ECGs were collected about 2 minutes prior to the PK samples
#4: The study time points on Day 6 were to be analyzed only if needed to determine signal *(Source: P-47, Clinical Study Report).*

4.2.6.5 Baseline

The sponsor used pre-day time-matched QTc values as the baseline.

4.2.7 ECG Collection

For safety ECGs acquisition standard digital 12-lead ECGs was performed.

For endpoint analysis, continuous 12-lead ECGs was collected using a Mortara H12+ 12-Lead Digital Holter Recorder provided by the ECG central laboratory, (b) (4) Each. 12-lead ECG signals was continuously captured on compact flash memory cards for 24 hours intervals on Days -1, 6 and 10.

ECGs were read and interpreted by a trained cardiologist who remained blinded to patient treatment assignment.

4.2.8 Sponsor's Results

4.2.8.1 Study Subjects

The total number of subjects enrolled were 162 (males and females), 18 to 45 years of age, normal ECGs, BMI 18 to 32 kg/m^2.

4.2.8.2 Statistical Analyses

4.2.8.2.1 Primary Analysis

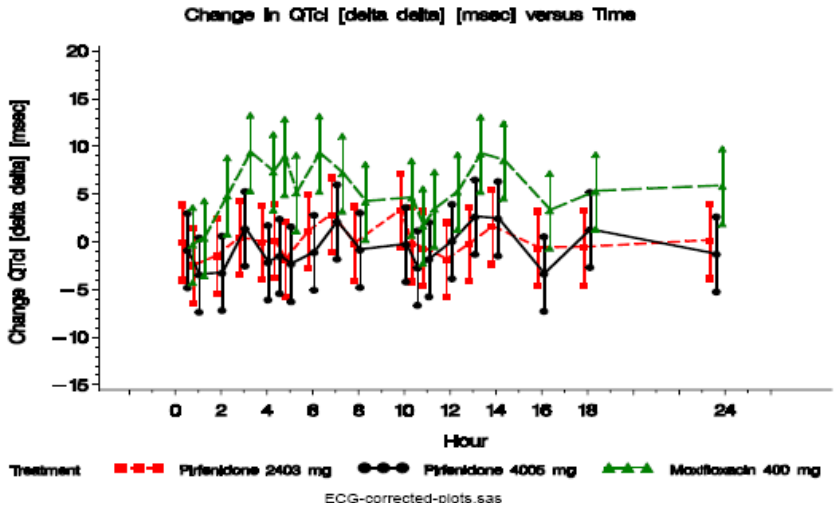
The primary endpoint was the change from the baseline in ΔQTcI. The sponsor used Linear Mixed Effect Model including treatment, time point, gender and treatment and time point interaction terms. Table 4 presents sponsor's ΔΔQTcI result. The upper bounds of the one-sided 95% CIs for the mean differences between pirfenidone (doses of 2403 mg/d and 4005 mg/d) and placebo in QTcI at each time point were less than 10 ms. Moxifloxacin was included as a positive control in order to validate the assay sensitivity of the study and the analysis results are also presented in Table 4. However, only the upper bounds of the one-sided 95% CIs for the mean differences between moxifloxacin and placebo in QTcI at each time point were reported. Figure 2 presented graph of ΔΔQTcI over time.

Table 4: Sponsor's Primary ΔΔQTcI Analyses

	Therapeutic Pirfenidone (2403 mg/d)		Supratherapeutic Pirfenidone (4005 mg/d)		Positive Control	
Time (h)	Estimate[a]	Upper[b]	Estimate[a]	Upper Bound[b]	Estimate[a]	Upper Bound[b]
0.5	-0.1	3.8	-1.2	2.7	-0.8	3.1
1	-2.6	1.3	-3.8	0.1	-0.1	3.8
2	-1.6	2.3	-3.6	0.3	4.3	8.3
3	0.3	4.2	1.1	5.0	8.8	12.8
4	-0.2	3.7	-2.5	1.4	6.8	10.8
4.5	-0.0	3.9	-1.8	2.1	8.4	12.3
5	-1.9	2.0	-2.7	1.3	4.6	8.6
6	1.0	4.9	-1.4	2.5	8.7	12.6
7	2.7	6.6	1.8	5.6	6.6	10.6
8	-0.3	3.6	-1.2	2.7	3.7	7.6
10	3.2	7.1	-0.6	3.3	4.1	8.0
10.5	-0.4	3.5	-3.1	0.8	1.1	5.0
11	-0.8	3.1	-2.2	1.7	2.9	6.8
12	-2.0	1.9	-0.3	3.6	4.7	8.6
13	-0.4	3.5	2.2	6.1	8.6	12.5
14	1.4	5.3	2.1	5.9	7.9	11.8
16	-0.8	3.1	-3.7	0.2	2.7	6.6
18	-0.8	3.1	0.9	4.8	4.7	8.6
23.5	-0.1	3.8	-1.7	2.2	5.3	9.2

[a]Mixed Model ANOVA is fit for placebo-corrected change from baseline and includes terms for treatment, gender, time, and a time by treatment interaction.
[b]Upper Bound = upper one-sided 95% ANOVA model based confidence limit.
p-value for gender effect (gender main effect and treatment by gender IA) is 0.3324 Tx*gender IA = 0.2670.
Data source: ecg_all2.sas7bdat Program source: CI-ECG-corrected.sas Listing source: 16.2.6

Figure 2: Sponsor's Graph ΔΔQTcI for Treatment and Moxifloxacin Groups



4.2.8.2.2 Categorical Analysis

Categorical analysis was used to summarize QTcI >450, >480 and >500 ms, and changes from baseline > 30, ≥ 30 and < 60, and > 60 ms.

No subject observed a QTcI > 480 ms or a change from baseline QTcI > 60 ms.

4.2.8.3 Safety Analysis

There were no deaths or clinically relevant SAEs. No syncope nor seizures, sudden death or ventricular tachy arrhythmias were reported in this study.

There were three discontinuations: Two subjects (0252 and 0285; both in the supratherapeutic dose group) discontinued treatment late in the treatment regimen due to a treatment-emergent AEs (dyspepsia; nausea); 1 subject (0067) in the positive control group elected to withdraw consent half-way through the treatment regimen:

- **Subject 0067** withdrew consent on Day 5 after completing 4 full days of scheduled placebo doses on Days 1 4 plus two placebo doses on Day 5.
- **Subject 0252** discontinued treatment on the afternoon of Day 10 before the last dose, after taking a total of 29 individual doses and a maximal daily dose of 4005 mg of pirfenidone. She discontinued due to dyspnea and also experienced dry eye, nausea, oral and facial hypoaesthenia (numb lip and face), nervousness (shaky), and headache on the same day.

  Note: By examining adjacent ECGs of subject 0252 on day 10 this reviewer did not find changes in wave morphology or changes in segment/interval duration.
- **Subject 0285** discontinued treatment on the morning of Day 10 before the first daily dose, after taking a total of 27 individual doses and a maximal daily dose of 4005 mg of pirfenidone. She discontinued due to nausea and also experienced abdominal pain, headache, and increased respiratory rate the same day.

The incidence of treatment-emergent AEs (TEAEs) was higher in the pirfenidone-treated groups than in the positive control and placebo groups. More of the subjects in the supratherapeutic and therapeutic dose groups had TEAEs that were considered to be related to study treatment (24/41, 58.5%, and 18/40, 45.0%, respectively) than subjects in the positive control group (14/41, 34.1%) and placebo group (15/40, 37.5%) being slightly higher in the supratherapeutic dose (dose response).

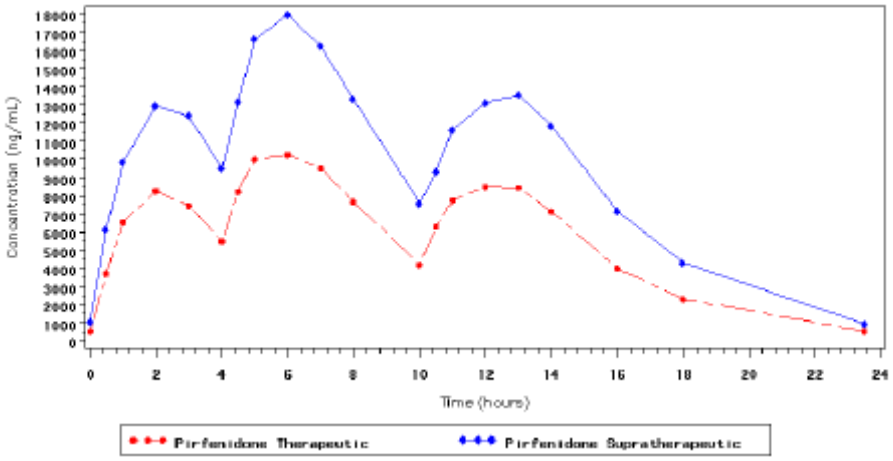
Most AEs reported with both doses were headache and nausea followed by vomiting and dyspepsia. No subject experienced a serious adverse event.

4.2.8.4 Clinical Pharmacology

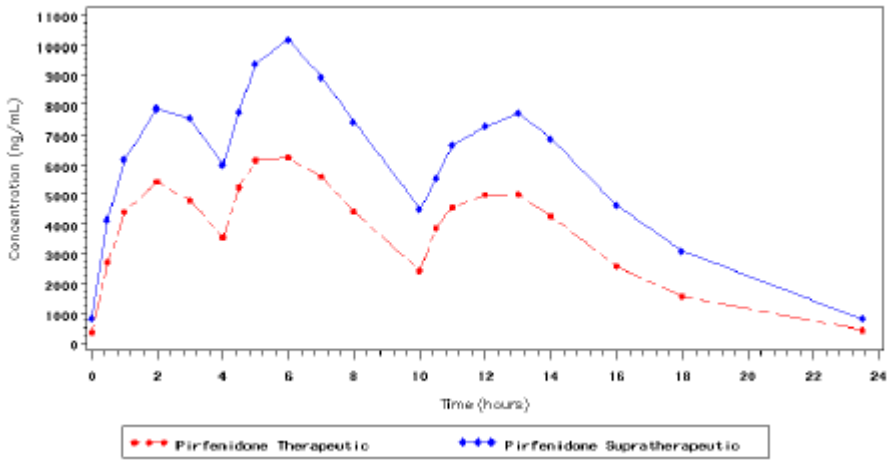
4.2.8.4.1 Pharmacokinetic Analysis

The pirfenidone and its major metabolite 5-carboxy-pirfenidone concentration time profile were shown in Figure 3. The major pharmacokinetic parameters were summarized in Table 5.

Figure 3: Pirfenidone (A) and 5-Carboxy-Pirfenidone (B) Mean Concentration Time Profile (under Linear Scale)



(A)



(B)

Table 5: Major Pharmacokinetic Parameters (Arithmetic Mean ± SD) for Pirfenidone (A) and 5-Carboxy-Pirfenidone (B)

Pirfenidone PK Parameter	Pirfenidone Dose Escalated to 2403 mg/day (therapeutic dose)	Pirfenidone Dose Escalated to 4005 mg/day (supratherapeutic dose)
CL_t/F (hr/mL)	0.0167 (±0.0074)	0.0168 (±0.0082)
C_{max} (ng/mL)	12300.25 (±3796.45)	19802.50 (±6450.90)
t_{max} (hr)	1.49 (±0.92)	1.80 (±0.84)
$t_{1/2}$ (hr)	2.39 (±0.54)	2.39 (±0.52)

(A)

5-Carboxy-Pirfenidone PK Parameter	Pirfenidone Dose Escalated to 2403 mg/day (therapeutic dose)	Pirfenidone Dose Escalated to 4005 mg/day (supratherapeutic dose)
CL_t/F (hr/mL)	0.0232 (±0.0055)	0.0239 (±0.0081)
C_{max} (ng/mL)	7341.00 (±1502.89)	11128.25 (±2631.76)
t_{max} (hr)	1.58 (±0.94)	1.69 (±0.85)
$t_{1/2}$ (hr)	2.82 (±0.82)	2.92 (±0.77)

(B)

(Source: Appendix 16.6.2: Pharmacokinetic Study Report)

4.2.8.4.2 Exposure-Response Analysis

The sponsor did not explore the exposure-response relationship. According to the analysis plan, the sponsor would not model the exposure-response relationship unless there was evidence of an effect of pirfenidone on cardiac repolarization. Because the sponsor's primary analysis indicated no QT prolongation effect, the exposure-response analysis was not conducted.

(Source: P-57, Clinical Study Report, Section 9.7.1.2.1.10)

5 REVIEWERS' ASSESSMENT

5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

We evaluated the linear relationships between different correction methods (QTcB and QTcF) versus RR. We used mean sum of squared slopes (MSSS) as the criterion. The smaller this value is, the better the correction. Based on the results listed in Table 6, QTcF appears to produce the smallest MSSS. However, the difference of overall MSSS between QTcF and QTcI is small.

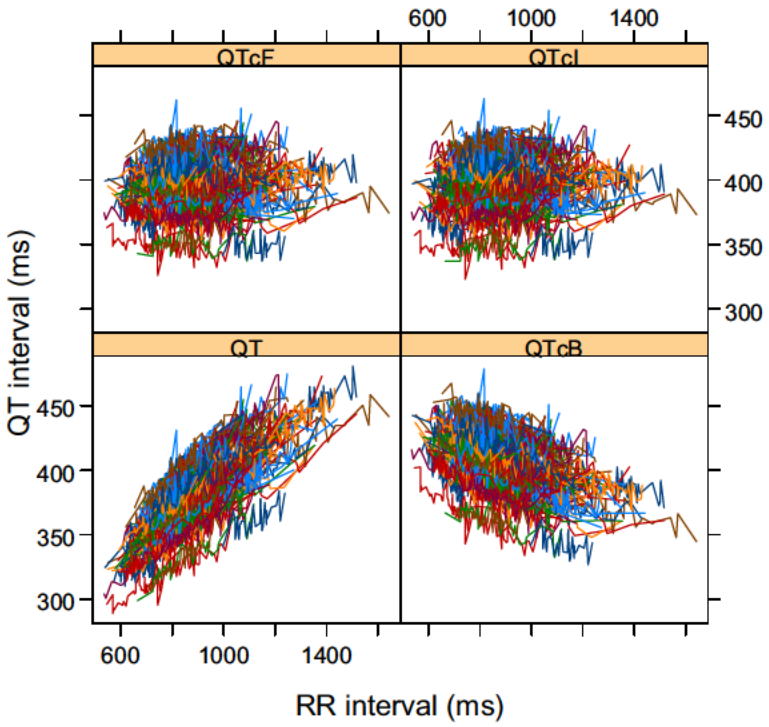
Table 6: Average of Sum of Squared Slopes for Different QT Correction Methods

	Treatment									
	All+		placebo		Pirfenidone 2403 mg		Pirfenidone 4005 mg		Moxifloxacin	
method	N	MSSS*	N	MSSS*	N	MSSS*	N	MSSS*	N	MSSS*
QTcB	160	0.0055	40	0.0050	40	0.0055	40	0.0056	40	0.0057
QTcF	160	0.0010	40	0.0006	40	0.0008	40	0.0012	40	0.0014
QTcI	160	0.0019	40	0.0016	40	0.0017	40	0.0022	40	0.0024

Note: +All: Combined all treatment groups
*MSSS: Mean of Sum of Squared Slope

The observed QT-RR interval relationship is presented in Figure 4 together with the Bazett's (QTcB), Fridericia (QTcF), and individual correction (QTcI).

Figure 4: QTcF, QTCI, QT and QTcB versus RR



5.2 STATISTICAL ASSESSMENTS

5.2.1 QTc Analysis

We performed the same analysis using both QTcF and QTcI and the results were consistent; therefore, only the results of QTcI are presented.

We used mixed model to analyze the ΔQTcI effect. The model includes treatment, time, and treatment-by-time point interaction as fixed effects. The analysis results are listed in Table 7 and Table 8. The largest upper bounds of 2-sided 90% CIs for the mean difference between pirfenidone 2403 mg/d and placebo, and between pirfenidone 4005 mg/d an placebo were 3.2 ms at 10 hours and 2.2 ms at 13 hours after dose posing, respectively.

Table 7: Analysis Results of ΔΔQTcI between Pirfenidone 2403 mg/d and Placebo Group

	Pirfenidone 2403 mg/d		Placebo		ΔΔQTcI	
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI
0.5	-3.2	1.6	-3.2	1.5	-0.0	(-3.6, 3.6)
1	-4.4	1.5	-1.8	1.5	-2.6	(-6.1, 1.0)
2	-2.2	1.5	-0.6	1.6	-1.6	(-5.2, 2.0)
3	-0.6	1.5	-1.0	1.6	0.3	(-3.2, 3.9)
4	-1.4	1.5	-1.2	1.5	-0.2	(-3.7, 3.4)

	Pirfenidone 2403 mg/d		Placebo		ΔΔQTcI	
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI
4.5	-3.4	1.5	-3.4	1.5	-0.0	(-3.6, 3.6)
5	-3.4	1.5	-1.5	1.5	-1.9	(-5.5, 1.6)
6	0.2	1.5	-0.8	1.5	1.0	(-2.6, 4.6)
7	1.2	1.5	-1.5	1.5	2.7	(-0.8, 6.3)
8	0.7	1.5	1.0	1.5	-0.3	(-3.9, 3.3)
10	-0.4	1.5	-3.6	1.5	3.2	(-0.4, 6.7)
10.5	-1.7	1.5	-1.3	1.5	-0.4	(-4.0, 3.2)
11	-2.6	1.5	-1.7	1.5	-0.8	(-4.4, 2.7)
12	-5.1	1.5	-3.1	1.5	-2.0	(-5.6, 1.5)
13	-3.7	1.5	-3.3	1.5	-0.4	(-3.9, 3.1)
14	-1.4	1.5	-2.8	1.5	1.4	(-2.1, 4.9)
16	-4.3	1.5	-3.4	1.5	-0.8	(-4.4, 2.7)
18	-3.8	1.5	-3.0	1.5	-0.8	(-4.4, 2.8)
23.5	-1.8	1.5	-1.7	1.5	-0.1	(-3.6, 3.5)

Table 8: Analysis Results of ΔΔQTcI between Pirfenidone 4005 mg/d and Placebo Group

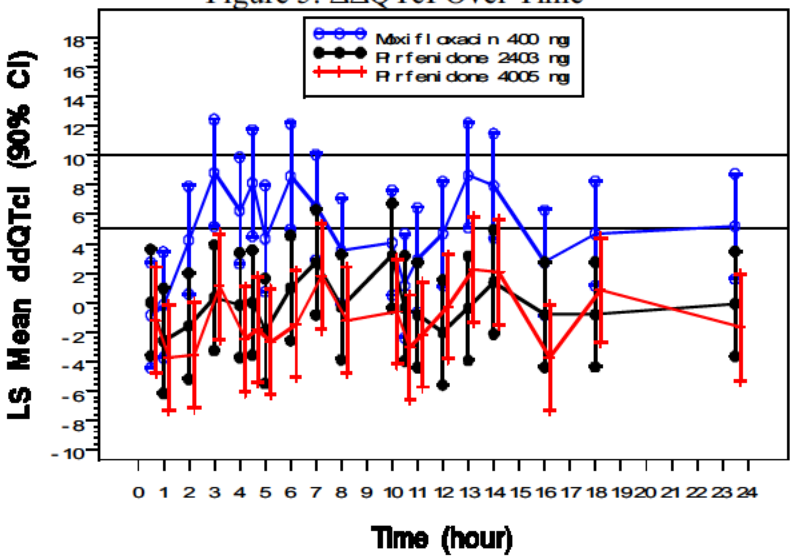
	Pirfenidone 4005 mg/d		Placebo		ΔΔQTcI	
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI
0.5	-4.4	1.5	-3.2	1.5	-1.2	(-4.8, 2.4)
1	-5.6	1.5	-1.8	1.5	-3.8	(-7.3, -0.2)
2	-4.2	1.5	-0.6	1.6	-3.6	(-7.2, 0.0)
3	0.1	1.5	-1.0	1.6	1.1	(-2.5, 4.7)
4	-3.7	1.5	-1.2	1.5	-2.5	(-6.0, 1.1)
4.5	-5.2	1.5	-3.4	1.5	-1.8	(-5.4, 1.7)
5	-4.2	1.5	-1.5	1.5	-2.7	(-6.3, 0.9)
6	-2.3	1.5	-0.8	1.5	-1.5	(-5.1, 2.1)
7	0.3	1.5	-1.5	1.5	1.8	(-1.8, 5.3)
8	-0.2	1.5	1.0	1.5	-1.2	(-4.8, 2.4)
10	-4.2	1.5	-3.6	1.5	-0.6	(-4.2, 2.9)
10.5	-4.4	1.5	-1.3	1.5	-3.1	(-6.6, 0.5)
11	-3.9	1.5	-1.7	1.5	-2.2	(-5.7, 1.4)
12	-3.4	1.5	-3.1	1.5	-0.3	(-3.8, 3.2)
13	-1.1	1.5	-3.3	1.5	2.2	(-1.3, 5.8)

	Pirfenidone 4005 mg/d		Placebo		ΔΔQTcI	
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI
14	-0.8	1.5	-2.8	1.5	2.1	(-1.5, 5.6)
16	-7.2	1.5	-3.4	1.5	-3.7	(-7.3, -0.2)
18	-2.2	1.5	-3.0	1.5	0.8	(-2.7, 4.4)
23.5	-3.4	1.5	-1.7	1.5	-1.7	(-5.3, 1.9)

5.2.1.1 Graph of ΔΔQTcI Over Time

The following figure displays the time profile of ΔΔQTcI for pirfenidone (doses of 2403 mg/d and 4005 mg/d) and moxifloxacin treatment groups.

Figure 5: ΔΔQTcI Over Time



5.2.1.2 Assay Sensitivity Analysis

We used the same statistical model to analyze moxifloxacin and placebo data. Table 9 presents results of ΔΔQTcI between moxifloxacin and placebo group. The largest unadjusted 2-sided 90% lower confidence interval is 5.2 ms (≥ 5 ms) at 3 hours. Using the most conservative Bonferroni adjustment, the largest lower bound is 3.8 ms (adjusted by 4 time points).

Table 9: Analysis Result of ΔΔQTcI between Moxifloxacin and Placebo Group

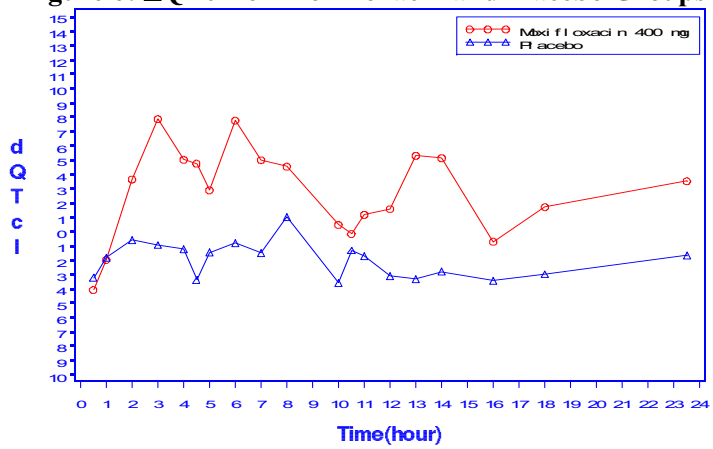
	Moxifloxacin		Placebo		ΔΔQTcI		
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI	Adjusted 90% CI
0.5	-4.1	1.5	-3.2	1.5	-0.9	(-4.4, 2.7)	(-5.7, 4.0)
1	-2.0	1.5	-1.8	1.5	-0.2	(-3.7, 3.4)	(-5.0, 4.7)
2	3.6	1.6	-0.6	1.6	4.2	(0.6, 7.9)	(-0.7, 9.2)
3	7.8	1.6	-1.0	1.6	8.8	(5.2, 12.4)	(3.8, 13.7)

	Moxifloxacin		Placebo		ΔΔQTcI		
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI	Adjusted 90% CI
4	5.0	1.6	-1.2	1.5	6.2	(2.6, 9.9)	(1.3, 11.2)
4.5	4.7	1.6	-3.4	1.5	8.1	(4.5, 11.7)	(3.2, 13.0)
5	2.9	1.6	-1.5	1.5	4.3	(0.7, 8.0)	(-0.6, 9.3)
6	7.7	1.5	-0.8	1.5	8.6	(5.0, 12.1)	(3.7, 13.4)
7	5.0	1.5	-1.5	1.5	6.5	(2.9, 10.1)	(1.6, 11.4)
8	4.5	1.5	1.0	1.5	3.5	(-0.1, 7.1)	(-1.4, 8.4)
10	0.5	1.5	-3.6	1.5	4.1	(0.5, 7.6)	(-0.8, 8.9)
10.5	-0.2	1.5	-1.3	1.5	1.1	(-2.4, 4.7)	(-3.7, 6.0)
11	1.2	1.5	-1.7	1.5	2.9	(-0.6, 6.4)	(-1.9, 7.7)
12	1.6	1.5	-3.1	1.5	4.7	(1.1, 8.2)	(-0.1, 9.5)
13	5.3	1.5	-3.3	1.5	8.6	(5.1, 12.2)	(3.8, 13.4)
14	5.1	1.5	-2.8	1.5	7.9	(4.4, 11.5)	(3.1, 12.8)
16	-0.7	1.5	-3.4	1.5	2.7	(-0.8, 6.3)	(-2.1, 7.6)
18	1.7	1.5	-3.0	1.5	4.7	(1.1, 8.2)	(-0.1, 9.5)
23.5	3.5	1.5	-1.7	1.5	5.2	(1.6, 8.8)	(0.3, 10.1)

- Bonferroni method was applied for multiple endpoint adjustment for 4 time points.

Figure 6 presents moxifloxacin and placebo profiles over time for ΔQTcI. The ΔQTcI values are presented in Table 9 above.

Figure 6: ΔQTcI for Moxifloxacin and Placebo Groups



5.2.1.3 Categorical Analysis

Categorical analysis was used to summarize the absolute QTcI>450, ≥ 450 and ≤ 480, ≥ 480 and ≤ 500, and > 500 ms, and changes from baseline < 30, ≥ 30 and ≤ 60, and > 60 ms. The results are listed in Table 10 and Table 11.

No subject observed a QTcI > 480 ms and ΔQTcI (change from baseline) > 60 ms.

Table 10: Categorical Analysis of QTcI

	Total N		Value<=450		450<Value<=480	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin 400 mg	40	793	39 (97.5%)	791 (99.7%)	1 (2.5%)	2 (0.3%)
Pirfenidone 2403 mg	40	799	40 (100%)	799 (100%)	0 (0.0%)	0 (0.0%)
Pirfenidone 4005 mg	40	799	40 (100%)	799 (100%)	0 (0.0%)	0 (0.0%)
Placebo	40	797	40 (100%)	797 (100%)	0 (0.0%)	0 (0.0%)

Table 11: Categorical Analysis of ΔQTcI

	Total N		Value<=30		30<Value<=60	
Treatment Group	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
Moxifloxacin 400 mg	40	783	38 (95.0%)	780 (99.6%)	2 (5.0%)	3 (0.4%)
Pirfenidone 2403 mg	40	794	39 (97.5%)	793 (99.9%)	1 (2.5%)	1 (0.1%)
Pirfenidone 4005 mg	40	796	39 (97.5%)	795 (99.9%)	1 (2.5%)	1 (0.1%)
Placebo	40	783	40 (100%)	783 (100%)	0 (0.0%)	0 (0.0%)

5.2.2 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 12 and Table 13. The largest upper bounds of 2-sided 90% CIs for the mean differences between pirfenidone 2403 mg/d and placebo, and between pirfenidone 4005 mg/d an placebo were 3.6 ms and 2.3 ms at 23.5 hours after dose posing, respectively.

Table 12: Analysis Results of ΔΔPR between Pirfenidone 2403 mg/d and Placebo Group

	Pirfenidone 2403 mg/d		Placebo		ΔΔPR	
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI
0.5	2.0	1.6	2.6	1.5	-0.6	(-4.2, 3.0)
1	0.7	1.5	1.9	1.5	-1.2	(-4.8, 2.3)
2	2.0	1.5	3.4	1.6	-1.4	(-5.0, 2.2)
3	1.1	1.5	1.5	1.6	-0.4	(-3.9, 3.2)
4	0.5	1.5	3.2	1.5	-2.7	(-6.3, 0.8)
4.5	1.4	1.5	2.6	1.5	-1.2	(-4.8, 2.3)
5	-1.2	1.5	2.4	1.5	-3.6	(-7.1, -0.0)
6	0.2	1.5	1.8	1.5	-1.6	(-5.2, 2.0)
7	1.3	1.5	5.0	1.5	-3.6	(-7.2, -0.1)
8	2.5	1.5	3.0	1.5	-0.5	(-4.1, 3.1)

	Pirfenidone 2403 mg/d		Placebo		ΔΔPR	
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI
10	0.5	1.5	2.8	1.5	-2.3	(-5.9, 1.3)
10.5	4.3	1.5	3.6	1.5	0.6	(-2.9, 4.2)
11	1.7	1.5	2.1	1.5	-0.4	(-4.0, 3.2)
12	-3.2	1.5	1.5	1.5	-4.7	(-8.2, -1.1)
13	1.0	1.5	2.7	1.5	-1.7	(-5.3, 1.8)
14	-0.6	1.5	1.2	1.5	-1.8	(-5.3, 1.7)
16	0.6	1.5	3.7	1.5	-3.1	(-6.7, 0.4)
18	0.6	1.5	5.7	1.5	-5.1	(-8.6, -1.5)
23.5	8.4	1.5	4.7	1.5	3.6	(0.1, 7.2)

Table 13: Analysis Results of ΔΔPR between Pirfenidone 4005 mg/d and Placebo Group

	Pirfenidone 4005 mg/d		Placebo		ΔΔPR	
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI
0.5	2.6	1.5	2.6	1.5	-0.0	(-3.6, 3.6)
1	-1.8	1.5	1.9	1.5	-3.7	(-7.3, -0.2)
2	-0.7	1.5	3.4	1.6	-4.1	(-7.7, -0.5)
3	-2.4	1.5	1.5	1.6	-3.9	(-7.5, -0.3)
4	-2.3	1.5	3.2	1.5	-5.5	(-9.1, -2.0)
4.5	-2.9	1.5	2.6	1.5	-5.5	(-9.1, -2.0)
5	-4.0	1.5	2.4	1.5	-6.4	(-10.0, -2.8)
6	-2.7	1.5	1.8	1.5	-4.5	(-8.1, -0.9)
7	-0.2	1.5	5.0	1.5	-5.2	(-8.8, -1.6)
8	-0.5	1.5	3.0	1.5	-3.6	(-7.1, -0.0)
10	-0.9	1.5	2.8	1.5	-3.7	(-7.3, -0.1)
10.5	1.8	1.5	3.6	1.5	-1.8	(-5.3, 1.8)
11	-0.4	1.5	2.1	1.5	-2.5	(-6.1, 1.0)
12	-2.7	1.5	1.5	1.5	-4.2	(-7.7, -0.7)
13	-1.4	1.5	2.7	1.5	-4.1	(-7.7, -0.6)
14	-0.1	1.5	1.2	1.5	-1.3	(-4.8, 2.3)
16	1.5	1.5	3.7	1.5	-2.2	(-5.8, 1.4)
18	2.6	1.5	5.7	1.5	-3.1	(-6.7, 0.5)
23.5	7.0	1.5	4.7	1.5	2.3	(-1.3, 5.9)

5.2.3 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in Table 14 and Table 15. The largest upper bounds of 2-sided 90% CIs for the mean differences between pirfenidone 2403 mg/d and placebo, and between pirfenidone 4005 mg/d an placebo were 0.3 ms and 0.1 ms at 6 hours after dose posing, respectively.

Table 14: Analysis Results of ΔΔQRS between Pirfenidone 2403 mg/d and Placebo Group

	Pirfenidone 2403 mg/d		Placebo		ΔΔQRS	
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI
0.5	-0.3	0.6	1.1	0.6	-1.3	(-2.6, -0.1)
1	-0.5	0.6	1.3	0.6	-1.8	(-3.1, -0.5)
2	0.6	0.6	0.4	0.6	0.2	(-1.1, 1.5)
3	-0.5	0.6	0.3	0.6	-0.9	(-2.2, 0.5)
4	0.1	0.6	0.0	0.6	0.0	(-1.3, 1.3)
4.5	-0.3	0.6	0.3	0.6	-0.6	(-1.9, 0.7)
5	-0.1	0.6	0.5	0.6	-0.6	(-1.9, 0.7)
6	0.1	0.6	-0.1	0.6	0.3	(-1.0, 1.6)
7	0.2	0.6	0.6	0.6	-0.4	(-1.8, 0.9)
8	-0.5	0.6	0.4	0.6	-0.9	(-2.2, 0.4)
10	-0.7	0.6	-0.3	0.6	-0.4	(-1.7, 0.9)
10.5	-0.6	0.6	1.0	0.6	-1.6	(-2.9, -0.3)
11	-0.9	0.6	0.7	0.6	-1.5	(-2.9, -0.2)
12	-0.7	0.6	-0.4	0.6	-0.3	(-1.6, 1.0)
13	-0.8	0.6	-0.0	0.6	-0.8	(-2.1, 0.5)
14	-1.0	0.6	0.2	0.6	-1.1	(-2.4, 0.2)
16	-1.2	0.6	0.6	0.6	-1.8	(-3.1, -0.5)
18	-1.5	0.6	0.3	0.6	-1.8	(-3.1, -0.5)
23.5	0.1	0.6	0.8	0.6	-0.8	(-2.1, 0.5)

Table 15: Analysis Results of ΔΔQRS between Pirfenidone 4005 mg/d and Placebo Group

	Pirfenidone 4005 mg/d		Placebo		ΔΔQRS	
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI
0.5	0.0	0.6	1.1	0.6	-1.1	(-2.4, 0.3)
1	-0.5	0.6	1.3	0.6	-1.8	(-3.1, -0.5)
2	0.1	0.6	0.4	0.6	-0.3	(-1.6, 1.0)
3	-0.1	0.6	0.3	0.6	-0.4	(-1.8, 0.9)

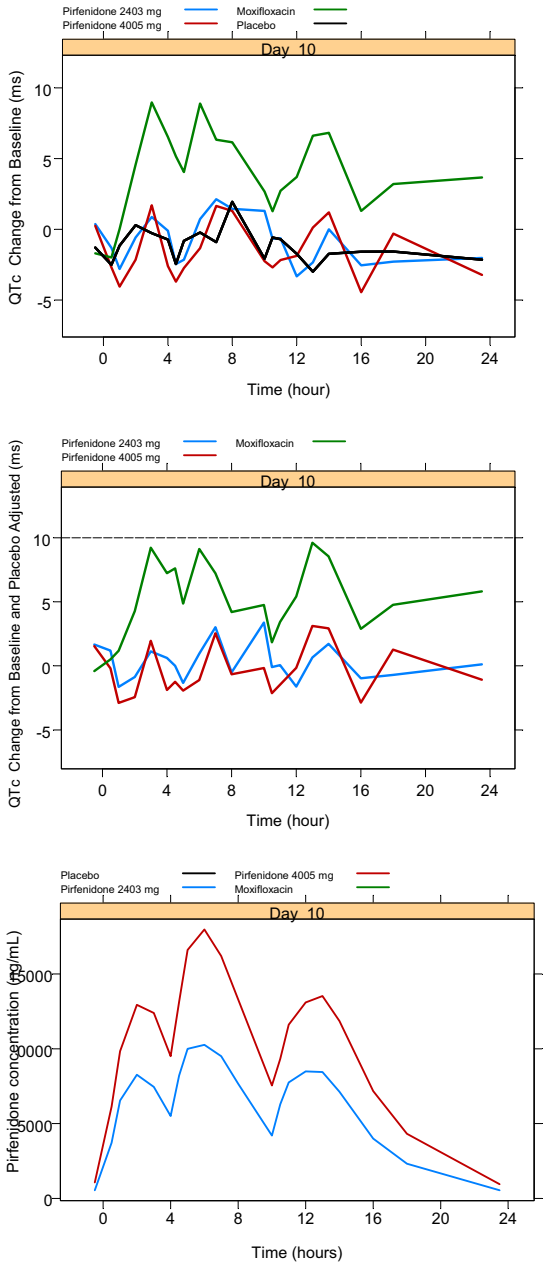
	Pirfenidone 4005 mg/d		Placebo		ΔΔQRS	
Time (hr)	LS Mean (ms)	Std Err.	LS Mean (ms)	Std Err.	LS Mean Diff (ms)	90% CI
4	-0.2	0.6	0.0	0.6	-0.2	(-1.5, 1.1)
4.5	-0.2	0.6	0.3	0.6	-0.5	(-1.8, 0.8)
5	-0.8	0.6	0.5	0.6	-1.3	(-2.6, 0.0)
6	0.0	0.6	-0.1	0.6	0.1	(-1.2, 1.5)
7	-0.3	0.6	0.6	0.6	-0.9	(-2.2, 0.4)
8	-0.5	0.6	0.4	0.6	-0.8	(-2.1, 0.5)
10	-0.5	0.6	-0.3	0.6	-0.2	(-1.5, 1.1)
10.5	-0.5	0.6	1.0	0.6	-1.5	(-2.8, -0.2)
11	-0.9	0.6	0.7	0.6	-1.5	(-2.8, -0.3)
12	-0.5	0.6	-0.4	0.6	-0.1	(-1.4, 1.2)
13	-0.1	0.6	-0.0	0.6	-0.1	(-1.4, 1.2)
14	-0.4	0.6	0.2	0.6	-0.5	(-1.8, 0.8)
16	-0.8	0.6	0.6	0.6	-1.4	(-2.7, -0.1)
18	-1.0	0.6	0.3	0.6	-1.3	(-2.6, 0.0)
23.5	-0.7	0.6	0.8	0.6	-1.6	(-2.9, -0.2)

5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

5.3.1 QTcI and Pirfenidone Concentration Time Profiles

The mean ΔQTcI, ΔΔQTcI, Pirfenidone, and Moxifloxacin concentration time profile is illustrated in Figure 7.

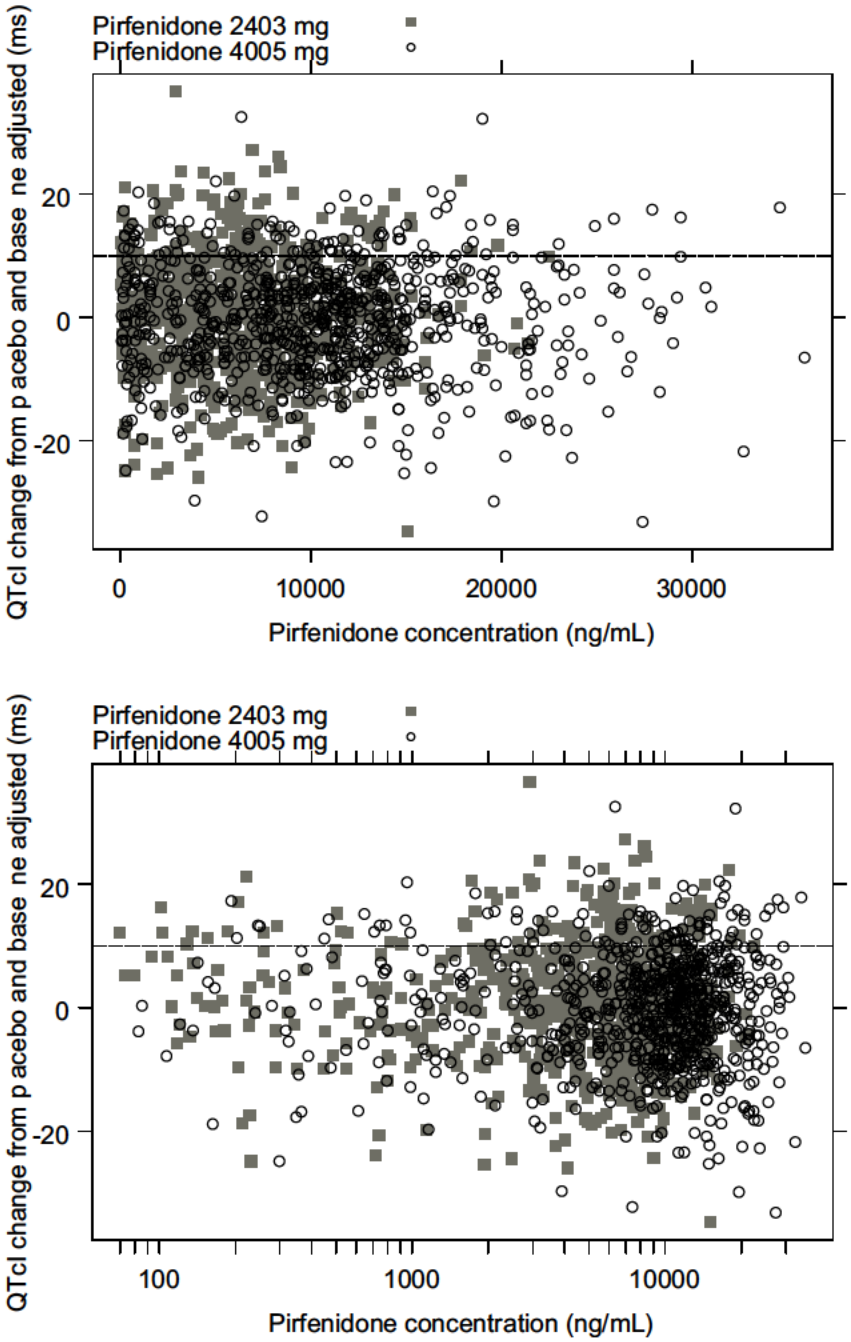
Figure 7: Mean Δ QTcI (change from baseline) (top), ΔΔ QTcI (placebo-adjusted change from baseline) (middle), Pirfenidone concentration (bottom) time profiles for Pirfenidone 2403 mg (blue line), Pirfenidone 4005 mg (red line), moxifloxacin (green line), and placebo (black line).



5.3.2 Pirfenidone Concentration-QTcI Analysis

The relationship between ΔΔ QTcI and Pirfenidone concentrations is visualized in Figure 8 with no evident exposure-response relationship.

Figure 8: ΔΔ QTcI vs. Pirfenidone concentration.



5.4 CLINICAL ASSESSMENTS

5.4.1 Safety assessment

None of the events identified to be of clinical importance per the ICH E 14 guidelines i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death occurred in this study.

5.4.2 ECG acquisition and interpretation

Waveforms from 162 subjects were reviewed in the ECG warehouse. Central ECG reading laboratory was [redacted] (b) (4) Annotations were on lead II, in less than 1.8% of the cases annotations were in multiple leads at same and adjacent time points. This reviewer confirmed that < 1 % of the ECGs had any significant QT bias according to the ECG warehouse algorithm. Overall, ECG acquisition and interpretation in this study appears acceptable.

5.4.3 PR and QRS intervals

There were no changes in the PR and QRS intervals as shown in Table 12 to Table 15.

6 APPENDIX

6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Highlights of Clinical Pharmacology

Therapeutic dose	*Include maximum proposed clinical dosing regimen.* 2403 mg/day	
Maximum tolerated dose	*Include if studied or NOAEL dose* MTD 4005 mg/day	
Principal adverse events	*Include most common adverse events-* Reference Table 1 below which presents the expected AEs in patients treated with pirfenidone for IPF. An "expected" event is defined as either: 1) an AE that in clinical trials consistently has been observed more frequently in patients treated with pirfenidone as compared to patients treated with placebo or comparator, and thus likely represents an adverse drug reaction, or 2) an event that frequently is observed in the patient population and thus likely is related to the underlying disease or concomitant conditions and expected to be observed in the population. *Dose limiting adverse events-* In the MTD study (PIPF-008), the prespecified criteria for MTD based on number and grade of AEs were not reached. However, per the protocol, the PI and the sponsor made a joint decision to stop the study based on safety considerations, specifically, the fact that 3 of the 8 pirfenidone-treated women in the study (37.5%) discontinued because of AEs including nausea, vomiting, shakiness, increased heart rate, headache, and tremor;and 2 of these women experienced Grade 2 vomiting. Study PIPF-008 was stopped after dosing in the 4806-mg/d dosing level was completed. Since the dose level of 4806 mg/d was considered to be intolerable due to the observed AEs and discontinuations, the next lower dose—4005 mg/d—was designated as the MTD. This dose is less than 2 times the therapeutic dose.	
Maximum dose tested	Single Dose	*Specify dose* 801 mg/day
	Multiple Dose	*Specify dosing interval and duration* In PIPF-005, 1335 mg TID was given for 2 full days plus one dose on day 3 for a total of for 7 doses.

Exposures Achieved at Maximum Tested Dose	Single Dose	*Mean (%CV) Cmax and AUC* Data from PIPF-005 , dose=801 mg while fed (no antacid), n=16: AUC0-∞ = 64.6 (33.4) mg•hr/L Cmax = 7720 (22.2) ng/mL
	Multiple Dose	*Mean (%CV) Cmax and AUC* Data from PIPF-005, dose = 1335 mg TID while fed, n=9: AUC0-24 = 328 (27.5) mg•hr/L Cmax = 19640 (17.6) ng/mL
Range of linear PK	*Specify dosing regimen* This is currently being explored through the construction of a population PK model. However, based on results of the multiple-dose cohort in PIPF-005, there is a suggestion that the linear range extends to 534 mg TID with modest non-linearity manifesting above that dose such that the mean CLt/F at 1335 mg TID was 25% lower than the mean CLt/F at 534 mg TID.	
Accumulation at steady state	*Mean (%CV); specify dosing regimen* PIPF-005 was not designed to assess this; based on half-life (~2 – 3 hrs), accumulation at steady-state should be minimal.	
Metabolites	*Include listing of all metabolites and activity* 5-carboxy-pirfenidone, 5-hydroxymethyl-pirfenidone, 4'-hydroxy-pirfenidone, 1-O-acyl-glucuronide. In pre-clinical models, none of the metabolites exhibited significant TNF-alpha inhibition at physiologically achievable concentrations.	
Absorption	Absolute/Relative Bioavailability	*Mean (%CV)* The bioavailability is not quantifiable due to the lack of an IV formulation. Based on the amount of parent and metabolites excreted in the urine (PIPF-005), at least 80% of the administered dose reaches the systemic circulation and is ultimately eliminated in the urine.
	Tmax	•*Median (range) for parent* Tmax = 3.5 (1 – 6) hr [pirfenidone, 801 mg single dose, fed (no antacid), n=16] • *Median (range) for metabolites* Tmax = 4 (1 – 6) hr [5-carboxy-pirfenidone, 801 mg single dose, fed (no antacid), n=16]

Distribution	Vd/F or Vd	*Mean (%CV)* Vss/F = 15.5 (36.3) L [801 mg single dose, fed (no antacid), n=16]
	% bound	*Mean (%CV)* ~60% based on the IB (PCLN-PIRF-110). No estimate of variability is provided
Elimination	Route	• *Primary route; percent dose eliminated* Renal; approximately 80%. The majority of pirfenidone was excreted as the 5-carboxy-pirfenidone metabolite (>95% of that recovered) with less than 1% occurring as unchanged drug and very little occurring as the 4'-hydroxymethyl or 5-hydroxy metabolites. • *Other routes*: Unknown.
	Terminal t½	• *Mean (%CV) for parent* $T_{1/2}$ = 2.41 (46.9) hr [pirfenidone, 801 mg single dose, fed (no antacid), n=16] • *Mean (%CV) for metabolites* $T_{1/2}$ = 1.53 (73.9) hr [5-carboxy-pirfenidone, 801 mg single dose, fed (no antacid), n=16]
	CL/F or CL	*Mean (%CV)* CLt/F = 13.8 (33.2) L/hr [pirfenidone, 801 mg single dose, fed (no antacid), n=16]

Intrinsic Factors	Age	*Specify mean changes in Cmax and AUC* InterMune studies to date have enrolled subjects greater than 45 years of age. The effects of age on PK parameters were studied in PIPF-005 with no relationships observed between drug exposure and subject age.
	Sex	*Specify mean changes in Cmax and AUC* In single-dose cohort, fed arms of PIPF-005, mean pirfenidone $AUC_{0-\infty}$ was 38% higher in women as compared to males. Mean Cmax was 14% higher in women as compared to men.
	Race	*Specify mean changes in Cmax and AUC* The effects of race on PK parameters were studied in PIPF-005 with no significant relationships between subject race and pirfenidone exposure.
	Hepatic & Renal Impairment	*Specify mean changes in Cmax and AUC* The effects of hepatic and renal impairment are being investigated in Studies PIPF-011 and PIPF-009, respectively
Extrinsic Factors	Drug interactions	*Include listing of studied DDI studies with mean changes in Cmax and AUC* The potential for drug interactions are being investigated in Study PIPF-010.
	Food Effects	*Specify mean changes in Cmax and AUC and meal type (i.e., high-fat, standard, low-fat)* Reference Table 2 below.
Expected High Clinical Exposure Scenario	*Describe worst case scenario and expected fold-change in Cmax and AUC. The increase in exposure should be covered by the supra-therapeutic dose.* Using the results from PIPF-005, the maximum observed pirfenidone AUC_{0-24} and Cmax at a dose of 801 mg were 228 mg*hr/L and 12900 ng/mL, respectively. Note that these values include both the single- and multiple-dose cohorts, values for doses other than the clinical dose (801 mg) were normalized to 801 mg. Given that the mean values for AUC_{0-24} and Cmax from the supratherapeutic dose in PIPF-007 were 238 mg*hr/L and 11128 ng/mL, respectively, the worst-case increase in exposure is covered by the supratherapeutic dose.	

Table D–1 Expected Adverse Events

System Organ Class	Expected Adverse Drug Reactions	Expected Events due to Underlying Disease or Concomitant Conditions
Gastrointestinal Disorders	Abdominal distension Abdominal discomfort Diarrhoea Dyspepsia Gastrooesophageal reflux disease Nausea Vomiting	
General Disorders and Administration Site Conditions	Fatigue Somnolence	
Infections and Infestations	Upper respiratory infections	Pneumonia
Investigations	Elevation of γ-GTP Weight decreased[a]	
Metabolism and Nutrition Disorders[b]	Anorexia (loss of appetite)[a] Decreased appetite[a]	
Neoplasm, Benign, Malignant, and Unspecified (Including Cysts And Polyps)		Lung neoplasm[c]
Nervous System Disorders	Headache[d] Dizziness[d]	
Respiratory, Thoracic, and Mediastinal Disorders		Cough Dyspnea (incl. dyspnea exacerbated) IPF progression[c] Respiratory failure[c] (incl. acute respiratory failure)
Skin and Subcutaneous Tissue Disorders	Photosensitivity reaction Rash	

IPF = idiopathic pulmonary fibrosis; SOC = system organ class; γ-GTP = γ-glutamyl transpeptidase.
[a]These terms were misclassified in the previous edition of the brochure and are now correctly classified.
[b]This SOC was added in this version of the brochure.
[c]Including fatal outcome.
[d]These new terms were added in this edition of the brochure.

Table 2

Summary Statistics for $AUC_{0-\infty}$ and Cmax by Treatment Block – PIPF-005

Treatment Block	Statistic	$AUC_{0-\infty}$ (mg•hr/L)		Cmax (mg/L)	
		Pirfenidone	5-Carboxy	Pirfenidone	5-Carboxy
A	Mean	72.7	35.2	15.7	7.22
	SD	19.9	7.01	4.80	3.39
B	Mean	74.3	33.3	17.1	6.91
	SD	22.8	5.78	5.23	3.09
C	Mean	64.6	33.2	7.87	4.62
	SD	21.3	6.74	2.30	1.14
D	Mean	62.9	33.6	7.72	4.61
	SD	17.9	7.16	1.71	1.41

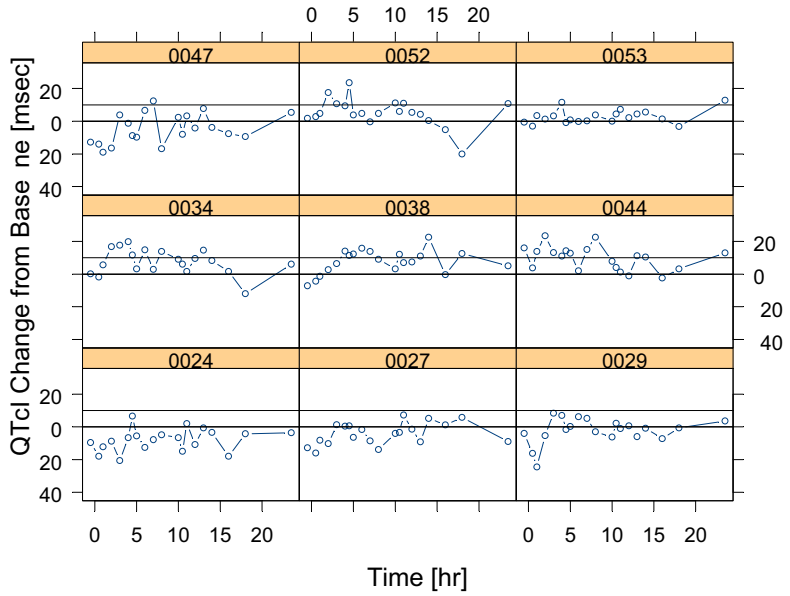
Note: Fed Arms (C and D) received a standard meal
$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity
Cmax = Maximum observed plasma concentration

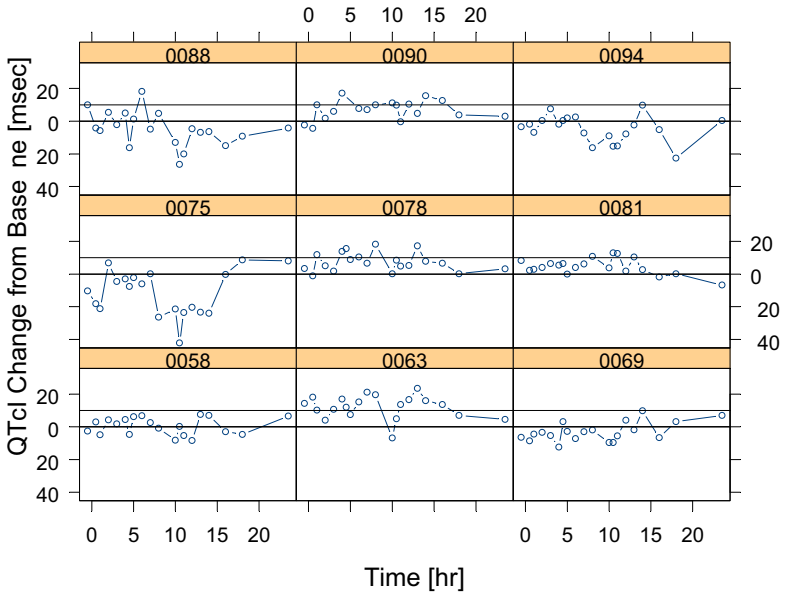
6.2 TABLE OF STUDY ASSESSMENTS

Dosing Arms	Study Days											FU
	-1	1	2	3	4	5	6	7	8	9	10	11
Therapeutic												
Total daily dose of pirfenidone (mg)	0	801		1602		2403		2403		2403		0
No. of pirfenidone capsules TID		1		2		3		3		3		
No. of placebo capsules TID		0		0		0		1		2		
Total no. of capsules/day		3	3	6	6	9	9	12	12	15	15	
Supratherapeutic												
Total daily dose of pirfenidone (mg)	0	801		1602		2403		3204		4005		0
No. of pirfenidone capsules TID		1		2		3		4		5		
Total no. of capsules/day		3	3	6	6	9	9	12	12	15	15	
Positive Control												
No. of placebo capsules TID	0	1		2		3		4		5		0
No. of moxifloxacin tablets TID		0		0		0		0		0	1	
Total no. of capsules and tablets/day		3	3	6	6	9	9	12	12	15	15 + 1 Moxi.	
Placebo												
No. of placebo capsules TID	0	1		2		3		4		5		0
Total no. of capsules/day		3	3	6	6	9	9	12	12	15	15	

d = day; FU = follow-up; No. = number; TDD = total daily dose; TID = three times per day; Moxi. = moxifloxacin tablet.
Notes: All doses were to be taken TID with food at the following time points: ~0800, ~1200, and ~1800.

6.3 QTCI CHANGE FROM BASELINE VERSUS TIME PLOTS FOR EACH INDIVIDUAL FOLLOWING A SINGLE DOSE OF 400 MG MOXIFLOXACIN

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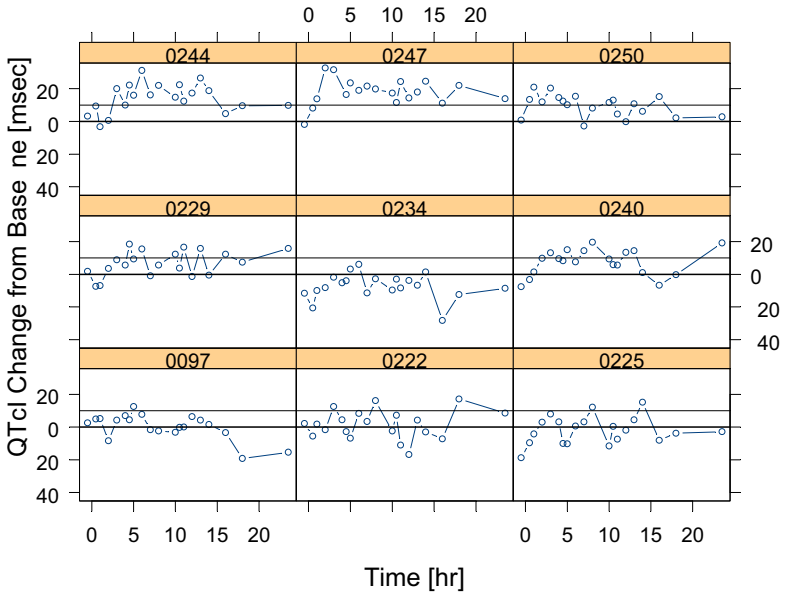
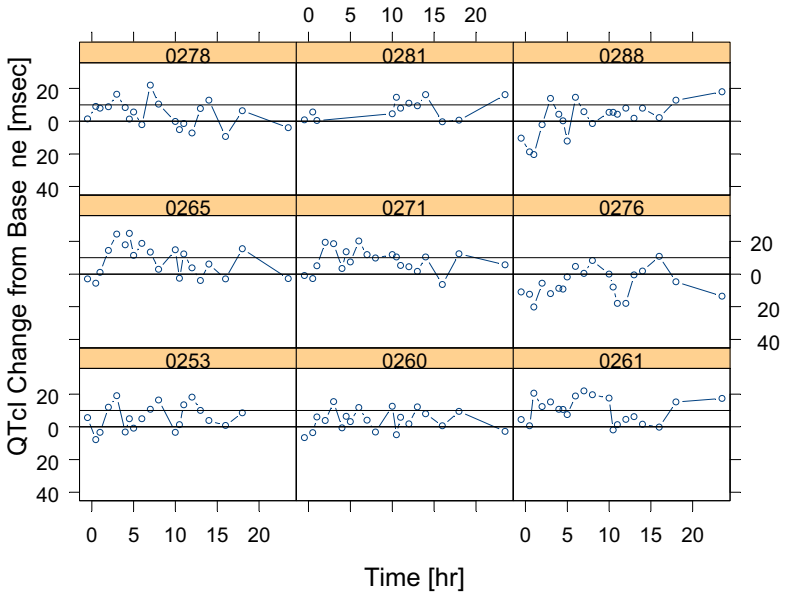
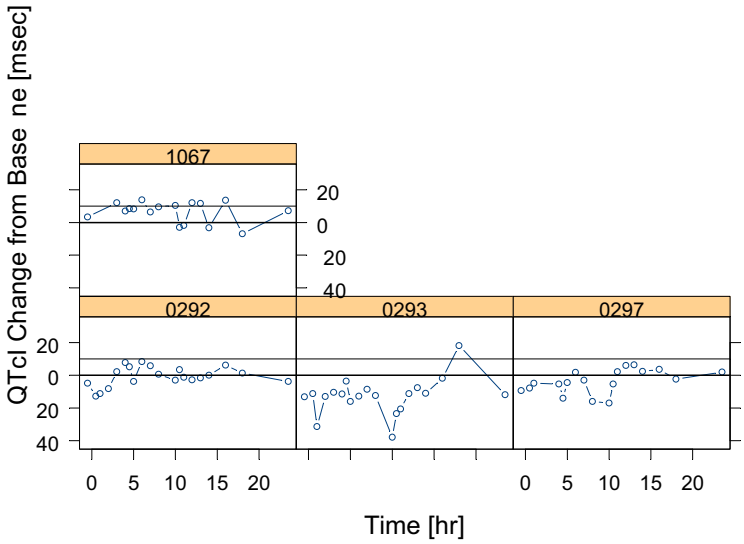
0090
0094
0075
0078
0081
0058
0063
0069
QTcI Change from Base ne [msec]
Time [hr]


0244
0247
0250
0229
0234
0240
0097
0222
0225
QTcI Change from Base ne [msec]
Time [hr]


0278
0281
0288
0265
0271
0276
0253
0260
0261
QTcI Change from Base ne [msec]
Time [hr]


1067
0292
0293
0297
QTcI Change from Base ne [msec]
Time [hr]

6.4 SPONSOR'S RESPONSE TO FAX DATED 13 NOVEMBER 2008

INTERMUNE®

20 November 2008

Badrul Chowdhury, M.D., Ph.D.
Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary and Allergy Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

Reference: IND 67,284 Pirfenidone
Serial No.: 0289
Subject: Response FDA Request for Information: QTc-Study Report
Electronic File: Electronic PDF, Single CD-ROM (0289), ~1.5 MB (determined to be virus-free using Trend Micro Internet Security, v15.30.1239)

Dear Dr. Chowdhury:

Reference is made to IND 67,284 for the use of pirfenidone as treatment for patients with idiopathic pulmonary fibrosis, which was originally submitted on 18 April 2003. We also refer to the following:

- QTc Study Report for PIPF-007 which was submitted to the Agency on 06 December 2007 (Serial No. 0212).
- A resubmission of various additionally requested components of the QTc Study Report, made on 31 July 2008 (Serial No. 0268).
- A fax received by the FDA Regulatory Project Manager, Ms. Ladan Jafari, on 13 November 2008, requesting additional information (attached as Appendix A).

The purpose of this submission is to provide the information requested as delineated in the fax referred to above.

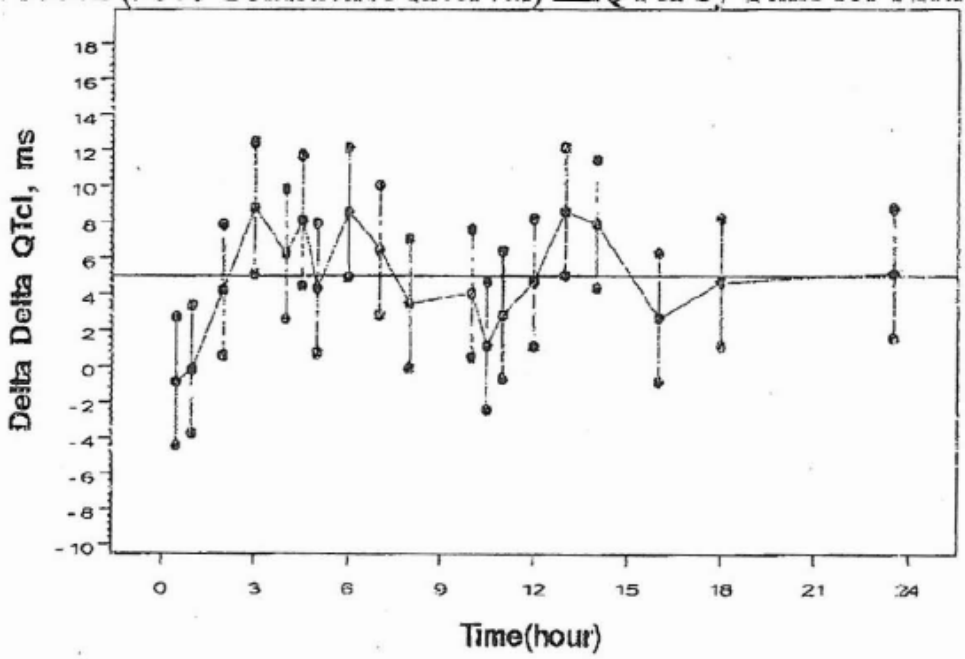
In the facsimile, Ms. Jafari wrote:

> "In thorough QT studies, it is important to have a high degree of confidence in the ability of the study to detect small changes of around 5 ms in the *QT / QTc* interval. When moxifloxacin is used as the positive control, we expect that (1) the ΔΔQTc-time profile follows the expected moxifloxacin concentration-time profile and (2) the mean effect on

the QTc is ≥ 5 ms (as evidence by the lower 90% confidence interval ≥5 ms) at one time point.

As shown in Figure 1, there are three peaks of similar magnitude in the ΔΔQTc-time profile corresponding somewhat to the three dosing events on Day 10. Per the dosing schedule, subjects in the placebo-plus-moxifloxacin arm received one 400-mg tablet moxifloxacin plus 5 placebo capsules in the morning (0800 h) and only 5 placebo capsules in the afternoon (1200 h) and evening (1800 h). Blood samples were not analyzed for moxifloxacin concentrations to confirm the correct dosing schedule. Is it possible that some subjects received moxifloxacin at the morning, afternoon, or evening doses?"

Figure 1: Mean (90% Confidence Interval) ΔΔQTcI by Time for Moxifloxacin



InterMune response to the questions above:

The trial was a parallel design study conducted in a total of 162 subjects with 40 subjects in the positive control moxifloxacin arm. According to the protocol, all moxifloxacin doses were to be administered in the morning. The dates, times and number of tablets administered per day were appropriately documented in the pharmacy study drug dispensation and accountability logs, and the clinical staff source documents. All subjects were dosed with moxifloxacin from 08:00 to 08:18. Study drug accountability was confirmed at the initial monitoring visit, midway through the study, and at the end of the study, and all pirfenidone and moxifloxacin doses were correctly administered and confirmed by the unblinded study drug accountability monitor. In addition, the clinical source documents were reviewed at each interim monitoring visit and all study

medication was administered per the protocol. Per the study documentation at the clinical site, the precise procedures for administering study drug, and the thorough monitoring of the study, it was confirmed that subjects randomized to the positive control group only received one dose of moxifloxacin.

The small sample size and study design, lead to the large degree of data variability as reflected by the shape of the ΔΔQTc-time profile. The three peaks in the ΔΔQTc-time profile for moxifloxacin that the reviewer refers to in Figure 1 are in part due to the small sample size. The morning peak, which should have been higher, accounts for the first two peaks. The last peak, occurring at around 12 hours, is a random peak and does not reflect a moxifloxacin effect since it was dosed in the morning for all subjects in the positive control arm.

Our interpretation of Figure 1 is that the data do not show three distinct peaks but rather a first peak that is flatter and is inclusive of the second peak, and a third peak that is due to data variability.

With regards as to whether the study has the ability to detect small QTc changes around 5 ms, we have looked at whether at any time point the lower CI on the moxifloxacin group relative to placebo was ≥ 5 ms to establish assay sensitivity. This can be accomplished by setting up the following statistical hypotheses:

H0: {μmoxi(i) - μplacebo(i)} ≤ 5, i 1,2,...,K and

H1: {μmoxi(i) - μplacebo(i)} > 5, i 1,2,...,K,

where μmoxi(i) and μplacebo(i) are the mean change from baseline of QTc for moxifloxacin and placebo at time point i, respectively. K is the number of time points picked to evaluate the moxifloxacin effect. Since multiple time points are examined, the overall type I error rate will be adjusted via Bonferroni adjustment, applied to adjust for α. If the Bonferroni adjustment is applied, the overall type 1 error rate will remain at α 0.05.

K would be selected based on the number of time points less than or equal to 5 hours. Five hours is chosen as this appears to the maximum time in which a moxifloxacin treatment arm may show a QTc effect. In this study, there are 7 time points less than or equal to 5 hours (i.e., 0.5, 1, 2, 3, 4, 4.5, and 5). Therefore, the alpha adjustment for multiplicity would be selected as 0.10 (two sided) divided by 7 0.01429.

In Appendix B, Table 14.2.1-16-X reflects the upper and lower confidence bounds of all ΔΔQTcI for treatment arms; Tables 14.2.1-17-X and 14.2.1-18-X reflect the same for ΔΔQTcF and ΔΔQTcB (both secondary endpoints). In all tables, confidence bounds reflect the one-sided 95% (two-sided 90%), with multiplicity adjustments made when necessary (i.e., moxifloxacin).

As can be seen in Tables 14.2.1-16-X through 14.2.1-18-X, the Hour 3 time point in the positive control arm (moxifloxacin) validates this trial regarding assay sensitivity by showing that the mean change from baseline in moxifloxacin of at least 5 ms.

We hope this response addresses your questions. Should you have any further questions, please do not hesitate to contact me at 415 466-2516.

With best regards,

Mike Johnston

Mike Johnston
Director, Regulatory Affairs

APPENDIX A

Copy of FDA Facsimile of 13 November 2008

IND 67,284

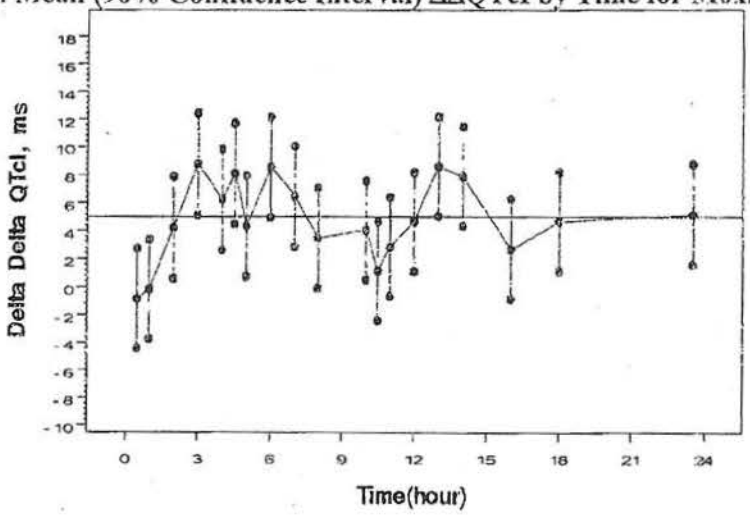
Dear Mr. Johnston:

We are reviewing your submission dated December 6, 2007, which contained the final study report for Protocol PIPF-007. We have the following request for information and ask that you respond to this request by the close of business on November 21, 2008.

In thorough QT studies, it is important to have a high degree of confidence in the ability of the study to detect small changes of around 5 ms in the QT/QTc interval. When moxifloxacin is used as the positive control, we expect that (1) the ΔΔQTc-time profile follows the expected moxifloxacin concentration-time profile and (2) the mean effect on the QTc is greater than 5 ms (as evidence by the lower 90% confidence interval ≥ 5 ms) at one timepoint.

As shown in Figure 1, there are three peaks of similar magnitude in the ΔΔQTc-time profile corresponding somewhat to the three dosing events on Day 10. Per the dosing schedule, subjects in the placebo-plus-moxifloxacin arm received one 400-mg tablet moxifloxacin plus 5 placebo capsules in the morning (0800 h) and only 5 placebo capsules in the afternoon (1200 h) and evening (1800 h). Blood samples were not analyzed for moxifloxacin concentrations to confirm the correct dosing schedule. Is it possible that some subjects received moxiflocacin at the morning, afternoon, or evening doses?

Figure 1: Mean (90% Confidence Interval) ΔΔQTcI by Time for Moxifloxacin



I may be reached at 301-796-1231 for any questions.

Ladan Jafari, Regulatory Health Project Manager for Safety

Linked Applications	Sponsor Name	Drug Name
IND 67284	INTERMUNE INC	PIRFENIDONE

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

/s/

LADAN G JAFARI
11/13/2008

APPENDIX B

Referenced Tables

Table 14.2.1-16-X
Placebo-Corrected Change from Baseline - Estimates from Mixed Model ANOVA [1]
QTc Individual (msec)
All Treated Subjects with Available ECG data on Day 10

	Therapeutic Pirfenidone (n=40)			Supratherapeutic Pirfenidone (n=40)			Positive Control (n=40)		
Time hr)	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]
0.5 Hr	-0.14	-2.65	2.38	-1.20	-3.68	1.28	-0.78	-4.51	2.95
1 Hr	-2.59	-5.07	-0.11	-3.75	-6.23	-1.28	-0.09	-3.81	3.64
2 Hr	-1.59	-4.07	0.89	-3.58	-6.06	-1.10	4.34	0.55	8.12
3 Hr	0.34	-2.14	2.82	1.07	-1.41	3.55	8.81	5.06	12.57
4 Hr	-0.17	-2.65	2.31	-2.48	-4.96	-0.00	6.81	3.06	10.57
4.5 Hr	-0.01	-2.48	2.47	-1.83	-4.30	0.65	8.39	4.63	12.14
5 Hr	-1.93	-4.41	0.55	-2.66	-5.16	-0.16	4.62	0.87	8.38
6 Hr	0.99	-1.49	3.47	-1.45	-3.94	1.05	8.71	4.98	12.44
7 Hr	2.73	0.25	5.21	1.76	-0.72	4.24	6.63	2.91	10.36
8 Hr	-0.31	-2.78	2.17	-1.20	-3.68	1.28	3.66	-0.07	7.39
10 Hr	3.17	0.69	5.65	-0.62	-3.10	1.86	4.06	0.36	7.76
10.5 Hr	-0.38	-2.88	2.12	-3.09	-5.56	-0.61	1.15	-2.55	4.85
11 Hr	-0.83	-3.32	1.67	-2.19	-4.66	0.29	2.89	-0.81	6.59

[1] Mixed Model ANOVA is fit for placebo-corrected change from baseline and includes terms for:
treatment, sex, time, and a time by treatment interaction. Alphas adjusted to .1 and 0.01429
[2] Upper Bound = upper one-sided 95% ANOVA model based confidence limit.
p-value for sex effect (sex main effect & tx by sex IA) is 0.3324, Tx*sex IA = 0.2670.
Program Name: CalCI-ECG-corrected.sas Output File Name: tables-LA16.rtf

Table 14.2.1-17-X
Placebo-Corrected Change from Baseline - Estimates from Mixed Model ANOVA [1]
QTc Fridericia (msec)
All Treated Subjects with Available ECG data on Day 10

	Therapeutic Pirfenidone (n=40)			Supratherapeutic Pirfenidone (n=40)			Positive Control (n=40)		
Time hr)	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]
12 Hr	-2.02	-4.51	0.48	-0.30	-2.78	2.17	4.68	0.98	8.38
13 Hr	-0.39	-2.87	2.08	2.23	-0.25	4.71	8.63	4.93	12.32
14 Hr	1.40	-1.08	3.87	2.06	-0.42	4.53	7.93	4.23	11.63
16 Hr	-0.83	-3.31	1.65	-3.73	-6.21	-1.25	2.71	-0.99	6.41
18 Hr	-0.79	-3.28	1.71	0.88	-1.62	3.38	4.68	0.99	8.38
23.5 Hr	-0.09	-2.57	2.39	-1.68	-4.18	0.81	5.25	1.52	8.98

[1] Mixed Model ANOVA is fit for placebo-corrected change from baseline and includes terms for:
treatment, sex, time, and a time by treatment interaction. Alphas adjusted to .1 and 0.01429
[2] Upper Bound = upper one-sided 95% ANOVA model based confidence limit.

Program Name: CalCI-ECG-corrected.sas Output File Name: tables-LA17.rtf

Table 14.2.1-17-X
Placebo-Corrected Change from Baseline - Estimates from Mixed Model ANOVA [1]
QTc Fridericia (msec)
All Treated Subjects with Available ECG data on Day 10

	Therapeutic Pirfenidone (n=40)			Supratherapeutic Pirfenidone (n=40)			Positive Control (n=40)		
Time hr)	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]
0.5 Hr	1.09	-1.39	3.58	0.02	-2.43	2.47	1.29	-2.39	4.97
1 Hr	-1.99	-4.44	0.46	-2.91	-5.35	-0.46	1.69	-1.99	5.37
2 Hr	-0.73	-3.17	1.72	-2.51	-4.96	-0.06	4.80	1.06	8.54
3 Hr	0.76	-1.68	3.21	1.91	-0.53	4.36	9.30	5.59	13.01
4 Hr	0.04	-2.41	2.49	-1.73	-4.17	0.72	7.66	3.95	11.37
4.5 Hr	-0.17	-2.62	2.28	-1.06	-3.50	1.39	8.19	4.48	11.90
5 Hr	-1.85	-4.30	0.60	-2.48	-4.95	-0.02	5.26	1.55	8.97
6 Hr	0.63	-1.82	3.08	-1.20	-3.67	1.27	9.20	5.52	12.88
7 Hr	2.98	0.53	5.42	1.90	-0.55	4.34	7.12	3.43	10.80
8 Hr	-0.66	-3.11	1.79	-0.66	-3.11	1.79	4.39	0.71	8.07
10 Hr	2.68	0.23	5.13	-0.19	-2.64	2.26	4.81	1.16	8.46
10.5 Hr	-0.31	-2.78	2.15	-1.92	-4.37	0.53	2.35	-1.31	6.00
11 Hr	-0.33	-2.80	2.14	-1.71	-4.16	0.74	3.56	-0.10	7.21

[1] Mixed Model ANOVA is fit for placebo-corrected change from baseline and includes terms for:
treatment, sex, time, and a time by treatment interaction. Alphas adjusted to .1 and 0.01429
[2] Upper Bound = upper one-sided 95% ANOVA model based confidence limit.

Program Name: CalCI-ECG-corrected.sas Output File Name: tables-LA17.rtf

Table 14.2.1-18-X
Placebo-Corrected Change from Baseline - Estimates from Mixed Model ANOVA [1]
QTc Bazett (msec)
All Treated Subjects with Available ECG data on Day 10

	Therapeutic Pirfenidone (n=40)			Supratherapeutic Pirfenidone (n=40)			Positive Control (n=40)		
Time hr)	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]
12 Hr	-1.94	-4.41	0.53	-0.25	-2.69	2.20	5.51	1.85	9.16
13 Hr	0.16	-2.29	2.60	2.75	0.30	5.20	9.15	5.49	12.80
14 Hr	0.79	-1.66	3.23	2.78	0.33	5.23	8.74	5.09	12.39
16 Hr	-0.86	-3.31	1.59	-2.55	-5.00	-0.10	2.94	-0.71	6.59
18 Hr	-1.40	-3.87	1.06	0.78	-1.68	3.25	4.81	1.15	8.46
23.5 Hr	-0.16	-2.60	2.29	-1.14	-3.61	1.33	5.62	1.94	9.30

[1] Mixed Model ANOVA is fit for placebo-corrected change from baseline and includes terms for:
treatment, sex, time, and a time by treatment interaction. Alphas adjusted to .1 and 0.01429
[2] Upper Bound = upper one-sided 95% ANOVA model based confidence limit.

Program Name: CalCI-ECG-corrected.sas Output File Name: tables-LA18.rtf

Table 14.2.1-18-X
Placebo-Corrected Change from Baseline - Estimates from Mixed Model ANOVA [1]
QTc Bazett (msec)
All Treated Subjects with Available ECG data on Day 10

	Therapeutic Pirfenidone (n=40)			Supratherapeutic Pirfenidone (n=40)			Positive Control (n=40)		
Time hr)	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]
0.5 Hr	4.48	1.20	7.76	2.39	-0.83	5.61	2.93	-1.91	7.78
1 Hr	1.25	-1.97	4.47	-0.09	-3.31	3.13	4.94	0.09	9.78
2 Hr	1.15	-2.07	4.37	0.63	-2.59	3.85	4.11	-0.83	9.05
3 Hr	3.32	0.10	6.55	5.03	1.81	8.26	10.83	5.94	15.73
4 Hr	2.54	-0.68	5.76	-0.71	-3.93	2.51	8.35	3.46	13.25
4.5 Hr	1.02	-2.21	4.24	2.50	-0.72	5.73	7.13	2.23	12.02
5 Hr	0.21	-3.01	3.43	1.73	-1.52	4.98	6.80	1.91	11.70
6 Hr	0.32	-2.90	3.54	1.44	-1.81	4.69	11.22	6.37	16.07
7 Hr	4.02	0.80	7.24	5.58	2.36	8.80	9.09	4.24	13.94
8 Hr	-1.77	-4.99	1.45	0.70	-2.52	3.92	6.42	1.57	11.26
10 Hr	2.60	-0.62	5.83	0.84	-2.38	4.06	4.91	0.11	9.71
10.5 Hr	1.39	-1.86	4.64	0.92	-2.30	4.15	3.67	-1.14	8.47
11 Hr	1.26	-2.00	4.51	0.47	-2.75	3.69	4.22	-0.59	9.02

[1] Mixed Model ANOVA is fit for placebo-corrected change from baseline and includes terms for:
treatment, sex, time, and a time by treatment interaction. Alphas adjusted to .1 and 0.01429
[2] Upper Bound = upper one-sided 95% ANOVA model based confidence limit.

Program Name: CalCI-ECG-corrected.sas Output File Name: tables-LA18.rtf

Table 14.2.1-16-X
Placebo-Corrected Change from Baseline - Estimates from Mixed Model ANOVA [1]
QTc Individual (msec)
All Treated Subjects with Available ECG data on Day 10

	Therapeutic Pirfenidone (n=40)			Supratherapeutic Pirfenidone (n=40)			Positive Control (n=40)		
Time hr)	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]	Estimate [1]	Lower Bound [2]	Upper Bound [2]
12 Hr	-0.66	-3.91	2.59	0.68	-2.54	3.90	7.13	2.32	11.93
13 Hr	3.42	0.20	6.65	4.77	1.55	7.99	10.28	5.47	15.08
14 Hr	2.91	-0.31	6.13	5.27	2.05	8.49	9.61	4.81	14.41
16 Hr	-1.51	-4.73	1.71	-1.39	-4.61	1.83	2.17	-2.63	6.97
18 Hr	-1.47	-4.72	1.78	2.30	-0.95	5.55	5.36	0.55	10.16
23.5 Hr	-1.86	-5.08	1.36	-1.65	-4.90	1.60	5.10	0.25	9.95

[1] Mixed Model ANOVA is fit for placebo-corrected change from baseline and includes terms for:
treatment, sex, time, and a time by treatment interaction. Alphas adjusted to .1 and 0.01429
[2] Upper Bound = upper one-sided 95% ANOVA model based confidence limit.
p-value for sex effect (sex main effect & tx by sex IA) is 0.3324, Tx*sex IA = 0.2670.
Program Name: CalCI-ECG-corrected.sas Output File Name: tables-LA16.rtf

4.4 Individual Study Review

4.4.1 Clinical Study PIPF-005

Study Title: The Pharmacokinetics of Oral Pirfenidone in Healthy Older Adults, Including Effects of Multiple-Dosing, Dose-Ranging, Food, and Antacids

Study Objectives:

- To characterize the pharmacokinetics (PK) of pirfenidone and metabolites in plasma and urine after single 801-mg doses in fasted, healthy older subjects
- To characterize the impact of food on the PK of pirfenidone and metabolites in plasma and urine after single 801-mg doses in healthy older subjects
- To characterize the impact of antacids on the PK of pirfenidone and metabolites in plasma and urine after single 801-mg doses in fasted, healthy older subjects
- To characterize the impact of food followed by antacids on the PK of pirfenidone and metabolites in plasma and urine after single 801-mg doses in healthy older subjects
- To characterize the plasma PK of pirfenidone and metabolites in healthy older subjects, including extent of accumulation, after multiple ascending daily doses (801, 1602, 2403, 3204, and 4005 mg/day administered in three equally divided doses)

Study Design

Single Dose Cohort:

This is a randomized, open-label, four-treatment crossover, single-dose study to evaluate the effect of food, antacids, and food taken with antacids on the pharmacokinetics of orally administered pirfenidone and 4 metabolites (5-carboxylic acid, 5-hydroxymethyl compound, 4'-hydroxy phenyl derivate, and 1-O-acyl glucuronide), in 16 healthy adults. Each subject went through each treatment sequence, but the order was randomized. Only one single dose level of pirfenidone was studied: 801 mg.

Treatment A = pirfenidone in fasted state
Treatment B = pirfenidone in fasted state + antacid
Treatment C = pirfenidone in fed state
Treatment D = pirfenidone in fed state + antacid

Plasma PK samples were collected at 0 (Predose), 0.5 (± 5 min),1, 2, 3, 4 h (± 10 min),6, 8, 12, 18, 24 (± 20 min) 36, 48, 72 h (± 6 h) post dose. Urine PK samples were collected over the following intervals following each study dose: 0-12, 12-24, 24-36, and 36-48 h.

Multiple Doses Cohort:

This is an open-label, multiple doses study with all subjects escalated through each of 5 dose levels, and pirfenidone was taken with water and food. The antacid used was Mylanta® Maximum Strength Liquid. Each dose level was dosed 7 times (TID for 2 days and 1 dose on the third day). PK samples were collected on Day 1 and Day 3 of each dose level. A pre-dose sample was also collected on Day 2 of each dose level. Subjects were randomized to 1 of 5 different PK sampling regimens (PK samplings at dose levels 1 and 3, 1 and 4, 2 and 4, 2 and 5, or 3 and 5). All subjects had a plasma PK sample drawn 48 h after the 7^{th} dose of dose level 5 (or their last dose of the study). For details, see Table 37. No urine samples were collected in this cohort.

Table 37 PK Sampling Scheme in Multiple Dose Cohort

Table 4-3 Multiple Dose Cohort Dose Escalation and PK Sampling Regimen[d]

Day	Total mg per day[a]	PK Sampling Related to Dose 1[b]	PK Sampling Related to Dose 2[b]	PK Sampling Related to Dose 3[b]
1	801 (one capsule TID)	Predose and 0.5, 1, 2, 3 and 4 h post dose	1, 2, 4 and 6 h post dose	No collection
2	801 (one capsule TID)	Pre morning dose	No collection	No collection
3	267 (one capsule in the morning)	Predose and 0.5, 1, 2, 3, 4, 6, 8 12 and 24 h post dose	No collection	No collection
4	1602 (2 capsules TID)	Predose and 0.5, 1, 2, 3 and 4 h post dose	1, 2, 4 and 6 h post dose	No collection
5	1602 (2 capsules TID)	Pre morning dose	No collection	No collection
6	534 (2 capsules in the morning)	Predose and 0.5, 1, 2, 3, 4, 6, 8 12 and 24 h post dose	No collection	No collection
7	2403 (3 capsules TID)	Predose and 0.5, 1, 2, 3 and 4 h post dose	1, 2, 4 and 6 h post dose	No collection
8	2403 (3 capsules TID)	Pre morning dose	No collection	No collection
9	801 (3 capsules in the morning)	Predose and 0.5, 1, 2, 3, 4, 6, 8 12 and 24 h post dose	No collection	No collection
10	3204 (4 capsules TID)	Predose and 0.5, 1, 2, 3 and 4 h post dose	1, 2, 4 and 6 h post dose	No collection
11	3204 (4 capsules TID)	Pre morning dose	No collection	No collection
12	1068 (4 capsules in the morning)	Predose and 0.5, 1, 2, 3, 4, 6, 8 12 and 24 h post dose	No collection	No collection
13	4005 (5 capsules TID)	Predose and 0.5, 1, 2, 3 and 4 h post dose	1, 2, 4 and 6 h post dose	No collection
14	4005 (5 capsules TID)	Pre morning dose	No collection	No collection
15	1335 (5 capsules in the morning[c])	Predose and 0.5, 1, 2, 3, 4, 6, 8 12 and 24 h post dose	No collection	No collection
16	No dosing	24 hr post last dose	No Collection	No Collection
17	No dosing	48 hr post last dose (all subjects)	No Collection	No Collection

[a] Each capsule will hold pirfenidone 267 mg. All dosing will be within one minute after meals with 240 mL of room-temperature water and with food (excluding grapefruit juice).

[b] The visit window for the 0.5 h collection is ± 5 min. The visit window for collections from 1–4 h is ± 10 min. The visit window for collections from 6–24 h is ± 20 min. The visit window for collections beyond 24 h is ± 6 h.

[c] The 4-hour PK sample after Dose 1 is the predose PK sample before Dose 2. The 24 h PK sample would be the predose sample for the following day.

[d] Subjects will be randomized to 1 of 5 different PK Sampling Regimen (Sampling for Dose Levels 1-3, 1-4, 2-4, 2-5 or 3-5). There will be 5 subjects per Sampling Regimen for a total of 25 subjects in the Multidose Cohort

Results – Single Dose Cohort

The arithmetic means (SD) of the plasma pharmacokinetic parameters are provided in Table 38 and Table 39. A validated GLP assay is not available detecting 1-O-acyl glucuronide metabolites, therefore, the PK analysis was not performed. The arithmetic mean (SD) of urine PK are provided in Table 41 and Table 42. The summary statistics and bioequivalence analysis on single dose cohort is provided in Table 40.

Table 38 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone Following Single Oral Dose of 801 mg in Healthy Subjects

Pirfenidone PK Parameters	Treatment A	Treatment B	Treatment C	Treatment D
N	16	16	16	16
AUC_{last} (hr×mg/L)	67.5 (20.4)	69.1 (22.9)	58.8 (22.2)	56.7 (19.3)
$AUC_{0\text{-}inf}$ (hr×mg/L)	68.1 (20.5)	69.5 (23.1)	59.2 (22.3)	57.1 (19.3)
C_{max} (mg/mL)	15.7 (4.80)	17.1 (5.23)	7.87 (2.30)	7.83 (1.77)
T_{max} (hr) [a]	0.5 [0.5 – 4.00]	0.500 [0.500 – 2.00]	3.50 [1.00 – 6.00]	3.00 [0.500 – 4.00]
$T_{1/2}$ (hr)	3.03 (0.996)	3.15 (0.996)	3.16 (0.960)	3.08 (0.915)
CL/F (L/hr)	12.9 (4.52)	13.0 (5.31)	15.9 (7.87)	16.1 (7.37)
Vz/F (L)	52.6 (12.4)	54.0 (11.8)	65.4 (15.8)	64.9 (13.5)
M:P ratio	0.494 (0.154)	0.462 (0.137)	0.566 (0.208)	0.586 (0.236)

[a] median [range]

Table 39 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma 5-Carboxy Pirfenidone Following Single Oral Dose of 801 mg in Healthy Subjects

Pirfenidone PK Parameters	Treatment A	Treatment B	Treatment C	Treatment D
N	16	16	16	16
AUC_{last} (hr×mg/L)	35.9 (7.53)	34.2 (6.13)	34.3 (7.03)	34.3 (7.44)
$AUC_{0\text{-}inf}$ (hr×mg/L)	36.4 (7.43)	34.4 (6.13)	34.6 (7.04)	34.7 (7.47)
C_{max} (mg/mL)	7.22 (3.39)	6.91 (3.10)	4.62 (1.13)	4.61 (1.41)
T_{max} (hr) [a]	1.00 [0.5 – 4.00]	1.00 [0.500-2.00]	4.00 [1.00 – 6.00]	3.00 [1.00 – 4.00]
$T_{1/2}$ (hr)	3.26 (1.04)	3.27 (1.12)	3.27 (1.00)	3.21 (0.979)

[a] median [range]
n.a. not applicable

Table 40 Summary Statistics and Bioequivalence Analysis of Plasma Pirfenidone Exposure

Table 6-5 Bioequivalence Analysis – Single-Dose Cohort

	Mean Ratio	Geometric Mean Ratio	90% Confidence Interval for the Geometric Mean Ratio[a]
		$AUC_{0-\infty}$	
Food Effect			
Ratio C/A	0.861	0.845	0.773, 0.922
Ratio D/B	0.823	0.817	0.772, 0.864
Antacid Effect			
Ratio B/A	1.02	1.01	0.956, 1.07
Ratio D/C	0.990	0.978	0.912, 1.05
		C_{max}	
Food Effect			
Ratio C/A	0.563	0.509	0.419, 0.617
Ratio D/B	0.512	0.467	0.384, 0.567
Antacid Effect			
Ratio B/A	1.17	1.10	0.941, 1.28
Ratio D/C	1.04	1.01	0.891, 1.14

[a]To be labeled equivalent, the 90% confidence interval for the geometric mean ratio must fall completely between 0.800 and 1.25.
$AUC_{0-\infty}$ = area under the concentration-time curve from time 0 to infinity
C_{max} = maximum observed plasma concentration

Source: Table 6 5, Study Report pipf nca 005

Table 41 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Urine Pirfenidone Following Single Oral Dose of 801 mg in Healthy Subjects

Parameters	Treatment A	Treatment B	Treatment C	Treatment D
N	16	16	16	16
Ae (mg)	4.26 (1.98)	4.44 (1.92)	2.96 (1.41)	3.25 (2.27)
Ae%	0.531 (0.246)	0.554 (0.240)	0.370 (0.176)	0.405 (0.284)
CLr (L/hr)	0.0626 (0.0219)	0.0672 (0.027)	0.0532 (0.0219)	0.0542 (0.0293)

Table 42 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Urine 5-Carboxy-Pirfenidone Following Single Oral Dose of 801 mg in Healthy Subjects

Parameters	Treatment A	Treatment B	Treatment C	Treatment D
N	16	16	16	16
Ae (mg)	733 (133)	734 (136)	724 (140)	742 (203)
Ae%	78.8 (12.1)	78.9 (14.6)	77.8 (15.0)	79.8 (21.8)
CLr (L/hr)	20.8 (4.49)	22.1 (5.84)	22.0 (6.56)	21.9 (6.08)

4'-hydroxy-pirfenidone: Plasma and urine concentrations at all the sampling time in all subjects were below the limit of quantitation.

PK Conclusions – Single Dose Cohort

- Food slows the rate and extent of absorption of pirfenidone.
- Antacid has no effect upon pirfenidone exposure under fed condition. Antacid had a significant effect on C_{max} of pirfenidone in the fasted state.
- Approximately 80% of the dose of pirfenidone was excreted in the urine as parent drug or as one of the four metabolites

Results - Multiple Doses Cohort

The arithmetic means (SD) of the pharmacokinetic parameters estimated by NCA are provided in Table 43 and Table 44.

Table 43 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone Following Multiple Oral Doses of 267 mg, 534 mg, 801 mg, 1068 mg, and 1335 mg Pirfenidone Three Times Daily

Dose Level	267 mg TID	534 mg TID	801 mg TID	1068 mg TID	1135 mg TID
N	9	9	8	9	9
AUC_{last} (hr×mg/L)	18.3 (7.65)	31.6 (11.3)	57.7 (20.6)	65.8 (15.4)	93.5 (40.8)
C_{max} (mg/L)	3.10 (1.47)	5.46 (1.05)	9.03 (1.99)	11.0 (2.56)	16.8 (5.06)
T_{max} (hr) [a]	3.00 – 4.00]	2.00 [1.00 – 4.00]	2.00 [2.00 – 4.00]	3.00 [2.00 – 4.00]	2.00 [0.500 – 4.00]
$T_{1/2}$ (hr)	3.18 (0.731)	2.87 (0.661)	3.05 (0.781)	2.52 (0.453)	3.13 (0.641)
CL/F (L/hr)	16.1 (5.75)	18.0 (5.23)	15.0 (4.77)	16.6 (3.24)	16.7 (10.9)
Vz/F (L)	69.1 (13.9)	70.8 (12.7)	62.2 (12.3)	58.7 (7.52)	70.1 (39.2)
M:P ratio	0.551 (0.154)	0.660 (0.188)	0.583 (0.191)	0.603 (0.138)	0.564 (0.242)

Table 44 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma 5-Carboxy-Pirfenidone Following Multiple Oral Doses of 267 mg, 534 mg, 801 mg, 1068 mg, and 1335 mg Pirfenidone Three Times Daily

Dose Level	267 mg TID	534 mg TID	801 mg TID	1068 mg TID	1135 mg TID
N	9	9	8	9	9
AUC_{last} (hr×mg/L)	10.6 (2.95)	23.0 (6.27)	36.3 (9.43)	45.0 (8.01)	54.9 (23.1)
C_{max} (mg/L)	1.85 (0.710)	3.99 (0.961)	5.63 (1.74)	7.12 (1.28)	9.23 (4.00)
T_{max} (hr) [a]	3.00 [0.500 - 4.00]	2.00 [1.00 – 4.00]	2.50 [2.00 – 4.00]	3.00 [2.00 – 4.00]	3.00 [0.500 – 4.00]
$T_{1/2}$ (hr)	3.06 (0.803)	2.92 (0.707)	3.42 (0.795)	2.74 (0.468)	3.26 (0.716)

PK Conclusion – Multiple Doses Cohort

Pirfenidone AUC_{last} and C_{max} increase in a dose-linear manner in the dose range from 801 mg/day to 4005 mg/day, although this cohort is not optimally designed for assessing dose linearity. No changes in T_{max} and $T_{1/2}$ were observed across the dose groups indicating pirfenidone PK is dose-independent.

4.4.2 Clinical Study PIPF-009

Study Title: An Open-Label Phase 1 Study to Determine the Pharmacokinetics and Safety of Pirfenidone in Subjects with Renal Insufficiency

Objectives: The objectives of this study were to determine:

– The pharmacokinetics of pirfenidone in subjects with renal insufficiency
– The safety of pirfenidone in subjects with renal insufficiency

Study Design: This is a Phase 1, single-dose, open-label, parallel-group study comparing the pharmacokinetics and safety of pirfenidone in subjects with mild, moderate, and severe renal insufficiency and in normal healthy subjects. Each subject received a single oral dose of 801 mg pirfenidone with a standardized meal in the morning.
The classification of renal impairment is based upon serum creatinine clearance using Cockcroft-Gault calculation (using actual body weight) at Screening.

- Normal renal function (estimated creatinine clearance >80 mL/min)
- Mild renal impairment estimated creatinine clearance 51-80 mL/min [inclusive]
- Moderate renal impairment (estimated creatinine clearance 30-50 mL/min [inclusive]
- Severe renal impairment (estimated creatinine clearance <30 mL/min)

Blood for PK sampling was drawn from each subject at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, and 32 hours postdose. Urine samples for PK analysis were collected at the following intervals, 0-12, 12-24, and 24-32 hours postdose.

Results:

The geometric mean of systemic exposure ($AUC_{0\text{-}inf}$) to pirfenidone increased ~1.4, 1.5, and 1.2-fold in subjects with mild, moderate and severe renal impairment, respectively. The effect of dialysis on pirfenidone PK has not been evaluated in this submission.

The C_{max} of 5-carboxyl-pirfenidone increased 1.8 to 3-fold in subjects with moderate and severe renal impairment, respectively. The $AUC_{0\text{-}inf}$ increased 1.7, 3.4, and 5.6-fold in mild, moderate, and severe renal impairment, respectively. The renal clearance of 5-carboxy-pirfendone decreased significantly.

The arithmetic means (SD) on plasma and urine PK parameters of pirfenidone and 5-carboxy-pirfendione is listed in Table 45 and Table 46, respectively.

Table 45 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone and 5-Carboxy-Pirfenidone in Healthy and Renal Impaired Subjects

	Pirfenidone				5-Carboxy-Pirfenidone			
Parameters	Mild	Moderate	Severe	Healthy	Mild	Moderate	Severe	Healthy
N	6	6	6	6	6	6	6	6
AUC_{last} (hr×mg/L)	57.9 19.8	60.8 20.8	45.7 10.8	42.1 17.4	47.8 13.1	98.1 27.1	166 67.0	28.2 4.85
$AUC_{0\text{-}inf}$ (hr×mg/L)	58.5 20.4	61.2 20.9	46.0 10.9	42.4 17.5	48.8 14.0	98.8 27.2	167 68.1	28.4 4.88
C_{max} (mg/L)	10.6 3.77	11.5 7.55	11.2 3.27	9.93 3.45	6.85 1.94	11.2 3.28	18.3 4.21	6.16 1.27
T_{max} [a] (hr)	1.50	2.00	1.50	1.50	2.50	3.5	4.00	2.00
$T_{1/2}$ (hr)	3.57 1.47	3.63 0.620	2.54 0.319	2.59 0.551	3.99 1.87	4.25 0.647	3.69 1.01	2.65 0.663
CL/F (L/hr)	15.0 4.68	14.9 6.78	18.5 5.47	23.1 13.3	n.a.	n.a.	n.a.	n.a.
Vz/F (L)	70.1 11.2	75.0 26.5	66.2 13.1	80.0 29.8	n.a.	n.a.	n.a.	n.a.
M:P Ratio	0.735 0.0854	1.62 0.831	3.11 1.03	0.673 0.314	n.a.	n.a.	n.a.	n.a.

[a] median [range]
n.a. not applicable

Table 46 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Urine Pirfenidone and 5-Carboxy-Pirfenidone in Healthy and Renal Impaired Subjects

	Pirfenidone				5-Carboxy-Pirfenidone			
Parameters	Mild	Moderate	Severe	Healthy	Mild	Moderate	Severe	Healthy
N	6	6	6	6	6	6	6	6
Ae (mg)	3.28 1.07	4.11 1.33	3.14 0.926	4.05 1.90	932 239	940 233	728 147	801 237
Ae%	0.410 0.134	0.512 0.166	0.392 0.115	0.506 0.237	100 25.7	101 25.0	78.2 15.8	86.1 25.6
CLr (L/hr)	0.0577 0.0093	0.0690 0.0104	0.0698 0.0178	0.100 0.0425	20.7 7.67	10.0 2.86	4.91 1.70	29.6 11.5

Conclusions:
The geometric mean of systemic exposure ($AUC_{0\text{-}inf}$) to pirfenidone increased ~1.4, 1.5, and 1.2-fold in subjects with mild, moderate and severe renal impairment, respectively. The C_{max} of 5-carboxy-pirfenidone increased 1.8 to 3-fold in subjects with moderate and severe renal impairment, respectively. The $AUC_{0\text{-}inf}$ increased 1.7, 3.4, and 5.6-fold in mild, moderate, and severe renal impairment, respectively. The renal clearance of 5-carboxy-pirfendone decreased significantly.

4.4.3 Clinical Study PIPF-010

Study Title: An Open-Label Phase 1 Study to Determine the Impacts of a Strong CYP1A2 Inhibitor and a CYP1A2 Inducer on the Pharmacokinetics and Safety of Pirfenidone in Healthy Subjects

Objectives:

- To determine the effect of fluvoxamine, a strong CYP1A2 inhibitor, on the pharmacokinetics of pirfenidone in healthy smoking and nonsmoking subjects
- To determine the effect of cigarette smoking, a CYP1A2 inducer, on the pharmacokinetics of pirfenidone in healthy smoking and nonsmoking subjects
- To determine the safety of pirfenidone in healthy subjects when concurrently introducing CYP1A2 induction or inhibition
- To compare the safety of pirfenidone in smokers versus nonsmokers

Study Design: This is a Phase 1, single-dose, open-label, two-period study comparing the pharmacokinetics and safety of pirfenidone with and without fluvoxamine treatment in healthy nonsmokers and healthy smokers. Each subject received a single oral dose of 801 mg pirfenidone with a standardized meal in the morning on Day 1. Each subject then received multiple doses of fluvoxamine via dose escalation steps from Day 2 to Day 10 following completing a 32-hour window for PK sample collections on Day 1. PK samples of pirfenidone and 5-carboxy-pirfenidone were again collected on Day 11 for 32 hours. Blood for PK sampling on Day 1 and Day 11 was drawn from each subject at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, and 32 hours postdose. Urine samples for PK analysis were collected at the following intervals, 0-12, 12-24, and 24-32 hours postdose.

Results:

Following repeated oral doses (10 day) of fluvoxamine (50 mg qhs for 3 days; 50 bid for 3 days, and 50 qam and 100 mg qhs for 4 days), systemic exposure (C_{max} and $AUC_{0\text{-}inf}$) to pirfenidone increased significantly (1.7 and 4-fold, respectively) in healthy nonsmoking subjects. The C_{max} of 5-carboxy-pirfenidone was significantly decreased without significant change in AUC in healthy nonsmoking subjects. The mean metabolite-to-parent ratio was decreased from 0.64 to 0.17 following the fluvoxamine treatment, indicating that the increase in exposure to pirfenidone is a result of fluvoxamine inhibition on pirfenidone metabolism.

The arithmetic means (SD) of pirfenidone and 5-carboxy-pirfenidone plasma PK parameters in smokers and nonsmokers are provided in Table 47. The arithmetic means (SD) of pirfenidone and 5-carboxy-pirfenidone urine PK parameters are provided in Table 48. The arithmetic means (SD) of pirfenidone and 5-carboxy-pirfenidone plasma PK parameters post fluvoxamine treatment in nonsmokers and smokers are provided in Table 49 and Table 50. The arithmetic means (SD) of pirfenidone and 5-carboxy-pirfenidone urine PK parameters are provided in Table 51 and Table 52.

Table 47 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone and 5-Carboxy-Pirfenidone in Smokers and Nonsmokers

	Pirfenidone		5-Carboxy-Pirfenidone	
Parameters	Smoker	Nonsmoker	Smoker	Nonsmoker
N	26	25	26	25
AUC_{last} (hr×mg/L)	22.7 (10.8)	46.1 (11.8)	25.1 (5.74)	32.6 (8.96)
$AUC_{0\text{-}inf}$ [a] (hr×mg/L)	22.9 (10.9)	46.3 (11.8)	25.3 (5.73)	32.9 (8.93)
C_{max} (mg/L)	6.25 (2.28)	8.82 (1.56)	7.43 (1.89)	6.11 (2.04)
T_{max} [b] (hr)	2.00 [1.00 – 4.00]	3.00 [1.00 – 4.00]	2.00 [1.00 – 4.00]	3.00 [1.00 – 4.00]
$T_{1/2}$ (hr)	1.65 (0.421)	2.80 (0.588)	1.69 (0.46)	2.9 (0.62)
CL/F (L/hr)	42.5 (18.2)	18.4 (4.49)	n.a.	n.a.
Vz/F (L)	93.6 (31.1)	72.2 (17.0)	n.a.	n.a.
M:P Ratio	1.14 (0.499)	0.644 (0.245)	n.a.	n.a.

[b] median [range]
n.a. not applicable

Table 48 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Urine Pirfenidone and 5-Carboxy-Pirfenidone in Smokers and Nonsmokers

	Pirfenidone		5-Carboxy-Pirfenidone	
Parameters	Smoker	Nonsmoker	Smoker	Nonsmoker
N	25	25	25	25
Ae (mg)	1.51 (0.952)	3.25 (1.56)	786 (82.2)	757 (73.2)
Ae%	0.188 (0.119)	0.405 (0.195)	84.5 (8.83)	81.4 (7.87)
CLr (L/hr)	0.0651 (0.0272)	0.0694 (0.0272)	32.6 (8.09)	25.2 (7.81)

Table 49 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone and 5-Carboxy-Pirfenidone in the Absence (Day 1) and Presence (Day 11) of Fluvoxamine in Nonsmokers

	Pirfenidone		5-Carboxy-Pirfenidone	
Parameters	Post-Fluvoxamine Treatment	Pre-Fluvoxamine Treatment	Post-Fluvoxamine Treatment	Pre-Fluvoxamine Treatment
N	25	25	25	25
AUC_{last} (hr×mg/L)	170 (32.5)	46.1 (11.8)	31.6 (8.74)	32.6 (8.96)
$AUC_{0\text{-}inf}$ [a] (hr×mg/L)	184 (37.8)	46.3 (11.8)	34.9 (10.3)	32.9 (8.93)
C_{max} (mg/L)	14.9 (2.37)	8.82 (1.56)	2.46 (0.669)	6.11 (2.04)
T_{max} [b] (hr)	3.00 [2.00 – 4.00]	3.00 [1.00 – 4.00]	3.00 [2.00 – 4.00]	3.00 [1.00 – 4.00]
$T_{1/2}$ (hr)	8.05 (1.22)	2.80 (0.588)	8.82 (2.00)	2.90 (0.620)
CL/F (L/hr)	4.56 (1.01)	18.4 (4.49)	n.a.	n.a.
Vz/F (L)	52.1 (10.5)	72.2 (17.0)	n.a.	n.a.
M:P Ratio	0.166 (0.0443)	0.644 (0.245)	n.a.	n.a.

[b] median [range]
n.a. not applicable

Table 50 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone and 5-Carboxy-Pirfenidone in the Absence (Day 1) and Presence (Day 11) of Fluvoxamine in Smokers

	Pirfenidone		5-Carboxy-Pirfenidone	
Parameters	Post-Fluvoxamine Treatment	Pre-Fluvoxamine Treatment	Post-Fluvoxamine Treatment	Pre-Fluvoxamine Treatment
N	26	26	26	26
AUC_{last} (hr×mg/L)	147 (44.2)	22.7 (10.8)	26.6 (6.29)	25.1 (5.74)
$AUC_{0\text{-}inf}$ [a] (hr×mg/L)	156 (52.3)	22.9 (10.9)	28.4 (7.40)	25.3 (5.73)
C_{max} (mg/L)	14 (2.29)	6.25 (2.28)	2.34 (0.585)	7.43 (1.89)
T_{max} [b] (hr)	2.00 [1.00 – 4.00]	2.00 [1.00 – 4.00]	2.00 [1.00 – 6.00]	2.00 [1.00 – 4.00]
$T_{1/2}$ (hr)	6.87 (1.89)	1.65 (0.421)	7.44 (2.06)	1.69 (0.46)
CL/F (L/hr)	5.68 (1.79)	42.5 (18.2)	n.a.	n.a.
Vz/F (L)	52.4 (9.57)	93.6 (31.1)	n.a.	n.a.
M:P Ratio	0.168 (0.0517)	1.14 (0.499)	n.a.	n.a.

[b] median [range]
n.a. not applicable

Table 51 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Urine Pirfenidone and 5-Carboxy-Pirfenidone in the Absence (Day 1) and Presence (Day 11) of Fluvoxamine in Nonsmokers

	Pirfenidone		5-Carboxy-Pirfenidone	
Parameters	Post-Fluvoxamine Treatment	Pre-Fluvoxamine Treatment	Post-Fluvoxamine Treatment	Pre-Fluvoxamine Treatment
N	25	25	25	25
Ae (mg)	10.7 (3.03)	3.25 (1.56)	651 (93.1)	757 (73.2)
Ae%	1.33 (0.378)	0.405 (0.195)	69.9 (10.0)	81.4 (7.87)
CLr (L/hr)	0.0621 (0.0125)	0.0694 (0.0272)	22.5 (8.37)	25.2 (7.81)

Table 52 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Urine Pirfenidone and 5-Carboxy-Pirfenidone in the Absence (Day 1) and Presence (Day 11) of Fluvoxamine in Smokers

	Pirfenidone		5-Carboxy-Pirfenidone	
Parameters	Post-Fluvoxamine Treatment	Pre-Fluvoxamine Treatment	Post-Fluvoxamine Treatment	Pre-Fluvoxamine Treatment
N	25	25	25	25
Ae (mg)	9.61 3.51	1.51 0.952	671 121	786 82.2
Ae%	1.20 0.438	0.188 0.119	72.1 13.0	84.5 8.83
CLr (L/hr)	0.0652 0.0169	0.0651 0.0272	26.1 6.85	32.6 8.09

Conclusions:
Systemic exposure to pirfenidone is lower in the smoker than the nonsmokers. Fluvoxamine administration results in 4-fold and 7-fold increase in pirfenidone exposure (AUC) in the nonsmokers and smokers, respectively.

4.4.4 Clinical Study PIPF-011

Study Title: An Open-Label Phase 1 Study to Determine the Pharmacokinetics and Safety of Pirfenidone in Subjects with Hepatic Insufficiency

Study Design: This is a Phase 1, single-dose, open-label, parallel-group study comparing the pharmacokinetics and safety of pirfenidone in subjects with moderate hepatic insufficiency and in normal healthy subjects. Each subject received a single oral dose of 801 mg pirfenidone with a standardized meal in the morning. Blood for PK sampling was drawn from each subject at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, and 32 hours postdose. Urine samples for PK analysis were collected at the following intervals, 0-12, 12-24, and 24-32 hours postdose.

Results:

The systemic exposure (C_{max} and $AUC_{0\text{-}inf}$) to pirfenidone increased ~1.4 to 1.6-fold in subjects with moderate hepatic impairment compared to 12 demographically matched healthy subjects. No difference in AUC to 5-carboxy-pirfenidone was found between the two groups.

The arithmetic means (SD) of pirfenidone and 5-carboxy-pirfenidone plasma PK parameters are provided in Table 53. The arithmetic means (SD) of pirfenidone and 5-carboxy-pirfenidone urine PK parameters are provided in Table 54.

The summary statistical analysis on plasma pharmacokinetic parameters of pirfenidone and its metabolite 5-carboxy-pirfenidone is listed in Table 55 and Table 56.

Table 53 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Plasma Pirfenidone and 5-Carboxy-Pirfenidone in Healthy and Moderate Hepatic Impaired Subjects

	Pirfenidone		5-Carboxy-Pirfenidone	
Parameters	Hepatic	Healthy	Hepatic	Healthy
N	12	12	12	12
AUC_{last} (hr×mg/L)	86.1 (42.5)	55.4 (27.2)	31.4 (9.87)	30.5 (4.69)
$AUC_{0\text{-}inf}$ (hr×mg/L)	89.8 (49.0)	55.8 (27.5)	32.4 (10.1)	30.8 (4.70)
C_{max} (mg/L)	16.8 (5.15)	11.9 (3.53)	5.08 (2.08)	6.18 (2.76)
T_{max} [a] (hr)	0.500 [0.433 – 1.00]	1.00 [0.500 – 4.00]	1.00 [0.500 – 8.00]	1.00 [0.500 – 4.00]
$T_{1/2}$ (hr)	4.75 (2.57)	3.15 (1.28)	5.24 (3.18)	3.26 (1.29)
CL/F (L/hr)	11.4 (5.42)	19.0 (11.2)	n.a.	n.a.
Vz/F (L)	65.2 (17.3)	69.6 (15.9)	n.a.	n.a.
M:P Ratio	0.378 (0.154)	0.615 (0.354)	n.a.	n.a.

[a] median [range]
n.a. not applicable

Table 54 Arithmetic Mean (SD) of Pharmacokinetic Parameters for Urine Pirfenidone and 5-Carboxy-Pirfenidone in Healthy and Moderate Hepatic Impaired Subjects

	Pirfenidone		5-Carboxy-Pirfenidone	
Parameters	Hepatic	Healthy	Hepatic	Healthy
N	12	12	12	12
Ae (mg)	2.91 (2.38)	3.09 (1.95)	594 (208)	639 (132)
Ae%	0.363 (0.297)	0.385 (0.244)	63.8 (22.4)	68.7 (14.1)
CLr (L/hr)	0.0324 (0.0138)	0.0546 (0.0213)	20.6 (8.60)	21.7 (6.76)

Table 55 Summary Statistical Analysis of Pharmacokinetic Parameters of Pirfenidone in Healthy and Hepatic Impaired Subjects

Parameter	Geometric Mean (Hepatic Group, Test)	Geometric Mean (Healthy Group, Reference)	Ratio of Geometric Mean (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	16.1	11.4	1.41	115	173
AUC_{last} (hr×mg/L)	77.0	48.5	1.59	109	230
$AUC_{0\text{-}inf}$ (hr×mg/L)	78.9	48.9	1.61	110	237
$T_{1/2}$ (hr)	4.28	2.88	1.49	108	205

Table 56 Summary Statistical Analysis of Pharmacokinetic Parameters of 5-Carboxy-Pirfenidone in Healthy and Hepatic Impaired Subjects

Parameter	Geometric Mean (Hepatic Group, Test)	Geometric Mean (Healthy Group, Reference)	Ratio of Geometric Mean (Test/Reference)	90% CI, Lower	90% CI, Upper
C_{max} (mg/L)	4.45	5.62	0.791	53.6	117
AUC_{last} (hr×mg/L)	29.9	30.2	0.993	83.0	119
$AUC_{0\text{-}inf}$ (hr×mg/L)	31.1	30.4	1.02	86.3	121
$T_{1/2}$ (hr)	4.60	3.00	1.53	110	214
CLr (L/hr)	18.8	20.8	0.906	68.9	119

Conclusions:

Systemic exposure (AUC) to pirfenidone is 60% higher in subjects with the moderate hepatic impairment. The exposure to 5-carboxy-pirfenidone in these patients are similar to the healthy volunteers.

4.4.5 Study pcln-pirf-110

Study Title: *In vitro* Protein Binding of [^{14}C]-S-7701

Objectives: To determine the *in vitro* protein binding of [^{14}C]-S-7701 (pirfenidone)

Methods: Serum and purified human serum protein solution sample containing [^{14}C]-S-7701 (1, 10 and 100 µg/mL); ultrafiltration ((b) (4)

RESULTS:

The binding ratios of [^{14}C]-S-7701 at the concentration of 1, 10, and 100 µg/mL were 57.95, 58.10 and 49.67% in human serum, respectively. Human serum showed a tendency of decrease at 100 µg/mL. However, the saturation would not have large impact on pharmacokinetics of S-7701 because the plasma concentration of unbound S-7701 may increase only by 1.0 - 1.2-fold. The binding ratios of [14C]-S-7701 at the concentration of 1, 10, and 100 µg/mL were 35.29, 34.77

and 32.25% in HSA, 7.37, 4.21 and 2.66% in human AGP, 1.92, 3.48 and 3.18% in human γ-globulin, respectively.

CONCLUSIONS:

The binding ratio can be considered constant over the therapeutic concentration range of 1 to 10 µg /mL.

The *in vitro* protein bindings of [^{14}C]-pirfenidone in purified human sera protein solution indicated that albumin was the major binding protein.

4.4.6 Study pcln-pirf-093

Study Title: Measurement of Serum Protein Binding of S-7701 in Phase 1 Clinical Study (single administration)

Objectives: The purpose was to investigate the safety and pharmacokinetics of single oral administration of S-7701 in healthy adult male volunteers to obtain the information required to proceed with a repeated administration study and a phase II clinical trial.

Methods: Ultrafiltration

Results/Conclusions:

S-7701 serum protein binding rates ranges from 54 to 62% with serum concentrations ranged from 2.10 to 12.1 µg/mL. S-7701 serum protein binding rates showed serum concentration dependency with binding rates increases as serum concentration decreases. Linear regression analysis on serum concentration and protein binding rates showed that the slope was negative (-0.5205, 95%CI: -0.9824, -0.0587).

4.4.7 Study pcln-pirf-122

Study Title: Assessment of P-gp Interactions in Cell Monolayers

Objectives: The purpose of this study was to characterize the permeability and P-gp interactions of selected test article(s) in Caco-2 and LLC-PK1 cell monolayers.

Results:
The positive control P-gp substrate digoxin showed active efflux with a polarization ratio of 10.4, which is consistent with a properly functioning model. The A to B permeability of pirfenidone was greater than that of the high permeability comparator propranolol. Recovery of the test article from the cell monolayers (mass balance) and from the plastic plate without cells (non-specific binding) was high (89-100%), indicating that binding had no effect on the permeability assay. Sponsor decided to conclude the study without proceeding to the LLC-PK1 study steps.

Conclusions:

Due to the high passive permeability of the pirfenidone, a conclusion regarding potential transport by P-gp cannot be drawn. The polarization ratio of approximately 1 could indicate either lack of test article transport by P-gp, or the masking of such transport by the high passive permeability.

It is unlikely that pirfenidone to be a P-gp substrate based upon the finding that the mean net flux ratios ($Permeability_{app, B A}$/$Permeability_{app, A B}$) were 1.1, 1.2, and 1.2 at pirfenidone concentrations of 10, 100, 1000 µM pirfenidone test systems, respectively.

4.4.8 Study pcln-pirf-124

Study Title: Assessment of PGP Inhibition by Pirfenidone in Caco-2 cell Monolayers

Objectives: The purpose of this study was to determine if pirfenidone inhibits P-gp mediated digoxin efflux in Caco-2 cell monolayers.

Methods: Bidirectional transport of the known P-gp substrate digoxin (5 µM) was assayed in the presence of increasing concentrations of pirfenidone (1.0, 3.0, 10, 30, 100, 300, 1000 µM).

Results:

Pirfenidone showed weak inhibition (10 to 30%) of P-gp facilitated digoxin B-A efflux at concentrations of 100 µM and above (see table below).

Table 4 Inhibition of digoxin efflux by pirfenidone

Test article ID	Nominal conc [uM]	Incubation time [min]	Papp [cm/sec] A to B			Papp [cm/sec] B to A			Efflux Ratio [B-A/A-B]	% Inhibtion
digoxin 5 uM	5.0	90	1.3E-06	1.4E-06	1.4E-06	1.2E-05	1.3E-05	1.3E-05	9.2	
dig5 + ketoconazole 25 uM	5.0	90	4.3E-06	4.6E-06	8.5E-06	5.2E-06	6.1E-06	6.9E-06	1.0	100%
dig5 + cyclosporine 10 uM	5.0	90	4.3E-06	7.0E-06	5.4E-06	5.3E-06	5.5E-06	6.7E-06	1.1	98%
dig5 + pirfenidone 1 uM	5.0	90	1.4E-06	1.5E-06	1.5E-06	1.2E-05	1.3E-05	1.3E-05	8.6	7%
dig5 + pirfenidone 3 uM	5.0	90	1.4E-06	1.4E-06	1.4E-06	1.3E-05	1.3E-05	1.4E-05	9.5	-4%
dig5 + pirfenidone 10 uM	5.0	90	1.3E-06	1.4E-06	1.4E-06	1.3E-05	1.3E-05	1.4E-05	9.7	-7%
dig5 + pirfenidone 30 uM	5.0	90	1.5E-06	1.4E-06	1.5E-06	1.4E-05	1.4E-05	1.4E-05	9.7	-6%
dig5 + pirfenidone 100 uM	5.0	90	1.6E-06	1.5E-06	1.5E-06	1.1E-05	1.2E-05	1.3E-05	7.7	18%
dig5 + pirfenidone 300 uM	5.0	90	1.5E-06	1.4E-06	1.5E-06	1.3E-05	1.2E-05	1.2E-05	8.3	10%
dig5 + pirfenidone 1000 uM	5.0	90	1.8E-06	1.9E-06	1.9E-06	1.3E-05	1.2E-05	1.3E-05	6.8	29%
Permeability Comparators										
Propranolol (50 uM)	50	90	8.5E-06	9.1E-06	9.0E-06					
Mannitol (50 uM)	50	90	5.9E-07	m.s.	6.5E-07					

m.s. - missing sample (data point censored, suspected experimental error)

Conclusions:

The IC_{50} values of pirfenidone were estimated to be greater than 1000 µM.

4.4.9 Study pcln-pirf-111

Study Title: Reaction phenotyping: Identification of CYP enzymes involved in the metabolism of pirfenidone

Objective: To determine the role of flavin-containing monooxygenases (FMO) and cytochrome P450 (CYP) enzymes in the metabolism of pirfenidone, and to identify the cytochrome P450 (CYP) enzyme(s) involved in the metabolism of pirfenidone.

Methods:

Incubations of pirfenidone with heat-inactivated human liver microsomes, recombinant FMO enzymes and human liver microsomes in the presence of 1-benzylimidazole (a chemical that inhibits CYP enzyme activity but not FMO activity) were carried out to evaluate the involvement of FMO enzymes in the metabolism of pirfenidone.

The conversion of pirfenidone to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone by individual recombinant human CYP enzymes (rCYP enzymes), namely rCYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 3A4, 3A5, 4A11, and 4F2 (2) an evaluation of the effects of specific inhibitory monoclonal antibodies against selected CYP enzymes, namely CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 on the conversion of pirfenidone to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone by human liver microsomes and (3) an evaluation of the sample-to-sample variation in the rate of formation of 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone by a bank of 16 samples of human liver microsomes and its correlation with the sample-to-sample variation in the activity of the major CYP enzymes and FMO activity were carried out in the human liver microsomes.

Results:

- Pirfenidone was converted to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone by human liver microsomes. Formation of both metabolites required the presence of NADPH. Formation of 5-hydroxymethyl-pirfenidone increased proportionally with respect to incubation time and protein concentration at all three concentrations of pirfenidone (10, 100 and 1,000 µM) evaluated. In addition, 5-hydroxymethyl-pirfenidone formation increased with increasing substrate concentration (10,100 and 1000 µM). Formation of 5-carboxy-pirfenidone increased with respect to incubation time and protein concentration at 100 and 1,000 µM pirfenidone (this metabolite was not detected at 10 µM). In addition, 5-carboxy-pirfenidone formation increased with increasing substrate concentration (100 and 1,000 µM).

- The kinetic constants, Km and Vmax, for the conversion of pirfenidone to 5-hydroxymethyl-pirfenidone were calculated to be 3.77 mM and 3310 pmol/mg/min, respectively. The kinetic constants, Km and Vmax, for the formation of 5-carboxy-pirfenidone were calculated to be 1.01 mM and 10.1 pmol/mg/min, respectively. Based on these values, the *in vitro* intrinsic clearance value (Vmax/Km) for 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone were determined to be 0.88 and 0.0010 µL/mg/min, respectively.

- Heating human liver microsomes to 50°C for 1 min, which inactivates FMO, had only a marginal effect (<10%) on the conversion of pirfenidone to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone. In contrast, the non-specific inhibitor 1-benzylimidazole completely inhibited metabolite formation.

- In incubations of pirfenidone at 100 and 1,000 µM with a panel of recombinant human CYP enzymes (rCYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1, 2J2, 3A4, 3A5, 4A11, and 4F2), 5-hydroxymethyl-pirfenidone was formed above the limit of quantification by rCYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1 and 2J2. In incubations of pirfenidone at 100 µM, 5-carboxy-pirfenidone was formed above the limit of quantification by rCYP1A2 and rCYP3A4. In incubations of pirfenidone at 1,000 µM, 5-carboxy-pirfenidone was formed above the limit of quantification by rCYP3A4.

- The conversion of pirfenidone (100 and 1,000 µM) to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone by human liver microsomes was inhibited by monoclonal antibody against CYP1A2 (by 44% and 48%, respectively). Weak inhibition was also observed with antibody against CYP2C8 (7%) at 100 µM pirfenidone and by antibodies against CYP2C8 and CYP2D6 (13 and 11%, respectively) at 1,000 µM pirfenidone. Formation of 5-carboxy-pirfenidone was completely inhibited by monoclonal antibody against CYP1A2. No other antibody tested inhibited 5-carboxy-pirfenidone formation.

- Pirfenidone (100 µM) was incubated with a bank of 16 samples of human liver microsomes to determine the inter-individual differences in metabolite formation. The sample-to-sample variation in the rate of formation of 5-hydroxymethyl-pirfenidone and 5-

carboxy-pirfenidone both correlated highly with CYP1A2 activity (r = 0.851 and 0.934, respectively).

Conclusions:

Pirfenidone was converted to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone by NADPH-fortified human liver microsomes. The result of experiments with human recombinant CYP enzymes implicated several CYP enzymes such as CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C18, 2C19, 2D6, 2E1 and 2J2 in the metabolism of pirfenidone. However, the results of the antibody inhibition experiments and correlation analysis suggest that CYP1A2 is the major CYP enzyme responsible for the conversion of pirfenidone to 5-hydroxymethyl-pirfenidone and 5-carboxy-pirfenidone in human liver microsomes. The overall results indicate CYP1A2 as the major CYP involved in the metabolism, however, results from experiments with human recombinant CYP enzymes and correlation analysis indicate that other CYP enzymes participate in the overall metabolism of pirfenidone.

4.4.10 Study pcln-pirf-112

Study Title: Identification of Cyp Isozymes Involved in Oxidative Metabolism of S-7701

Objective: To identify CYP isozymes involved in the oxidative metabolism of S-7701 in human liver microsomes.

Methods: Antibody inhibition experiments on *in vitro* metabolic activity against S-7701 by human liver microsomes were conducted, using production of 5-hydroxymethyl-S-7701 as the measure of activity.

Results:

The anti-sera against CYP1A2, CYP2C9/10 and CYP2C19 each showed about 25% inhibition of activity compared to pre-immune serum. The anti-CYP2D6 and anti-CYP2E1 showed 16 and 10% inhibition of activity, respectively, while anti-CYP3A4 showed no inhibition at all. The extent of inhibition by each anti-serum was less than expected, not exceeding 30% in any case. However, when each CYP isozyme was individually inhibited, the involvement of other CYP isozymes increased, supplementing metabolic activity and potentially lessening the extent of apparent inhibition.

Total inhibitory potency was studied using mixed antisera that had shown inhibition of CYP isozymes. The variability in activity when three types of anti-sera (anti-CYP1A2, anti-CYP2C9/10, and anti-CYP2C19) or five types (all except anti-CYP3A4) were added to the reaction system was examined. There was 66% inhibition of activity with the mixture of three types of anti-sera and 86% inhibition of activity with the mixture of five types of anti-sera, compared to the activity with the addition of preimmune serum. This indicated that the oxidative metabolism of S-7701 could be almost completely explained by the involvement of five CYP isozymes, not including CYP3A4.

Conclusions:

The multiple CYP isozymes are involved in the oxidative metabolism of S-7701. The individual CYP isozymes account for only small proportions of total S-7701 metabolism. If a specific CYP isozyme is inhibited by a drug co-administered with S-7701, other CYP isozymes compensate for it. This suggests that there S-7701 is very safe in terms of interactions.

4.4.11 Study pcln-pirf-105

Study Title: *In vitro* evaluation of S-7701 and 5-carboxylic S-7701 as inducers of cytochrome P450 expression in cultured human hepatocytes

Objective: The aim of this study was to investigate the effect of S-7701 and 5-carboxylic S-7701 on the expression of cytochrome P450 (CYP) enzymes in primary cultures of human hepatocytes.

Methods: Each preparation of cultured human hepatocytes was treated with 0.1% (v/v) DMSO (vehicle), one of three concentrations of S-7701 or 5-carboxylic S-7701 (50, 100, or 250 μM) or one of two known CYP inducers (namely, β-naphthoflavone (33 μM) and rifampin (20 μM)) once daily for three consecutive days. Twenty-four hours after the last treatment, hepatocytes were harvested. Microsomes were prepared from hepatocytes, microsomal protein concentration was determined, and microsomes were used to measure rates of 7-ethoxyresorufin O-dealblase (EROD) (marker for CYP1A2), testosterone 6β-hydroxylase (marker for CYP3A4/5), diclofenac 4'-hydroxylase (marker for CYP2C9) and S-mephenytoin 4'-hydroxylase (marker for CYP2C19) activities in the microsomal samples were measured.

Results:

Treatment of hepatocytes with S-7701 had no significant effect on EROD activity, although there was a tendency towards an increase in EROD activity in hepatocytes treated with 250 μM S-7701. Treatment of hepatocytes with 5-carboxylic S-7701 had little or no effect on EROD activity compared with the vehicle control. The positive control, β-naphthoflavone caused a 6.3-fold increase in EROD activity.

Treatment of hepatocytes with S-7701 or 5-carboxylic S-7701 had little or no effect on diclofenac 4'-hydroxylase activity although there was a tendency towards an increase in diclofenac 4'-hydroxylase activity in hepatocytes treated with 250 μM S-7701. In contrast, the positive control, rifampin, caused a 3-fold increase in diclofenac 4'-hydroxylase activity.

Treatment of hepatocytes with S-7701 (250 μM) caused a significant increase (2.2-fold) in S-mephenytoin 4'-hydroxylase activity. In contrast, treatment of hepatocytes with 5-carboxylic S-7701 had no effect on S-mephenytoin 4'-hydroxylase activity at the concentrations examined. The positive control, rifampin, caused a 7-fold increase in S-mephenytoin 4'-hydroxylase activity

Conclusions: Under conditions where the positive controls caused appropriate increase in CYP1A2, CYP3A4, CYP2C9 and CYP2C19 activity, S-7701 (at 250 μM) caused a significant increase in CYP3A4 and CYP2C19 activity, but had no significant effect on CYP1A2 or CYP2C9 activity. Compared with rifampin, S-7701 appears to be a weak inducer of CYP3A4 and CYP2C19. In contrast, 5-carboxylic S-7701 (up to 250 μM) caused no increases in any of the CYP activities measured.

4.4.12 Study pcln-pirf-067

Study Title: Effects of S-7701 on Human Liver Cyp .Enzymes

The aim of this study was to evaluate the effects of S-7701 on CYP2C9, 2C19, and 3A4.

The concentration dependency of inhibition was studied using the metabolic activity values obtained under the conditions listed below.

For CYP2C9 analysis, the final concentration of the substrate (tolbutamide) was set at 25 μM, and the final concentrations of S-7701 were set at 10, 50, 100, 250, 500, 750, and 1000 μM.

For CYP2C19 analysis, the final concentration of the substrate (mephenytoin) was set at 50 μM, and the final concentrations of S-7701 were set at 10, 50, 100, 250, 500, 750, and 1000 μM.

For CYP3A4 analysis, the final concentration of the substrate (terfenadine) was set at 0.5 μM, and the final concentrations of S-7701 were set at 50, 100, 250, 500, and 1000 μM.

Results:

The activities of the CYP enzymes tended to decrease in proportion to the increase of S-7701 concentrations. When S-7701 was added at the highest concentration of 1000 μM, the CYP2C9, 2C19, and 3A4 retained 70, 73, and 94% of their activities, respectively, as indicated in the figure below.

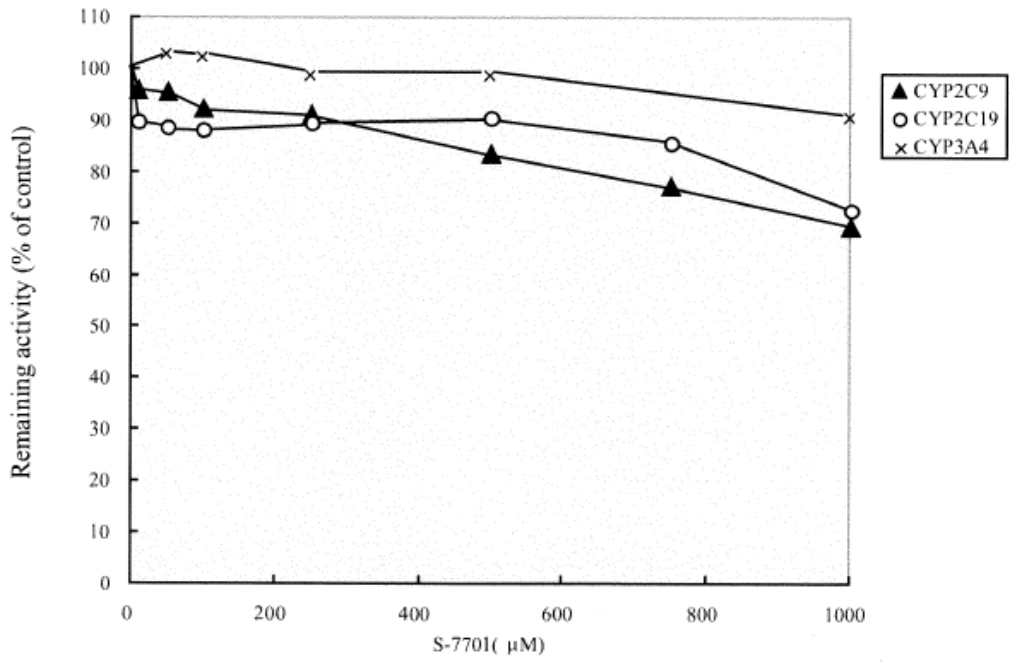


Fig 1. Effect of S-7701 on the catalytic activities of CYP2C9, CYP2C19 and CYP3A4 in human liver microsomes.

Conclusions:

CYP2C9, 2C19, and 3A4 enzymes retained at least 70% of their activity at the highest concentration of 1000 μM.

4.4.13 Study pcln-pirf-068

Study Title: Inhibitory Effect of S-7701 and Its Metabolite on Human Liver CYP Enzymes

Objectives: To evaluate the inhibitory effects of S-7701 and metabolite 5-carboxylic acid S-7701 upon CYP isoforms using human liver microsomes. To evaluate the reversibility of enzyme inhibition of S-7701 and its metabolite S-7701 5-carboxylic acid on CYP3A4 using human liver microsomes.

Results:

The inhibition rates on the metabolism of the CYP1A model substrate ethoxyresorufin at S-7701 concentrations of 100, 250, and 500 μM were 3.2, 8.5, and 14.5% respectively. Similarly, the inhibition rates on the metabolism of the CYP2A6 model substrate coumarin were 4.9, 4.3, and 10.3% respectively, and those on the metabolism of the CYP2D6 model substrate (±)-bufuralol were 0.4, -0.5, and -0.3% respectively. And the inhibition rates on the metabolism of the CYP2E1 model substrate chlorzoxazone were 1.6, 1.1, and 1.9% respectively. Moreover, the inhibition rates on the metabolism of CYP3A4 model substrate testosterone were 2.5, 10.6, and 13.0% respectively.

For S-7701, however, no studies of the inhibitory effect on CYP2C8/9 and 2C19 were conducted.

At S-7701 5-carboxylic acid metabolite concentrations of 100,250, and 500 μM, the inhibition rates on the metabolism of the CYP1A model substrate ethoxyresorufin were 1.9, 2.8, and 1.9% respectively. Similarly, the inhibition rates on the metabolism of the CYP2A6 substrate coumarin were 0.8, 1.2, and -2.9% respectively, and those on the metabolism of the CYP2C8/9 model substrate tolbutamide were -2.4, 5.0, and -8.6% respectively. And the inhibition rates on the metabolism of the CYP2C19 model substrate S-(+)-mephenytoin were -3.3, -5.3, and -0.1% respectively, and those on the metabolism of the CYP2D6 model substrate (±)-bufuralol were 4.3, 3.6, and 7.6% respectively. Moreover, the inhibition rates on the metabolism of for the CYP2E1 model substrate chlorzoxazone were 2.4, 3.9, and 2.0% respectively, and those for the CYP3A4 model substrate testosterone were 0.6, 0.9, and 0.1%, respectively.

The inhibition rates after preincubation times of 5 and 30 minutes were 8.6 and 2.5% at 100 μM of S-7701, 14.6 and 6.1% at 250 μM of S-7701, and 13.8 and 4.9% at 500 μM of S-7701, respectively. The inhibition rates after preincubation times of 5 and 30 minutes were 2.9 and 3.1% at 100 μM of S-7701 5-carboxylic acid, 0.2 and 5.7% at 250 μM of S-7701 5-carboxylic acid, and 0.5 and 0.2% at 500 μM of S-7701 5-carboxylic acid, respectively.

Conclusions:

Within the concentration range investigated in the present study (100, 250, and 500 μM). S-7701 showed a slight inhibitory effect against CYP1 A, 2A6, and 3A4. Moreover; the 5-carboxylic acid metabolite of S-7701 showed no inhibitory effect against any of the CYP isoforms. Also found was that at the above concentration range, S-7701 and 5-carboxylic acid metabolite showed no irreversible enzyme-inhibiting activities. The IC_{50} values of S-7701 and 5-carboxylic acid were more than 500 μM.

S-7701 and its metabolite S-7701 5-carboxylic acid do not show an irreversible inhibitory effect against CYP3A4.

4.4.14 Study pcln-pirf-125

Study Title: *In Vitro* Evaluation of Pirfenidone as an Inhibitor of Human Cytochrome P4501A2, 2A6, 2D6 and 2E1 Enzymes

Objectives: To evaluate the ability of pirfenidone to directly inhibit the CYP enzymes in human liver microsomes (namely CYP1A2, CYP2A6, CYP2D6 and CYP2E1) with the aim of ascertaining the potential of pirfenidone to inhibit the metabolism of concomitantly administered drugs.

Methods:

The ability of pirfenidone to inhibit the CYP enzymes was investigated with a pool of sixteen individual human liver microsomal samples at the concentrations indicated below.

Table 1: Summary of experimental conditions for enzyme assays: Direct inhibition of CYP enzymes by Pirfenidone

Enzyme	CYP Reaction	Substrate concentration (µM)	Incubation volume (µL)	Protein [a] (µg/mL)	Incubation time (min)	Pirfenidone Target concentrations (µM)	Pirfenidone Solvent volume [b] (µL)
CYP1A2	Phenacetin O-dealkylation	40	200	100	5	0, 10, 30, 60, 100, 300, 600 and 1000	20
CYP2A6	Coumarin 7-hydroxylation	0.75	200	12.5	5	0, 10, 30, 60, 100, 300, 600 and 1000	20
CYP2D6	Dextromethorphan O-demethylation	7.5	200	100	5	0, 10, 30, 60, 100, 300, 600 and 1000	20
CYP2E1	Chlorzoxazone 6-hydroxylation	30	200	100	5	0, 10, 30, 60, 100, 300, 600 and 1000	20

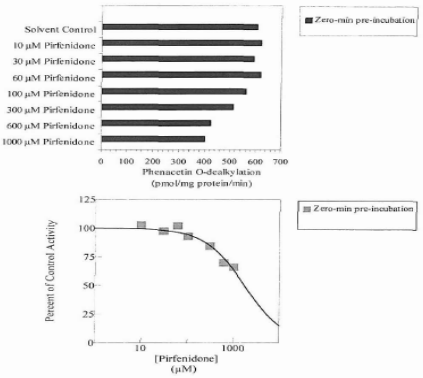
a The human liver microsomal sample used for these experiments was a pool of sixteen individuals (samples 286, 290, 312, 313, 315, 333, 334, 335, 336, 339, 348, 359, 364, 383, 389 and 390).

b High purity water was the vehicle used to dissolve the test article.

Results:

Under the experimental conditions examined, pirfenidone caused direct inhibition of CYPlA2, CYP2A6, CYP2D6 and CYP2E1, as approximately 34%, 27%, 21% and 27% inhibition was observed at 1000 µM. Determinations of IC_{50} for CYP1A2, 2A6, 2D6, and 2E1 are presented in the figure below.

Figure 1: Inhibition of CYP1A2 (phenacetin *O*-dealkylation) by Pirfenidone: IC_{50} determination

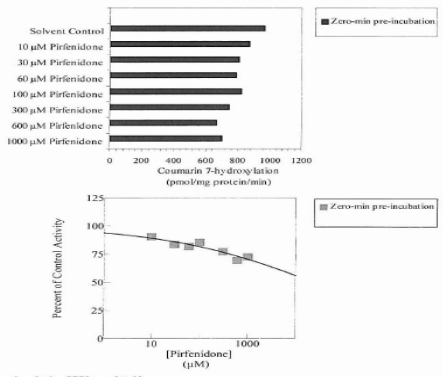


Zero-min pre-incubation IC50 result table

Parameter	Value	Std. Error
IC50 (µM)	> 1000 µM	NA
Slope Factor	NA	NA

Values are the average of duplicate determinations.
Numerical data are shown in Appendix 4.

Figure 2: Inhibition of CYP2A6 (coumarin 7-hydroxylation) by Pirfenidone: IC_{50} determination

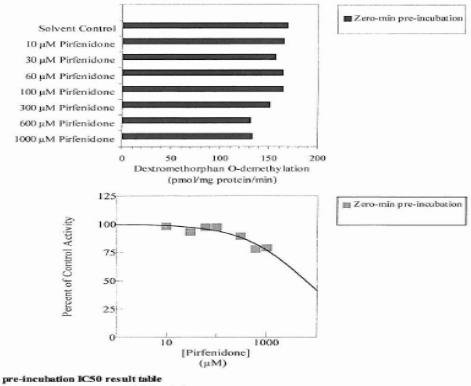


Zero-min pre-incubation IC50 result table

Parameter	Value	Std. Error
IC50 (µM)	> 1000 µM	NA
Slope Factor	NA	NA

Values are the average of duplicate determinations.
Numerical data are shown in Appendix 4.

Figure 3: Inhibition of CYP2D6 (dextromethorphan *O*-demethylation) by Pirfenidone: IC_{50} determination

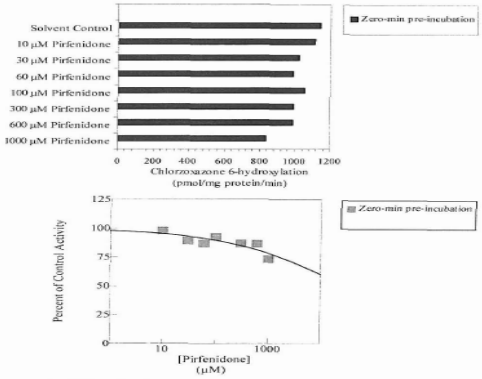


Zero-min pre-incubation IC50 result table

Parameter	Value	Std. Error
IC50 (µM)	> 1000 µM	NA
Slope Factor	NA	NA

Values are the average of duplicate determinations.
Numerical data are shown in Appendix 4.

Figure 4: Inhibition of CYP2E1 (chlorzoxazone 6-hydroxylation) by Pirfenidone: IC_{50} determination



Zero-min pre-incubation IC50 result table

Parameter	Value	Std. Error
IC50 (µM)	> 1000 µM	NA
Slope Factor	NA	NA

Values are the average of duplicate determinations.
Numerical data are shown in Appendix 4.

Conclusions:
The IC_{50} values reported for these enzymes were estimated to be greater than the highest concentration of pirfenidone examined (>1000 µM).

4.4.15 Study pcln-pirf-113

Study Title: *In Vitro* Evaluation of Pirfenidone as an Inhibitor of Human MAO Enzymes

Objectives: To evaluate the *in vitro* ability of pirfenidone to inhibit monoamine oxidase activity (specifically, MAO-A and MAO-B) in human liver mitochondria.

Methods: The inhibitory potency of pirfenidone was determined *in vitro* by measuring the activity of MAO-A and MAO-B in human liver mitochondria, in the presence or absence of pirfenidone.

Results:

Under the experimental conditions examined, there was no evidence that pirfenidone is a direct inhibitor of MAO-A, as no inhibition (0%) was observed at the highest concentration examined (1000 µM). In addition, there was no evidence of time-dependent inhibition of MAO-A after pirfenidone was pre-incubated with human liver mitochondria for 60 minutes. The IC_{50} values for MAO-A, for direct and time-dependent inhibition, were reported as >1000 µM.

Under the experimental conditions examined, pirfenidone directly inhibited MAO-B, as approximately 12% inhibition was observed at 1000 µM. In addition, there was no evidence of time-dependent inhibition of MAO-B after pirfenidone was pre-incubated with human liver mitochondria for 60 minutes. The IC_{50} values for MAO-B, for direct and time-dependent inhibition, were reported as >1000 µM,

Conclusions:

Pirfenidone caused little or no direct inhibition of MAO-A (0%) and MAO-B (12%). Pirfenidone caused no time-dependent inhibition of MAO-A or MAO-B.

4.4.16 Study pcln-pirf-114

Study Title: *In vitro* metabolism of pirfenidone in cryopreserved hepatocytes, kidney microsomes and intestine microsomes

Objectives: The aim of this study was to extend these *in vitro* metabolism studies by examining the metabolism of pirfenidone by extrahepatic microsomes (kidney and small intestine from both rat and human) and by cryopreserved rat and human hepatocytes.

Results:

Rat and human hepatocytes both converted pirfenidone to M1 (an alcohol) and M2 (the corresponding carboxylic acid), although rat hepatocytes metabolized pirfenidone faster than did human hepatocytes. Furthermore, rat hepatocytes converted pirfenidone to M1 faster than M1 was converted to M2 (such that both metabolites were detected), whereas the rate of M1 formation by human hepatocytes did not exceed the rate of conversion of M1 to M2 (such that only M2 was detected when pirfenidone was incubated with human hepatocytes).

Conclusions:

The results of the present study with human hepatocytes and extrahepatic microsomes together with the results of a previous study with human liver microsomes suggest that the initial step in pirfenidone metabolism, the methylhydroxylation to M1, is primarily catalyzed by CYP1A2, and that M1 is rapidly and predominantly formed in the liver with negligible contributions from the kidney or small intestine.

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

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/s/

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Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-535**	**Brand Name**	
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Pirfenidone**
Medical Division	**DPAP**	**Drug Class**	**Anti-inflammatory and antifibrotic agent**
CP/PM Reviewer	**Elizabeth Shang, Ph.D.**	**Indication(s)**	**Idiopathic Pulmonary Fibrosis**
CP Team Leader (Acting)	**Partha Roy, Ph.D.**	**Dosage Form**	**Capsule**
Pharmacometrics Team Leader	**Yaning Wang, Ph.D.**	**Dosing Regimen**	**801 mg (3 x 267-mg Capsules) Three Times a Day (TID)**
Date of Submission	**04 November, 2009**	**Route of Administration**	**Oral**
Estimated Due Date of OCP Review		**Sponsor**	**InterMune**
Medical Division Due Date		**Priority Classification**	**P**
PDUFA Due Date	**04 May, 2009**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**10**		
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**			
multiple dose:	**X**	**1**		
Patients-				
single dose:				
multiple dose:	**X**	**1**		
Dose proportionality -				
fasting / non-fasting single dose:				

fasting / non-fasting multiple dose:	**X**			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	**X**	**1**		
In-vivo effects of primary drug:				
In-vitro:	**X**			
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:	**X**	**1**		
hepatic impairment:	**X**	**1**		
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:	**X**	**1**		
Population Analyses -				
Data rich:	**X**	**1**		
Data sparse:	**X**			
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	**X**			
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	**X**			
Total Number of Studies		**17**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment

Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?		X		
2	Has the applicant provided metabolism and drug-drug interaction information?	X			
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			X	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	X			
5	Has a rationale for dose selection been submitted?	X			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	X			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	X			
8	Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?	X			
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			X	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			X	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	X			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			X	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
	General				

18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			X	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
_Yes_____

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

None.

A request has been generated on December 16, 2009 asking sponsor provide non-compartmental analyses on Studies PIPF-009, PIPF-010, AND PIPF-011. Sponsor has proposed to submit summary reports related to these analyses on January 8, 2010.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None

BACKGROUND

Pirfenidone is a new molecule entity intended for the treatment of idiopathic pulmonary fibrosis (IPF) currently approved in Japan (Pirespa® 200-mg tablet, Shionogi & Co., Ltd) (approval date: on October 16, 2008). On November 4, 2009, InterMune, Inc. submitted an electronic New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) seeking approval to market pirfenidone for the treatment of patients with IPF with declined lung function. It has been granted an orphan drug designation in U.S. since March 5, 2004. Although the exact mechanism of action is unknown, pirfenidone is thought to have both anti-inflammatory and antifibrotic activity mediated through TNF-alpha and TGF-beta. One dosage form has been developed by InterMune for the commercial usage to date: the 267 mg hard gelatin capsules. The proposed maintenance dosage and administration is 3 capsules of 267 mg i.e. 801 mg PO TID, a total daily dose of 2403 mg.

The clinical program consisted of two pivotal Phase 3 efficacy trials, PIPF-004 and PIPF-006, which absolute change from baseline in percent predicted at forced vital capacity (FVC) at Week 72 is the primary efficacy endpoint. PIPF-004 had positive results while PIPF-006 had negative results. InterMune also integrated a Phase 3 study (SP3) conducted in Japan sponsored by Shionogi in the NDA submission based upon sponsor's belief that this study contributes significantly to the totality of the data supporting the safety and efficacy of pirfenidone. The primary endpoint in SP3 trial is change from baseline in vital capacity (VC) at Week 52. It is noteworthy that the definitive diagnosis criterion for IPF in SP3 trial is different from Trial PIPF-004 and PIPF-006. The total daily dose of pirfenidone used in SP3 trial was ~25% lower than that in PIPF-004 and PIPF-006 (600 mg PO TID vs 801 mg PO TID). The formulation used in SP3 trial was 200-mg tablet.

The dosing regimen of 801 mg TID was chosen based upon five studies early in development: two Phase 2 studies conducted by Marnac and one Phase 2 uncontrolled open label study to make pirfenidone available for compassionate use conducted by Marnac, one Phase 2 study conducted in Japan (Shionogi: SP2) and two studies by independent investigators (Raghu et al. 1999; Nagai et al. 2002) at oral doses ranging from 1800 mg/day to 3600mg/day.

Waiver of conducting pediatric studies was granted because IPF does not occur in pediatric patient population.

CLINICAL PHARMACOLOGY PROGRAM

Human Biomaterial Studies

Serum Protein Binding Studies

Two in vitro studies were conducted to characterize the extent of serum protein binding of pirfenidone. Ex vivo serum protein binding study (PCLN-PIRF-093) was performed in a Phase

1 clinical study at Sekino Clinical Pharmacology Clinic in Japan sponsored by Shinogi &Co. Ltd. Ultrafiltration method was used to measure protein binding at 1 and 3 hours after oral administration of single dose of 600 mg pirfenidone (3 of 200-mg tablets) to healthy male Japanese volunteers. In vitro serum protein binding study (PCLN-PIRF-110) was performed at Developmental Research Laboratories, Shinogi &Co., Ltd in Osaka, Japan. In vitro serum protein binding of [^{14}C]-pirfenidone was investigated in human tissue obtained from healthy Japanese volunteers at concentrations of 1, 10, and 100 mcg/mL. Ultrafiltration was implemented as a testing method.

In Vitro Studies on Pirfenidone Metabolism

Three in vitro studies to characterize the enzymes responsible for the metabolism of pirfenidone were sponsored by Shinogi & Co, Ltd in Osaka, Japan.

Study PCLN-PIRF-112 investigated cytochrome P450 (CYP) enzymes responsible for pirfenidone metabolism using human liver microsomes by an antibody inhibition test. This study was conducted at Developmental Research Laboratories, Shinogi & Co, Ltd in Osaka, Japan.

Study PCLN-PIRF-111 examined the role of flavin-containing monooxygenases (FMO) and CYP P450 in pirfenidone metabolism in human liver microsomes. This study was conducted under contract at (b) (4).

Study PCLN-PIRF-114 investigated the metabolism of pirfenidone by cryopreserved human hepatocytes and by extrahepatic microsomes of the kidney and the small intestine.

In Vitro Studies on Effect of Pirfenidone upon CYP Enzymes

Four studies were carried out to investigate the potential for pirfenidone to induce or inhibit human CYP enzymes using in vitro human hepatocyte microsome preparations. All four studies were sponsored by Shinogi & Co, Ltd in Osaka, Japan.

Studies PCLN-PIRF-105 and PLCN-PIRF-125 examined the induction potential of pirfenidone and its major metabolite 5-carboxyl (5-CA) pirfenidone for CYP1A2, CYP2C9, CYP2C19, and CYP3A4/5. The concentrations of pirfendione and 5-CA-pirfenidone used were 50, 100, and 250 µM in PCLN-PIRF-105. The concentrations of pirfenidone and 5-CA-pirfenidone ranged from 10 to 1000 µM in PCLN-PIRF-125. Both studies were conducted under contract at (b) (4)

Study PCLN-PIRF-067 examined the inhibition potential of pirfenidone for CYP2C9, CYP2C19, and CYP3A4 at concentrations ranging from 10 to 1000 µM. This study was conducted at Developmental Research Laboratories, Shinogi & Co, Ltd in Osaka, Japan.

Study PLCN-PIRF-068 examined the direct and time-dependent inhibition potential of pirfenidone and 5-CA pirfenidone for CYP1A2, CYP2A6, CYP2C8/9 (only 5-CA pirfenidone), CYP2D6, CYP2E1, and CYP3A4 at concentrations of 100, 250, and 500 µM. This study was conducted under contract at (b) (4) .

In Vitro Studies on Effect of Pirfenidone upon Monoamine Oxidase (MAO) Enzymes

PCLN-PIRF-113 investigated the inhibitory potential of pirfenidone at concentrations ranging from 10 µM to 1000 µM for MAO-A and MAO-B using in vitro human hepatocyte mitochondrial preparations.

In Vitro Assessment of Interaction between P-gp and Pirfenidone

Study PLCN-PIRF-122 examined the potential of pirfenidone to be a substrate of P-gp mediated transporter in Caco-2 cell monolayers at concentrations ranging from 10 µM to 1000 µM. Study PLCN-PIRF-124 examined the potential for pirfenidone to inhibit P-gp mediated digoxin efflux at concentrations ranging from 1 µM to 1000 µM in Coca-2 cell monolayers. Both studies were conducted under contract at (b) (4)

Clinical Studies Examining PK and/or Pharmacodynamics (PD)

Five Phase 1 clinical pharmacology studies were performed in assessing human pharmacokinetics (PK) and the effects of intrinsic and extrinsic factors upon pirfenidone human PK. Human PK samples were also collected and analyzed in one Phase 3 trial and Phase 1 Thorough QT (TQT) study. The summary of clinical studies with pirfenidone PK sample collected and analyzed was listed in **Table 1**.

Population pharmacokinetics (pop PK) analysis was conducted on data pooled from four Phase 1 clinical studies (PIPF-005, PIPF-007, PIPF-009, and PIPF-010) and one Phase 3 clinical trial (PIPF-004) to assess PK variability and the influence of demographic factors, e.g. age, gender, obesity, race.

A statistical PK-PD model was developed and used to analyze one of the two pivotal Phase 3 trials, PIPF-004. The data for PK-PD analysis came from 88 patients who participated in the PK sub-study of PIPF-004. The relationships between patient average PK exposure (AUC_{0-24}, Cmax, and Cmin) for pirfenidone and its major metabolite 5-CA-pirfenidone and safety and efficacy endpoints were explored. The pharmacodynamic endpoints included efficacy and safety outcomes. The outcomes serving as dependent variables for the PK-PD analysis is provided in **Table 2**.

Bioanalytical Methods and Reports

All the PK samples (both plasma and urine) were analyzed at (b) (4) using LC-MS/MS method. The studies were performed in compliance with the principles and requirements described in 21 CFR part 58. The standard curve ranges for plasma pirfenidone and its major metabolite 5-carboxy-pirfenidone were 30.0 ng/mL to 3000 ng/mL. The standard curve ranges for urine pirfenidone and 5-carboxy-pirfenidone were 0.250 ng/mL to 50.0 ng/mL and 25.0 ng/mL to 5000 ng/mL, respectively.

Two validation reports were included in the submission. Eight bioanalytical reports were included for Studies PIPF-005, PIPF-009, PIPF-011 and PIPF-010. PK samples were collected and apparently analyzed in Studies PIPF-007 and PIPF-004, however, there were no bioanalytical reports in the submission related to these two studies. Bioanalytical reports for Studies PIPF-007 and PIPF-004 will be requested from the sponsor.

RESULTS

Overview of PK and PD

All the PK parameters were derived from compartmental analyses.

Systemic absorption occurred after oral administration. The bioavailability of pirfenidone has not been determined in human due to lack of IV formulation, but was found to be 63% in dogs and 77% in cats. Following oral multiple dose of administration of 801 mg TID with food for 14 days, the mean (CV%) exposure of pirfenidone in Cmax and AUC_{0-24} was 14.7 (34.5) mcg/mL and 180 mg•hr/L, respectively. The mean (SD) Vss/F is 40.7 (13.1) L/hr. The serum protein binding is ~58% at a concentration of 10 mcg/mL. The mean (SD) $t_{1/2}$ is 2.39 (0.868) hr.

Pirfenidone was primarily metabolized by CYP1A2 (~48%) with multiple other CYPs contributing as well (each <13%). Pirfenidone was primarily metabolized to 5-CA-pirfenidone which was primarily excreted in urine. 5-CA-pirfenidone is deemed to be pharmacologically inactive.

Food and Antacid Effects

Single dose food effect study revealed a ~50% reduction in Cmax, prolonged Tmax (0.5 to 3-4 hours), and ~15-20% reduction in AUC for the fed state compared with fasted state. Taking pirfenidone with food also reduced the incidence of nausea and dizziness.

No antacid effect was found on pirfenidone PK.

Intrinsic Effects

Renal Impairment

No relationship between serum creatinine clearance (CLcr) and pirfenidone exposure ($AUC_{0\text{-}inf}$) was identified. However, clearance of the 5-CA-pirfenidone decreases with decrease of CLcr. Consequently, exposure of the 5-CA pirfenidone increases. The impact on the exposure of the 5-CA-pirfenidone is not statistically significant until CLcr falls below 50 mL/min.

Hepatic Impairment

Subjects with moderate hepatic impairment (Child-Pugh Classification) had ~60% higher exposure of pirfenidone ($AUC_{0\text{-}inf}$). No change in exposure of 5-CA-pirfenidone was found between normal and moderate hepatic impairment subjects.

Age, Gender, Race and Weight Effects

Population PK analysis found that age and gender have small effects on pirfenidone PK. However, these effects have no impact on efficacy or safety. The sponsor did not propose any dosage adjustment.

Population PK analysis also found that body weight (BMI≥30 kg/m^2) has no significant effect on the pirfenidone PK.

Extrinsic Effects

Drug-drug interaction study showed that co-administration of fluvoxamine resulted in a 6-fold increase in AUC(0-inf) of pirfenidone and 2-fold increase in Cmax. No effect of fluvoxamine upon 5-CA-pirfenidone $AUC_{0\text{-}inf}$ was observed. Increase in accumulation of pirfenidone and 5-CA-pirfenidone was predicted to be 68% and 41%, respectively.

Smoking resulted in ~50% reduction in pirfenidone $AUC_{0\text{-}inf}$.

PK-PD Relationship

Among the various relationships between efficacy and safety outcomes (**Table 2**) and PK exposure examined in the PK-PD analysis, the only exposure-response which remained statistically significant was between PK exposure and photosensitivity (safety outcome). A doubling of Cmax of 5-CA-pirfenidone, the metabolite, was associated a ~doubling of the risk of photosensitivity. Failure to detect statistical significant relationships between PK exposure and efficacy outcomes and other safety outcomes may be due to sampling bias, patient self-selection, and the smaller sample size (N=88).

CONCLUSIONS

It is fileable from clinical pharmacology perspective.

Table 1. Summary of study designs in six trials with PK samples collected and analyzed.

Trial No.	Study Design	Population	Age (y)	Dose Administered	Formulation Used	Sampling Scheme	PK Analytes	Biologic Matrix for PK Samples
PIPF-005	Two cohort study (SD, crossover, food effect, antacid effect and escalating MD)	Healthy adults; n=16 in SD, n=24 in MD	50-66	SD: 801 mg MD: 801-4005 mg/day given TID	267 mg capsules	SD: Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 36, 48, 72 hours post dose MD: 21 samples per dose; sampled on 2 of the 5 doses (randomly assigned); 9 samples on Day 1 after the first dose; 3 pre-dose samples on Days 1, 2, and 3 before 8 AM dose; 9 samples on Day 3 following single last dose of the dose level.	Pirfenidone and 3 metabolites (5-carboxy-pirfenidone, 5-hydroxymethyl-pirfenidone, 4-hydroxy-pirfenidone).	Plasma and Urine
PIPF-007	Double-blind, randomized, parallel, MD, TQT study	Healthy adults; n=80	18-45	Therapeutic group: 2403 mg/day given TID on Day 9 Supratherapeutic group: 4005 mg/day	267 mg capsules	On Day 10: Pre-dose, 0.5, 1, 2, 3, 4, 4.5, 5, 6, 7, 8, 10, 10.5, 11, 12, 13, 14, 18, 23.5 hours post dose	Pirfenidone, 5-carboxy-pirfenidone	Plasma and Urine
PIPF-009	SD renal-impairment study	Normal, mild, moderate, and severe (without dialysis) renal impairment; n=24	40-80	SD: 801 mg	267 mg capsules	Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 32	Pirfenidone, 5-carboxy-pirfenidone	Plasma and Urine

PIPF-010	SD, crossover, drug-drug interaction study	Smokers and non-smokers; n=54	18-75	Two SD: 801 mg (with and without fluvoxamine)	267 mg capsules	Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 32 (with and without fluvoxamine)	Pirfenidone, 5-carboxy-pirfenidone	Plasma and Urine
PIPF-011	SD hepatic impairment study	Normal and moderate hepatic impairment; n=24	40-80	SD: 801 mg	267 mg capsules	Pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 12, 18, 24, 32	Pirfenidone, 5-carboxy-pirfenidone	Plasma and Urine
PIPF-004 (Phase 3)	Double-bind, randomized, placebo-controlled, Phase 3, three-arm study of the safety and efficacy	Adult patients with IPF; n=174 in 2403 mg/day arm, n=87 in 1197 mg/day arm	40-80	2403 mg/day (801 mg PO TID); 1197 mg/day; (399 mg PO TID)	2403 mg/day: 267 mg capsules; 1197 mg/day: 133 mg capsules	Pre-dose, 0.5, 1, 2, and 4 hours after dose on Weeks 2, 36, 60.	Pirfenidone, 5-carboxy-pirfenidone	Plasma

SD: single-dose, MD: multiple-dose, TQT: Thorough QT, IPF: idiopathic pulmonary fibrosis

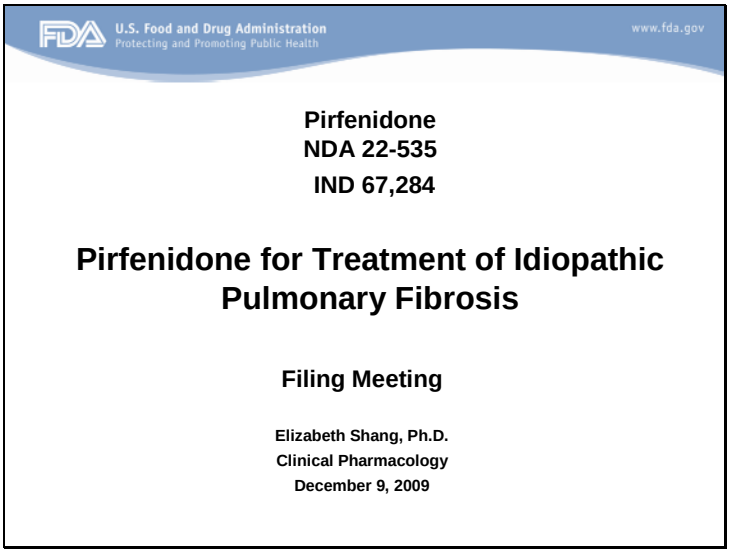
Table 2. Description of Efficacy and Safety Outcomes Evaluated in the PK-PD Analysis

Efficacy Outcomes	Safety Outcomes
Ranked Change from Baseline in Percent Predicted FVC at Week 72[a]	Occurrence of Nausea
Progression-Free Survival	Occurrence of Photosensitivity
	Occurrence of Rash
	Occurrence of Dizziness
	Maximum Percent Change in Body Weight
	Percent Change in Body Weight at Week 72

[a] Prespecified primary efficacy endpoint in the clinical analysis

Attachment of Filing Meeting Slides

Slide 1



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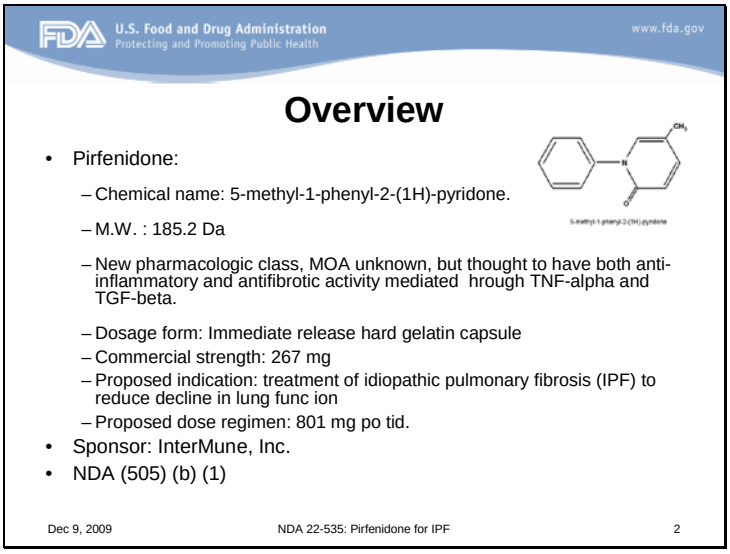

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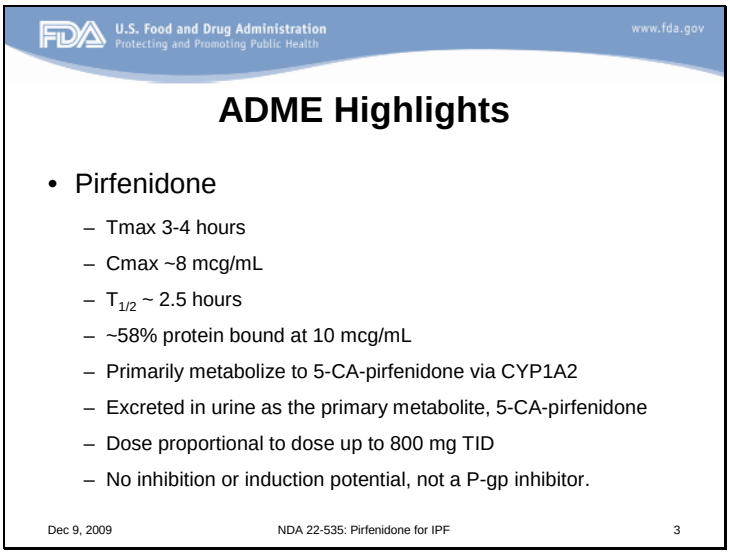

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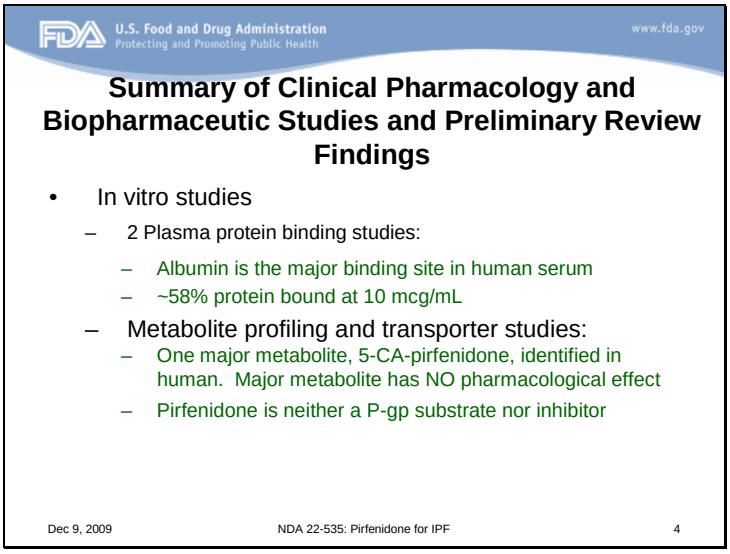

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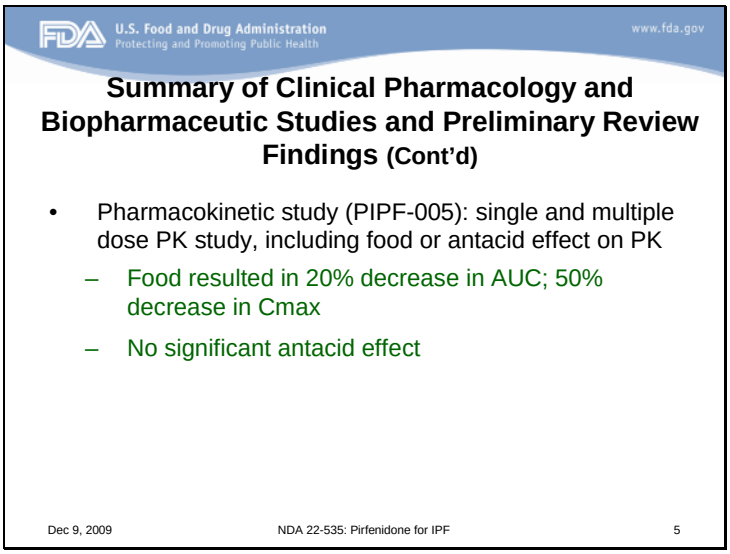

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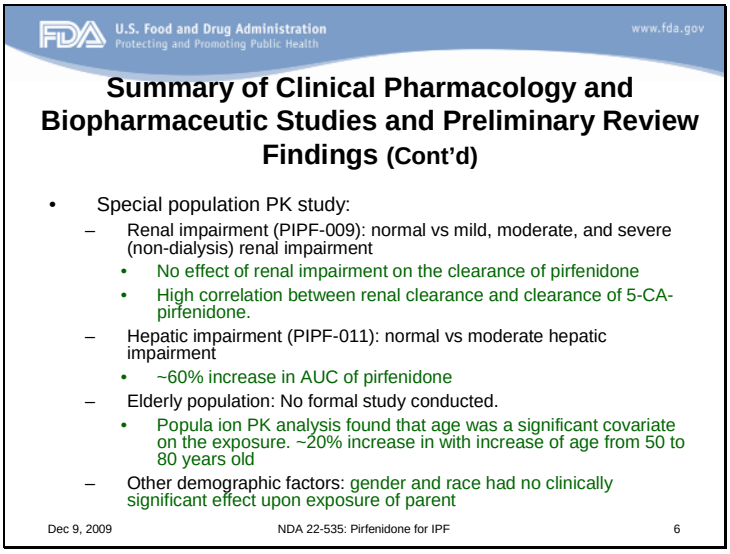

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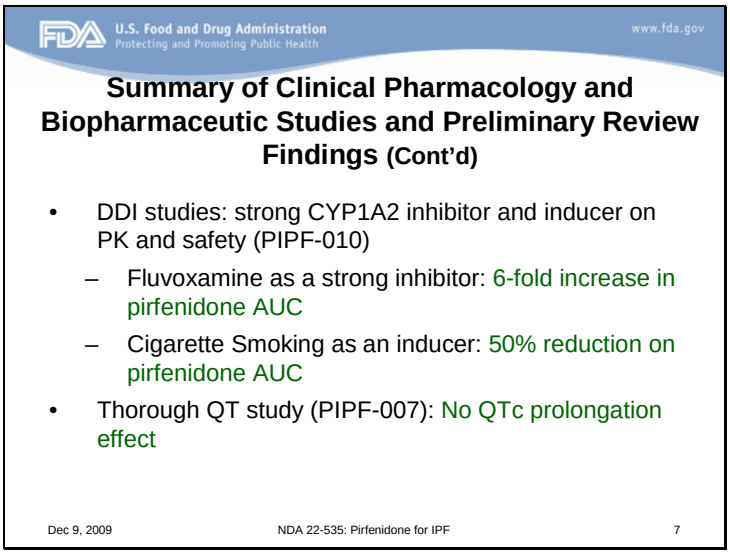

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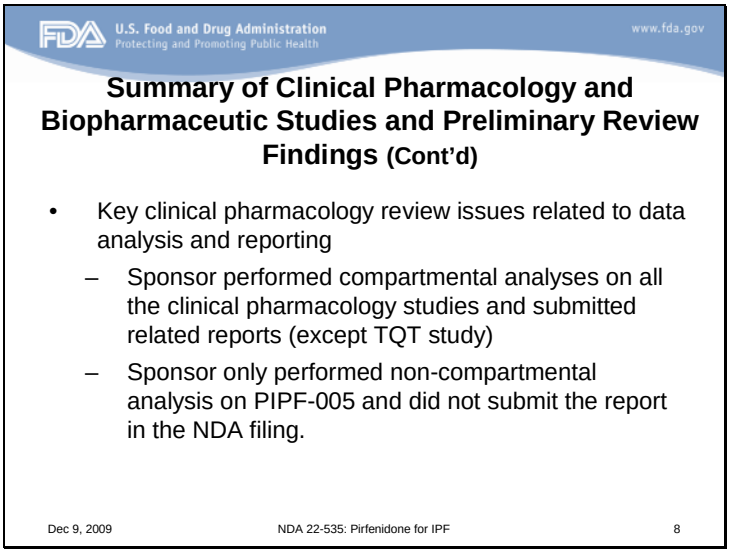

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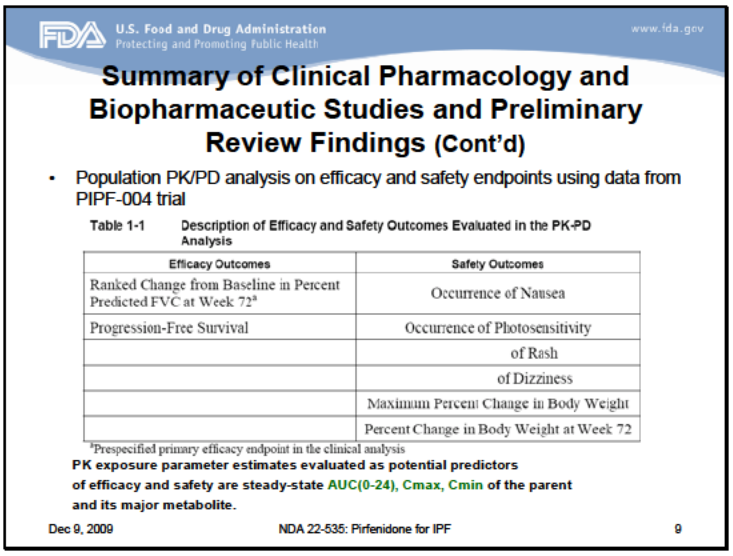

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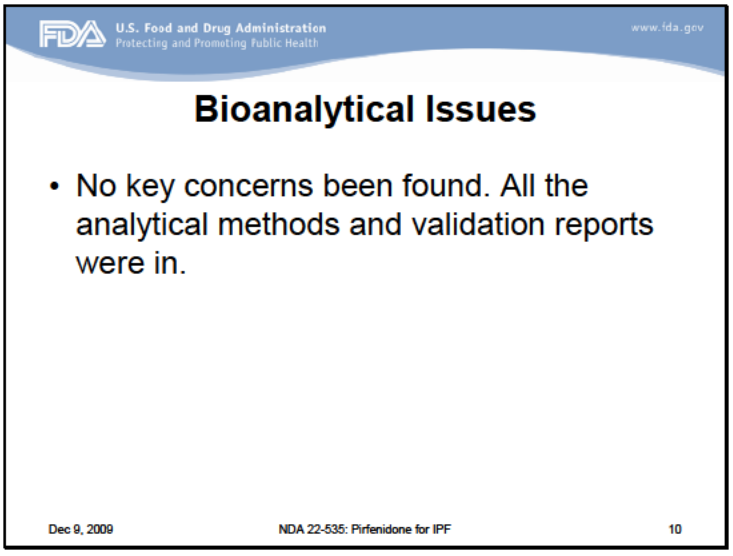

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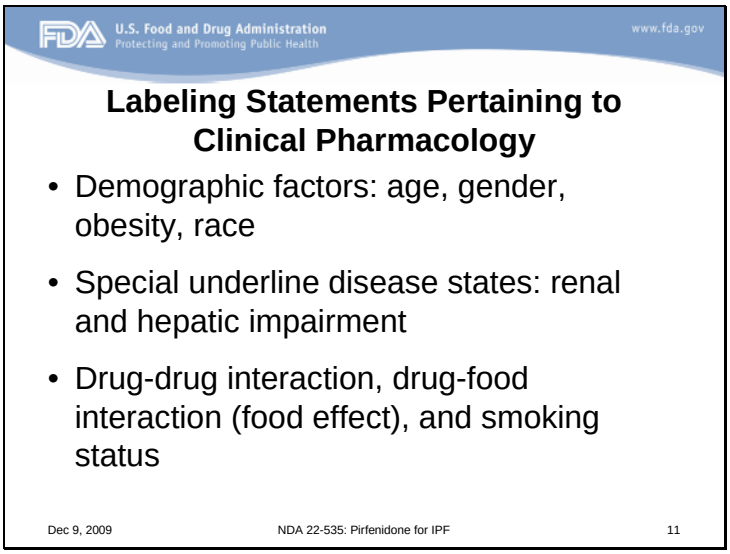

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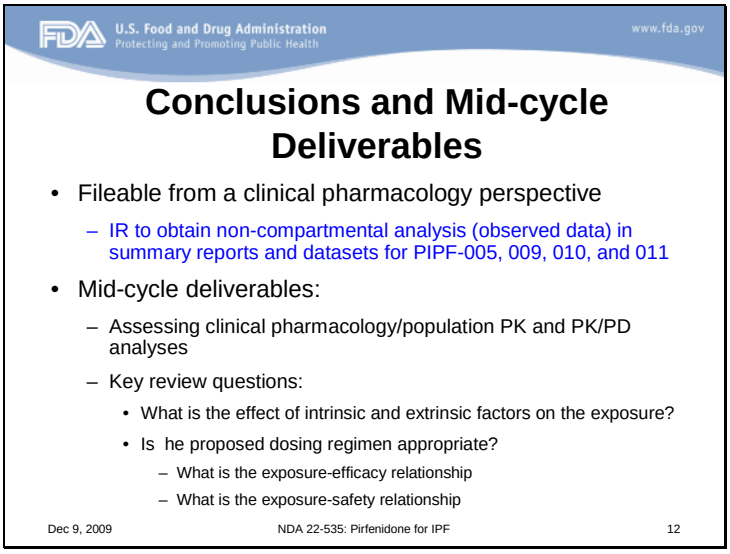

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22535	ORIG-1	INTERMUNE INC	PIRFENIDONE CAPSULE

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

/s/

YILI SHANG
12/31/2009

PARTHA ROY
12/31/2009