Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for pirfenidone

Proprietary Product Name: Esbriet

Sponsor: Roche Products Pty Ltd

First round report 23 September 2015
Second round report 24 November 2015

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of commonly used abbreviations

Abbreviation	Meaning
5-CA-pirfenidone	5-CA-pirfenidone
6MWT	6 Minute Walk Test
ADR	Adverse Drug Reaction
AE	Adverse Event
ALT	Alanine transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate transaminase
ATC	Anatomical Therapeutic Chemical Classification
CER	Clinical Evaluation Data
CHMP	Committee for Medicinal Products for Human Use
C_{max}	Peak plasma concentration
CNS	Central Nervous System
CSR	Clinical Safety Report
D_{LCO}	Diffusing capacity of the Lungs for Carbon Monoxide
DMC	Data Monitoring Committee
ECG	Electrocardiogram
EMA	European Medicines Agency
ESRD	End Stage Renal Disease
FDA	Food and Drug Administration (United States)
FEV_1	1 second Forced Expiratory Volume
FVC	Forced Vital Capacity
GAP	Gender/Age/2 lung Physiological variables (FVC and D_{LCO})
GCP	Good Clinical (Research) Practice
GORD	Gastro Oesophageal Reflux Disease

Abbreviation	Meaning
IPF	Idiopathic Pulmonary Fibrosis
ISS	Integrated Summary of Safety
ITT	Intention To Treat (analysis)
IVRS	Interactive Voice Response Software
LFT	Liver Function Tests
MAC	Mortality Assessment Committee
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention to Treat Test
NAC	N-acetyl-cysteine
PD	Pharmacodynamic
PEY	Person Exposure Years
PFTs	Pulmonary Function Tests
PK	Pharmacokinetic
POP-PK	Population Pharmacokinetics
PSUR	Post-market Safety Update Report
QTcB	Corrected QT interval using Bazett's formula
QTcF	Corrected QT interval using Fridercia's method
QTcI	Corrected QT Interval, individualisation optimisation of QT correction for HR
RISE	Resubmission Integrated Summary of Efficacy
RSU	Resubmission Safety Update
RSU	Resubmission Safety Update
SADR	Serious Adverse Drug Event
SAS	Special Access Scheme
SMQ	Standardised MedDRA (Medical Dictionary for Regulatory

Abbreviation	Meaning
	Activities) Query
SOC	System Organ Class
SPC	Summary of Product Characteristics
SpO_2	Mixed arteriovenous blood oxygen saturation
t½	Half-life
TDD	Total Daily dose
TDS	Three times daily (*latin: ter die sumendus*)
TEAE	Treatment Emergent Adverse Event
T_{LCO}	Transfer factor for Carbon Monoxide
T_{max}	Time to peak plasma concentration
UCSD SOBQ	University of California Shortness Of Breath Questionnaire
UIP	Usual Interstitial Pneumonia
ULN	Upper Limit of Normal
WHOCC	World Health Organisation Collaborating Centres

1. Introduction

This is a Category 1 submission to register the new chemical entity pirfenidone 267 mg hard capsules (Esbriet).

Pirfenidone (5-methyl-1-phenyl-2-(1H)-pyridone) is the first in its pharmacological class and is an immunosuppressant placed in the WHOCC ATC drug class of 'L04AX/other immunosuppressants' and has the ATC code L04AX05.

In this submission the sponsor proposed the following indication:

> *'Esbriet is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).'*

2. Clinical rationale

2.1. Background

Pirfenidone is an immunosuppressant; the mechanism of action has not been fully established.

The Clinical Overview states that pirfenidone is an orally active small molecule (molecular weight 185.2 daltons) described as an antifibrotic agent with anti-inflammatory properties. Nonclinical studies are quoted as demonstrating these characteristics, in particular in bleomycin-induced pulmonary fibrosis models.

Idiopathic pulmonary fibrosis (IPF) is a distinct form of chronic fibrosing interstitial pneumonia that is irreversible, causing respiratory insufficiency. The clinical course is characterised by debilitating loss of lung function, with an estimated median survival after diagnosis of only 2.5 to 5 years. One view of pathogenesis postulates fibroblastic foci and excess collagen following release of pro-fibrotic mediators, due to micro-injuries to alveolar epithelium.

2.2. Therapeutic context

In 2011 the American Thoracic Society and other international respiratory organisations published Evidence-based Guidelines for Diagnosis and Management for IPF.[1]

Early medical treatments for IPF were largely ineffective. Corticosteroids with or without adjunct immunosuppressive regimen is nonspecific and associated with significant adverse effects. A trial was stopped due to safety concerns in 2011 for N acetyl cysteine with azothioprine. N-acetyl-cysteine is available for some IPF patients in Australia through the SAS.

IPF accounts for approximately 23% of lung transplantations performed worldwide; this is usually for selected younger patients.

Nintedanib is approved for treatment of IPF by the USFDA, and recently was approved by the TGA.

Pirfenidone has been proposed for treatment of IPF for many years.[2] Pirfenidone is approved for treatment of IPF in other countries including the EU, USA and Canada. It is available through SAS in Australia. The clinical development program for the product proposed for registration, 'Esbriet', included 1,336 healthy subjects and patients with IPF or pulmonary fibrosis, including

[1] Raghu G et al. *Am J Respir Crit Care Med* 2011; 183: 788–824 An Official ATS/ERS/JRS/ALAT Statement: Idiopathic Pulmonary Fibrosis: Evidence-based Guidelines for Diagnosis and Management
[2] Raghu G et al. *Am J Respir Crit Care Med* 1999; 159: 1061–1069

1,098 patients assigned to receive pirfenidone doses 2,403 mg/day or higher. Post-marketing experience is based on cumulative exposure of over 15,000 patient-years.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

The submission included the following clinical information:

- 6 clinical pharmacology studies, including 5 that provided pharmacokinetic data and a pharmacodynamics study on ECG effects:
  - 1 population pharmacokinetic analysis
  - 3 pivotal efficacy/safety studies:
    - PIPF-004
    - PIPF-006
    - PIPF-016
  - 2 ongoing long-term safety studies
- Pooled analyses, Post-Marketing Safety Update Reports (PSUR), Integrated Summary of Efficacy, and Integrated Summary of Safety.

In addition the following were also provided:

- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety and literature references.
- European Medicines Agency (EMA) and Canadian regulatory reports were provided by the sponsor.

Comments: Overall the development program was comprehensively documented and the dossier well presented.

This clinical evaluation report (CER) is based on the submitted dossier. Other agency reports were viewed for additional information.

3.2. Paediatric data

The submission did not include paediatric data. IPF occurs only in the adult population.

3.3. Good clinical practice

The clinical study reports provided in addressed GCP appropriately for each study.

4. Pharmacokinetics

Table 1 shows the studies relating to each pharmacokinetic (PK) topic.

Table 1. Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID
PK in healthy adults	General PK (Single-dose, QT)*	PIPF 007
	General PK (Multi-dose)*	PIPF 005
	Bioequivalence† (Single dose)	Not applicable
	Bioequivalence† (Multi-dose)	Not applicable
	Food effect	PIPF 005
PK in special populations	Target population§ (Single and multiple dose)	PIPF 004
	Hepatic impairment*	PIPF 011
	Renal impairment*	PIPF 009
	Neonates/infants/children/adolescents	Not applicable
	Elderly	See Pop PK
Genetic/gender-related PK	Males versus females	See pop PK
PK interactions	CYPA12 inhibitor Fluvoxamine	PIPF 010
	Ciprofloxacin*	PIPF 017
	Smoking*	PIPF 010
Population PK analyses	Healthy subjects	PIPF-ORD1
	Target population	PIPF-ORD1, PIPF-ORD2
	Other-combined	PIPF-ORD1

*Indicates the primary aim of the study. †Bioequivalence of different formulations. §Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

4.1. Summary of pharmacokinetics

The information is derived from conventional pharmacokinetic studies and population PK analyses used to fit models in compartmental analyses, using data from Phase I studies and Phase III Study PIPF-004 (PIPF-ORD1). Non-compartmental analyses provided confirmatory results.

4.2. Pharmacokinetics in healthy subjects

This information is based primarily on Study PIPF-005. The objectives of the study were to characterise the PK of pirfenidone and metabolites in plasma and urine after single 801 mg doses in fasted healthy older subjects, and the impact of food, antacids, food and antacids, and the plasma PK of pirfenidone and metabolites of ascending daily doses 801, 1602, 2403, 3204, 4005 mg/day.

4.2.1. Absorption

After ingestion of single dose of 801 mg (n = 16 with food) pirfenidone had mean peak plasma concentration of 7.8 µµg/mL about 3 to 4 hours following administration. For the 801 mg three times daily (total daily dose = 2,403 mg) C_{max} was 11.85 µg/mL using data from the multiple dose cohort in Study PIPF-005 (n = 9 with food); time to peak drug plasma concentrations (T_{max}) (median) was at about 2 hours. Drug half-life (t½) was 1.39 h median, 1.5 h mean; the apparent terminal half-life was 2.24 h (median) and 2.39 h (mean).

Comment: The EMA's Committee for Medicinal Products for Human Use (CHMP) report suggested that 'slow absorption might account for gastric irritancy'.

4.2.1. Bioavailability

Oral bioavailability is considered to be high. In Study PIPF-005 urinary recovery of pirfenidone and the primary metabolite 5-carboxy-pirfenidone (5-CA-pirfenidone) was approximately 80% of administered dose.

4.2.1.1. Absolute bioavailability

According to the submission, absolute bioavailability has not been determined in humans due to lack of an intravenous formulation. The justification provided states that as pirfenidone is considered to be a highly soluble and highly permeable drug substance that demonstrates rapid in vitro dissolution in the proposed capsule dosage form, the rate and extend of drug absorption is unlikely to be dependent on drug dissolution and/or gastrointestinal transit time, with the capsules expected to behave like a solution.

4.2.1. Bioequivalence of clinical trial and market formulations

No specific information was provided.

4.2.1.1. Influence of food

Study PIPF-005 showed that food reduced the rate and extent of absorption (C_{max} reduced by 50%, AUC_{0-72} by 15 to 20%) compared to fasting state, with subjects less likely to experience GI or CNS adverse events when pirfenidone was administered with food.

4.2.1.2. Dose proportionality

Dose proportionality seen in the multiple dose cohort in PIPF-005 with a trend for decreased clearance with increasing dose (see Table 2). This was confirmed in population PK analyses; however non-linearity was not apparent at serum concentrations achieved following clinically relevant doses.

Table 2: Summary statistics of pirfenidone PK parameters stratified by dose in the multiple-dose cohort of Study PIPF-005

Dose Level	Statistic	CLt/F (L/h)	V_{ss}/F (L)	C_{max} (ng/mL)	T_{max} (h)
1	Mean	15.9	48.5	3700	
267 mg TID	SD	5.28	12.4	1828	
(801 mg/d)	Median	16.3	45.5	3135	2
(n = 10)	25th percentile	11.9	38.1	2350	1
	75th percentile	18.1	63.4	4470	3.5
2	Mean	16.8	39.4	7100	
534 mg TID	SD	3.37	12.0	2001	
(1602 mg/d)	Median	17.6	36.3	6450	2
(n = 9)	25th percentile	15.0	29.6	5545	1
	75th percentile	18.9	46.5	9095	2
3	Mean	14.1	38.3	11847	
801 mg TID	SD	3.23	15.7	2485	
(2403 mg/d)	Median	13.6	39.8	10900	2
(n = 9)	25th percentile	12.3	26.8	9853	1
	75th percentile	17.4	51.2	14200	2
4	Mean	13.2	37.8	14666	
1068 mg TID	SD	4.11	12.5	3322	
(3204 mg/d)	Median	14.6	41.0	14700	2
(n = 9)	25th percentile	13.0	30.9	12725	2
	75th percentile	15.1	47.2	17250	3
5	Mean	12.2	38.7	19644	
1335 mg TID	SD	3.35	11.9	3462	
(4005 mg/d)	Median	12.5	40.4	19600	2
(n = 9)	25th percentile	9.39	27.7	17250	2
	75th percentile	14.7	46.5	20850	4

Source: Tables 14.2–10 and 14.2–11
CLt/F = apparent total oral plasma clearance
V_{ss}/F = apparent total oral volume of distribution
C_{max} = peak plasma concentration
T_{max} = time to maximum plasma concentration

4.2.1.3. Bioavailability during multiple-dosing

The effect of multiple dosing was negligible within a dosing level, and significant accumulation was not observed.

4.2.1. Distribution

4.2.1.1. Volume of distribution

Mean apparent oral steady state volume of distribution was approximately 70 L in subjects from PIPF-004 (PIPF-ORD1).

4.2.1.2. Plasma protein binding

Pirfenidone binds to human plasma proteins, primarily to serum albumin. The overall mean binding ranged from 50% to 58% at concentrations observed in clinical studies (1 to 100 µg/mL).

4.2.2. Metabolism

From nonclinical and Study PIPF -005. 5-CA-pirfenidone is the main human metabolite, and appears to have limited biological activity; two other metabolites 5-HO-methyl-pirfenidone and a 5-O-acyl-glucuronide of 5-CA-pirfenidone are detectable inconsistently and at low levels.

4.2.2.1. Sites of metabolism and mechanisms / enzyme systems involved

In healthy human subjects significantly reduced pirfenidone clearance was observed secondary to concomitant administration of CYP1A2 inhibitors (Studies PIPF-010 and PIPF-017), supporting CYP1A2 as the primary route of metabolism.

4.2.2.2. Metabolites identified in humans

There were three identified metabolites: 5-hydroxymethyl-pirfenidone, 5-CA-pirfenidone and the 5–O-acyl-glucuronide metabolite of 5-CA-pirfenidone. Only 5-CA-pirfenidone is present in plasma and urine in significant quantities.

4.2.2.3. Active metabolites

None have been shown to be biologically active.

4.2.2.4. Consequences of genetic polymorphism

No information was provided.

4.2.3. Excretion

Following single dose administration of pirfenidone in healthy older adults, the mean apparent terminal elimination half-life was approximately 2.4 hours. In a multiple dose, dose ranging study in healthy older adults administered doses ranging from 267 mg to 1,335 mg three times a day, the mean clearance decreased by approximately 25% above a dose of 801 mg three times a day.

4.2.3.1. Routes and mechanisms of excretion

Approximately 80% of an orally administered dose of pirfenidone is cleared in the urine within 24 hours of dosing. The majority of pirfenidone is excreted as the 5-CA-pirfenidone metabolite (> 95% of that recovered).

4.2.3.2. Mass balance studies

There was no formal mass balance study; PIPF-005 showed human urine recovery of approximately 80% of administered dose.

4.2.3.3. Renal clearance

Less than 1% of pirfenidone excreted unchanged in urine. The metabolite 5-CA-pirfenidone is eliminated primarily through the kidney.

4.2.3.4. Intra- and inter-individual variability of pharmacokinetics

Summary data show wide ranges for PK parameters (SD and 25th -75th centiles) (see Table 2 above and Table 3 below).

Table 3: Summary statistics of derived PK parameters in the multiple-dose cohort of Study PIPF-005

	Statistic	V_{ss}/F (L/h)	$T_{1/2}$ (h)	$T_{1/2abs}$ (h)
Pirfenidone	Mean	40.7	2.39	1.50
	SD	13.1	0.868	0.721
	Median	40.7	2.24	1.39
	25th percentile	32.9	1.94	1.03
	75th percentile	40.7	2.24	1.39
5-Carboxy-Pirfenidone	Mean	20.5	2.08	NA
	SD	6.1	1.57	NA
	Median	19.8	1.85	NA
	25th percentile	15.7	1.00	NA
	75th percentile	25.2	2.47	NA

Source: Tables 14.2–10 and 14.2–11
V_{ss}/F = apparent total oral volume of distribution
$T_{1/2}$ = apparent terminal half-life associated with λz
$T_{1/2abs}$ = half-life for absorption

4.3. Pharmacokinetics in the target population

This was derived from a population PK approach developed in Phase I studies and applied to the data from a subset of subjects from Phase III Study PIPF-004. The submission provided the following arithmetic means (minimum-maximum) for pirfenidone PK parameters (see Table 4 for Study PIPF-004 data).

Table 4. Arithmetic means ((minimum –maximum) for pirfenidone PK parameters).

PIPF-004 Total daily dose (mg)	N	AUC 0-24 mg.hr/L	C max µg/mL	C Lt/F L/hr	Vss/F L
1,197	31	94 (46-281)	7.5(4-17)	14.7 (4-26)	70.1(38-114)
2,403	57	180 (86-544)	14.7(6.5-33.6)	15.8(4-28)	70.3(27-130)

C Lt/F = apparent oral clearance, Vss/F = apparent steady state volume of distribution. AUC_{0-24} = area under the plasma drug concentration-time curve in first 24 h post-dose).

4.4. Pharmacokinetics in other special populations

Hepatic impairment was likely to be of clinical significance.

4.4.1. Pharmacokinetics in subjects with impaired hepatic function

Study PIPF-011 demonstrated statistically significant difference in AUC between subjects with hepatic impairment and normal hepatic function (see Table 5 below). Patients with hepatic impairment will be expected to have variable and elevated serum levels of pirfenidone. Monitoring of LFTs and recommendations for dose adjustment or treatment discontinuation for elevated LFTs and/or hepatic symptoms are included in the proposed PI.

Table 5: Comparison of $AUC_{0-\infty}$ across hepatic impairment groups in Study PIPF-011

Hepatic Impairment Group	Statistic	$AUC_{0-\infty}$ (mg•hr/L)	
		Pirfenidone[a]	5-Carboxy-Pirfenidone[b]
Group 1 (Moderate)	Mean (SD)	91.5 (48.3)	32.4 (10.0)
n = 12	Median (25^{th}–75^{th})	80.7 (51.3–126)	28.6 (26.0–38.7)
Group 2 (Normal)	Mean (SD)	56.9 (27.8)	31.0 (4.93)
n = 12	Median (25^{th}–75^{th})	55.7 (32.8–78.5)	30.9 (27.3–33.6)

Source: Appendix 16.5
[a]p-value (Moderate versus Normal) = 0.043 (Mann-Whitney U)
[b]p-value (Moderate versus Normal) = 0.91 (Mann-Whitney U)
$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity

Group 1 (moderate hepatic impairment group, n = 12) participants were defined as having moderate liver cirrhosis (Child-Pugh Class B, score of 7-9) clinically stable other than abnormal LFTs

4.4.2. Pharmacokinetics in subjects with impaired renal function

Study PIPF-009 indicated that pirfenidone clearance was not primarily renal, but metabolite 5-CA-pirfenidone was eliminated through the renal pathway and increased serum concentrations of the metabolite were related to the degree of renal impairment (see Table 6 below). The recommendation for the proposed PI is 'use with caution' for mild, moderate or severe renal impairment, and not recommended for ESRD.

Table 6 Comparison of $AUC_{0-\infty}$ across renal impairment groups in Study PIPF-011

Renal Impairment Group	Statistic	$AUC_{0-\infty}$ (mg•hr/L)	
		Pirfenidone	5-Carboxy-Pirfenidone
Mild	Mean (SD)	59.1 (21.5)	49.3[a] (14.6)
n = 6	Median (25^{th}–75^{th})	51.6 (43.7–80.3)	43.0 (38.8–56.8)
Moderate	Mean (SD)	63.5 (19.5)	100[b] (26.3)
n = 6	Median (25^{th}–75^{th})	66.7 (47.7–76.7)	96.3 (75.2–123)
Severe	Mean (SD)	46.7 (10.9)	168[c] (67.4)
n = 6	Median (25^{th}–75^{th})	49.4 (40.7–55.8)	150 (123–248)
Normal	Mean (SD)	42.6 (17.9)	28.7 (4.99)
n = 6	Median (25^{th}–75^{th})	42.0 (33.1–55.6)	30.8 (24.1–32.1)

Source: Appendix 16.5
[a]p-value versus Normal = 1.00 (pair-wise comparison with Bonferroni)
[b]p-value versus Normal = 0.009 (pair-wise comparison with Bonferroni)
[c]p-value versus Normal < 0.0001 (pair-wise comparison with Bonferroni)
$AUC_{0-\infty}$ = area under the concentration-time curve from time zero to infinity

4.4.3. Pharmacokinetics according to age and other factors

Based on population PK analyses there was a relationship between age and dose normalised AUC and C_{max}; modelling suggests an 80 year old would have approximately 23% higher exposure than a 50 year old. This was considered relatively small and unlikely to be clinically significant. Other factors affecting AUC_{0-24} predicted were height (90^{th} centile 24% lower), smoking (non-smoker 23% higher than smoker) race (White 21% lower than Non-white). Mean C_{max} of pirfenidone was 13.2 µg/mL in females and 11.9 µg/mL in males (p = 0.03), probably related to smaller body size. There was considerable overlap in distributions and the absolute difference was approximately 10% so it was considered unlikely to be clinically significant.

4.5. Pharmacokinetic interactions

4.5.1. Pharmacokinetic interactions demonstrated in human studies

From Studies PIPF-010 and PIPF-017, co-administration of pirfenidone and fluvoxamine (a strong inhibitor of CYP1A2 with inhibitory effects on other CYP isoenzymes (CYP2C9, 2C19, and 2D6)) resulted in a 4 fold increase in exposure to pirfenidone in non-smokers.

The exposure to pirfenidone in smokers was 50% of that observed in non-smokers. Smoking has the potential to induce hepatic enzyme production and thus increase clearance and decrease exposure.

Co-administration of pirfenidone and 750 mg of ciprofloxacin (a moderate and selective inhibitor of CYP1A2) increased the exposure to pirfenidone by 81%.

4.5.2. Clinical implications of in vitro findings

The in vitro metabolism studies predicted PK interactions that were markedly less than those found in the clinical studies described above, for example with fluvoxamine and ciprofloxacin the interactions were underestimated.

4.6. Evaluator's overall conclusions on pharmacokinetics

Oral absorption, dose proportionality and aspects of metabolism of pirfenidone have been characterised sufficiently to make recommendations with respect to administration with food, dose titration, hepatic impairment and interaction with other medicines. Pirfenidone is cleared rapidly and is not expected to accumulate appreciably with multiple dosing at the proposed dosage in patients with normal hepatic and renal function.

5. Pharmacodynamics

5.1. Studies providing pharmacodynamic data

Information was derived from animal models and in vitro studies:

- Study PIPF-005 escalating doses were tested in the multiple dose cohort and the presence of food reduced the rate and extent of absorption of pirfenidone.
- Study PIPF-008 studied escalating doses in healthy young adults.
- Study PIPF-007 studied ECG effects of oral pirfenidone at clinical and supra therapeutic doses compared to placebo or placebo and moxifloxacin in healthy volunteers.
- Study PIPF-004 had PK/PD exploratory analyses of data from 88 subjects who had PK exposure estimates. However, there were lower AE rates and differing rates of lung function decline compared with the full study population, so the subset of patients in the PK/PD analysis do not appear to be representative of the overall population in PIPF-004.

5.2. Summary of pharmacodynamics

The text source for the PI Pharmacodynamics section is based on a nonclinical publication.

5.2.1. Mechanism of action

The mechanism of action is not fully known.

5.2.2. Pharmacodynamic effects

5.2.2.1. Primary pharmacodynamic effects

A PK/PD evaluation in a subset of Study PIPF-004 patients (n = 88) was conducted using PK exposure estimates for 1,197 mg/day and 2,403 mg/day dosage groups, and also characterising low versus high exposure (low exposure threshold 75th percentile of exposure measure obtained for the patients receiving 1,197 mg/day). Analysis showed a weak positive relationship between exposure and the primary endpoint of change from baseline in percent predicted forced vital capacity (FVC).

5.2.3. Secondary pharmacodynamic effects

In Study PIPF-005 higher C_{max} values increased the odds of experiencing a GI AE. This was consistent with Study PIPF-008; as the total daily dose (TDD) increased, so did the number of AEs reported. The AE rate was higher in women.

Study PIPF-007 analysed ECG effects at baseline, Day 6 and Day 10 from 160 participants in 4 groups; pirfenidone 2,403 mg/day, pirfenidone 4,005 mg/day, placebo and moxifloxacin Day 10, and placebo only. Upper bound of the 95% confidence interval was < 10 ms for the therapeutic (Group I) and supra therapeutic (Group II) treatment groups at all the time points. The results indicate that the mean effect of pirfenidone on the QTcI interval is not greater than approximately 5 ms and that pirfenidone is unlikely to have a significant effect on cardiac repolarization. No clinically significant changes in heart rate and in PR and QRS intervals or morphology were observed. Increased AEs were associated with the high dose especially in female subjects.

The Study PIPF-004 subset analysis also identified a weak relationship between higher drug exposure and shorter progression free survival (PFS); however this was based on only 20 patients who had IPF progression in the PK/PD population. There were appreciably higher occurrences of common AEs of nausea, photosensitivity, rash and dizziness, as well as reduction in body weight in the higher dose group, but relationships were considered to be not significant on multivariable modelling of pirfenidone exposure as predictor.

Of note, the C_{max} of 5-CA-pirfenidone was associated with approximately a doubling of the risk of photosensitivity, and 5-CA-pirfenidone is considered an indicator of overall drug exposure.

5.3. Gender differences in pharmacodynamic response

Generally women had less tolerance, with increased occurrence of adverse events, particularly GI and CNS effects, associated with higher doses.

5.4. Pharmacodynamic interactions

No information was available. See PK interactions above.

5.5. Evaluator's overall conclusions on pharmacodynamics

PK/PD correlation was demonstrated for common adverse effects including GI and dermatologic AEs.

6. Dosage selection for the pivotal studies

The PK based Study PIPF-005 (see also Pharmacokinetics, and Pharmacodynamics above) showed reduced incidence of AEs at a dose of 801 mg/day (as 267 mg capsules three times daily) when taken with food. The Maximum Tolerated Dose Study PIPF-008 confirmed that at

doses above 2,403 mg/day, women were likely to have significant adverse effects (GI and CNS) resulting in discontinuation.

However the CSR for Study PIPF-004 stated that the maximum tolerated dose was not determined in these studies, and that selection of doses and frequency of administration was based on a published Phase II study in IPF patients (published by Azuma et al; 2005) 'Double-blind, placebo controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis' that used a maximum dose of pirfenidone 600 mg TDS and empirical experience generated by investigators in the USA since 1995.[3]

Doses of 1,197 mg/day and 2,403 mg/day were chosen for Study PIPF-004 and 2,403 mg/day for Study PIPF-006 and Study PIPF-016. The 2,403 mg dose was considered to be that needed to achieve efficacy based on previous clinical experience, and the 1,197 mg dose was included for additional qualitative safety and efficacy information.

7. Clinical efficacy

The proposed indication is '*Esbriet is indicated for the treatment of idiopathic pulmonary fibrosis (IPF).*'

7.1. Pivotal efficacy studies

There were three Phase III randomised, double blind, placebo controlled, efficacy studies using the pirfenidone at the proposed dose in patients with IPF; Studies PIPF-004, PIPF-006, and PIPF-016.

7.1.1. Study PIPF-004

Studies PIPF-004 and PIPF-006 were closely similar and concurrently conducted pivotal efficacy and safety studies submitted to the EMA for assessment for authorisation, and initially to the FDA.

7.1.1.1. Study design, objectives, locations and dates

Study PIPF-004 was a randomised double blind placebo controlled three arm study of safety and efficacy of pirfenidone in patients with IPF. The objectives were to assess safety and efficacy of treatment with pirfenidone daily doses of 1,197 mg and 2,403 mg. This study was conducted by 64 investigators at 64 sites in United States, Canada, Mexico, United Kingdom, France, Italy, Poland and Australia, from July 2006 to November 2008.

Patients (n = 435) were randomised 2: 2: 1 to receive pirfenidone 2,403 mg/day (n = 174), placebo (n = 174), or pirfenidone 1,197 mg/day (n = 87) respectively. The study included a 28 day washout period (for patients to discontinue all prohibited medications before screening), a 40 day screening period, a 72 week study treatment period, and a final follow-up visit 3 to 4 weeks after the treatment completion visit.

All patients were to receive study treatment from randomisation until approximately 72 weeks after the last patient had been randomised in the study. The treatment dose was to be escalated over 15 days to a full maintenance dose beginning with one capsule 3 times daily on Days 1 to 7, then 2 capsules 3 times daily on Days 8 to 14, to a full maintenance dose of 3 capsules 3 times daily on Day 15. Dose modification guidelines were provided for commonly seen AEs including fatigue, GI effects and photosensitivity rash.

[3] Azuma A, et al. Double-blind, placebo-controlled trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2005; 171: 1040–1047

7.1.1.2. Inclusion and exclusion criteria

Eligible male and female patients aged 40 to 80 years must have had a confident clinical and radiographic diagnosis of IPF without evidence or suspicion of an alternative diagnosis that may have contributed to the patients' interstitial lung disease, and they must have had evidence of IPF disease progression.

Detailed inclusion criteria were as follows:

- Clinical symptoms consistent with IPF, including insidious onset of otherwise unexplained dyspnoea on exertion of ≥ 3 months duration
- Diagnosis of IPF, defined as the first instance a patient was informed of having IPF, within 48 months of randomization
- Age 40 through 80 years, inclusive
- High-resolution computed tomography (HRCT) scan showing a pattern of disease consistent with a confident (definite) radiographic diagnosis of usual interstitial pneumonia (UIP)/IPF. For patients with surgical lung biopsy showing definite or probable UIP, the HRCT criterion of probable (UIP)/IPF was sufficient
- For patients < 50 years of age: open or video-assisted thoracoscopic surgical (VATS) lung biopsy showing definite or probable UIP within 48 months of randomisation. In addition, there were no features that supported an alternative diagnosis on transbronchial biopsy or bronchoalveolar lavage (BAL), if performed
- For patients ≥ 50 years of age: at least one of the following diagnostic findings, as well as the absence of any features on specimens resulting from these procedures, which supported an alternative diagnosis within 48 months of randomisation:
  - Open or VATS lung biopsy that showed definite or probable UIP
  - Transbronchial biopsy that showed no features of an alternative diagnosis
  - BAL that showed no features of an alternative diagnosis.
- IPF disease severity and progression:
  - Percent predicted FVC ≥50% at screening and Day 1 (before randomisation). The change in FVC between screening and Day 1 must have been ≤ 10% relative difference
  - Haemoglobin (Hgb)-corrected carbon monoxide diffusing capacity/carbon monoxide transfer capacity (DL_{CO}/TL_{CO}) ≥ 35% of predicted value at screening only
  - Either FVC or Hgb-corrected DL_{CO} ≤ 90% of predicted value at screening
  - No evidence of improvement in measures of IPF disease severity over the year preceding study entry
  - Distance walked ≥ 150 metres with O_2 saturation ≥ 83% on ≤ 6 L/minute of O_2 during the 6-Minute Walk Test (6MWT) oxygen titration procedure performed at screening.
- Ability to understand and sign a written informed consent form.
- Ability to understand the importance of adherence to study treatment and the study protocol, including the concomitant medication restrictions throughout the study period.

Patients were excluded from participating in the study based on disease related, medical, laboratory, and concomitant therapy criteria. Patients who met any of the following criteria were ineligible to participate in the study:

Disease-related exclusions

- Not a suitable candidate for enrolment or unlikely to comply with the requirements of this study, in the opinion of the investigator
- Premature withdrawal from a randomised IPF clinical trial in the 2 years before study entry for any reason other than sponsor decision or current participation in a clinical drug trial
- Forced expiratory volume in one second (FEV1)/FVC ratio < 0.7 after administration of bronchodilator at the screen visit and day 1 before randomisation
- Bronchodilator response defined by an absolute increase of ≥ 12% and an increase of 200 mL in the predicted FEV1 or FVC or both after bronchodilator use compared to the values seen before bronchodilator at the screen visit and day 1 before randomisation
- Residual volume (RV) > 120% of predicted (before administration of bronchodilator)
- History of clinically significant environmental exposure known to cause PF (including but not limited to drugs, asbestos, beryllium, radiation, domestic birds)
- Known explanation for interstitial lung disease, including but not limited to radiation, sarcoidosis, hypersensitivity pneumonitis, bronchiolitis obliterans organizing pneumonia, human immunodeficiency virus (HIV), viral hepatitis and cancer
- Diagnosis of any connective tissue disease, including but not limited to scleroderma, systemic lupus erythematosus, and rheumatoid arthritis
- Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis, urinary tract infection, or cellulitis
- In the clinical opinion of the investigator, the patient was expected to need and be eligible for a lung transplantation within 72 weeks after randomisation
- Unable to undergo pulmonary function testing, which included meeting the following reproducibility standards:
  - At screening, the 2 highest acceptable FVC values were within 0.100 litre
  - At day 1, the 2 highest acceptable FVC values were within 0.100 litre
  - At screening, 2 of the 3 acceptable DL_{CO} values were within 2 units (for carbon monoxide transfer capacity [TL_{CO}], within 0.67 SI units) of each other.

Medical exclusions

- Any history of malignancy likely to have resulted in death or significant disability or likely to have required significant medical or surgical intervention within 2 years after study entry. This did not include minor surgical procedures for localized carcinoma (for example, basal cell carcinoma)
- Any condition other than IPF which, in the opinion of the investigator, was likely to result in the death of the patient within 2 years after study entry
- History of advanced cirrhosis or clinically significant liver disease
- History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within 6 months before study entry, including but not limited to the following:
  - Myocardial infarction, unstable angina pectoris, coronary artery bypass surgery, or coronary angioplasty
  - Congestive heart failure requiring hospitalisation
  - Uncontrolled arrhythmias

  - Asthma or chronic bronchitis requiring hospitalization in the 6 months before study entry
- Any condition, which, in the opinion of the investigator, might have been significantly exacerbated by the known side effects associated with the administration of pirfenidone
- Poorly controlled diabetes (defined by glycosylated haemoglobin [HbA1C] > 10)
- Pregnancy or lactation. Women of childbearing capacity were required to have a negative serum pregnancy test before treatment and must have agreed to maintain highly effective methods of contraception by practicing abstinence or by using at least two methods of birth control from the date of consent through the end of the study. If abstinence was not practised, then one of the two methods of birth control should have been an oral contraceptive (for example, oral contraception and a spermicide).
- History of alcohol or substance abuse in the 2 years before study entry
- History of any condition or habit associated with altered consciousness and a risk of aspiration in the 2 years before study entry
- Family or personal history of long QT Syndrome

Laboratory exclusions

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

Concomitant therapy exclusions

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

There were pre-specified permitted therapies for IPF and respiratory decompensation, including pulse-dose steroids. There were no restrictions applied to steroids used for reasons other than IPF therapy.

7.1.1.3. Study treatments

Test products

A total of 1,197 mg/day of pirfenidone administered orally in three divided doses (three 133 mg capsules three times per day for a total of 9 capsules per day) with food.

A total of 2,403 mg/day of pirfenidone administered orally in 3 divided doses (three 267 mg capsules 3 times per day for a total of 9 capsules per day) with food.

Reference therapy

Placebo capsules administered orally in 3 divided doses (3 placebo capsules 3 times per day for a total of 9 capsules per day) with food.

Subjects were cautioned to use sunblock and appropriate clothing to minimise sun exposure throughout the study.

7.1.1.4. Efficacy variables and outcomes

The main efficacy assessment measurements were standardised spirometry measurements of FVC to measure lung function. Other measurements included forced expiratory volume (FEV_1,) oxygen saturation by pulse oximetry (SpO_2), distance walked in 6 minutes (6MWT), CO diffusing capacity (DL_{CO}) and carbon monoxide transfer capacity (TL_{CO}).[4,5,6,7]

The primary efficacy outcome was:

- Absolute change in percent predicted FVC from Baseline to Week 72.

Secondary efficacy outcomes included:

- Time to worsening of IPF (worsening defined as the first occurrence of acute IPF exacerbation, IPF related death, lung transplantation, or respiratory hospitalisation)
- Progression free survival (progression defined as the first occurrence of a 10% absolute decline from baseline in % predicted FVC, a 15% absolute decline from Baseline in % predicted Hgb-corrected DL_{CO}, or death)
- Categorical assessment of absolute change in percent predicted FVC from baseline to Week 72
- Other selected measures of pulmonary function such as change in worst oxygen saturation or distance walked during 6MWT.

Plasma samples were obtained from a subset of patients at selected sites in North America at Weeks 2, 36 and 72 for drug concentration measurement.

7.1.1.5. Randomisation and blinding methods

Patients were randomised 2:2:1 to pirfenidone 2,403 mg/day, placebo or pirfenidone 1,197 mg/day using an IVRS on Day 1 of visit.[8] All pirfenidone and placebo capsules were supplied in opaque, hard, white gelatin capsules that were visually indistinguishable. Pirfenidone was

[4] FEV_1 = Volume that has been exhaled at the end of the first second of forced expiration.
[5] SpO_2 = Haemoglobin-Oxygen saturation of peripheral (mixed arterial-venous) circulation
[6] 6MWT = Six Minute Walk Test, a performance-based measure of functional exercise capacity used in many chronic diseases. Guyatt GH et Al. The 6-minute walk: a new measure of exercise capacity in patients with chronic heart failure. Can Med Assoc J 1985; 132: 919–23.
[7] DL_{CO}/TL_{CO} as described above is the extent to which oxygen passes from the air sacs of the lungs into the blood and is a measure of the efficacy of alveolar gas exchange
[8] Interactive Voice Response Systems (IVRS) allow touchpad telephones to record data, with some software systems allowing more complex tasks such as patient randomisation through randomisation algorithms.

supplied in either 267 mg or 133 mg capsules for the 2,403 mg/day or 1,197 mg/day doses, respectively. The sponsor supplied all study treatment.

The sponsor, site investigators, study personnel, and patients were blinded to treatment assignments. Personnel involved in conducting PFTs, measuring arterial blood gas (ABG) samples, or administering the 6MWT were instructed not to inquire about or be involved in the assessment of AEs and pulmonary symptoms. Identical packaging and labelling were used for the active and placebo study treatments.[9] There was an independent Data Monitoring Committee (DMC) to review unblinded safety and efficacy data at regular intervals during the study and to evaluate the conduct and integrity of the study.

7.1.1.6. Analysis populations

The primary efficacy analysis compared the treatment effect of pirfenidone 2,403 mg/day versus placebo in the MITT (modified intent to treat) population (defined for the primary efficacy analysis as all randomised patients in the 2,403 mg/day and the placebo groups who received any amount of study treatment). The treatment adherent population was all MITT patients who received 80% of the prescribed doses of study treatment.

7.1.1.7. Sample size

For the primary efficacy comparison of change in percent predicted FVC between the 2,403 mg/day and placebo groups, 160 patients per group were expected to provide 97% power to detect a 50% relative reduction in the rate of FVC change from baseline to Week 72 at 0.05 significance level. This assumed an absolute percent predicted FVC change between baseline and Week 72 of 5.5% in the placebo arm and 2.75% in pirfenidone arm with a standard deviation of 6.0%.

7.1.1.8. Statistical methods

The primary efficacy outcome variable was the absolute change in percent predicted FVC from baseline to Week 72. Baseline FVC was defined as the mean of the maximum acceptable FVC measurements obtained during the screening and the Day 1 visits. The FVC at Week 72 was defined as the mean of the maximum acceptable FVC measurements obtained on two separate days at the Week 72 Visit. The data were analysed using a rank analysis of covariance (ANCOVA) model with a standardised rank change in FVC as the outcome variable and standardized rank baseline FVC as a covariate. The analysis was stratified by geographic region, that is, USA compared with rest of world (ROW). The test of significance for the primary analysis of the primary efficacy outcome variable was to use a two sided alpha of 0.0498, to account for interim analyses. Strategies for handling missing data were pre-specified in the protocol and SAP.[10]

Descriptive statistics were used to analyse the primary efficacy results from the pirfenidone 1,197 mg/day group. Secondary and exploratory efficacy analyses were conducted for the pirfenidone 2,403 mg/day and placebo dose groups to evaluate treatment effect.

7.1.1.9. Participant flow

The majority of patients in each treatment group completed study treatment, including 78.2% (136 out of 174), 82.2% (143 out of 174), and 80.5% (70 out of 87) of patients in the pirfenidone 2,403 mg/day, placebo, and pirfenidone 1,197 mg/day groups, respectively. Patients who discontinued study treatment before their treatment completion visit were encouraged to remain on study, regardless of cause (except lung transplantation patients). Most patients followed this recommendation as reflected by the high number of study completers as shown in Table 7 below.

[9] PFT, ABG
[10] SAP = Data management and data strategy software provider.

Table 7. Disposition of patients in Study PIPF-004 (all randomised patients)

Disposition	Number of Patients, n (%)		
	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 174)	Placebo (N = 174)
Patients Who Completed the Study	73 (83.9%)	146 (83.9%)	144 (82.8%)
Patients Who Withdrew Early from the Study[a]	14 (16.1%)	28 (16.1%)	30 (17.2%)
Reasons for Withdrawal from the Study			
Adverse event	3 (3.4%)	8 (4.6%)	3 (1.7%)
Death	9 (10.3%)	12 (6.9%)	18 (10.3%)
Lung transplantation	0	3 (1.7%)	4 (2.3%)
Subject's personal decision	2 (2.3%)	4 (2.3%)	5 (2.9%)
Other[b]	0	1 (0.6%)	0

[a] Patients were considered to have withdrawn from the study if they did not complete their scheduled Treatment Completion Visit (including patients who completed treatment and those who permanently discontinued treatment. [b] The other reason for premature withdrawal from the study was deportation (n = 1)

7.1.1.10. Major protocol violations/deviations

A total of 19.6% (34 out of 174), 20.1% (35 out of 174), and 17.2% (15 out of 87) of patients in pirfenidone 2,403 mg, placebo, and pirfenidone 1,197 mg groups respectively reported important protocol deviations, most related to concomitant use of prohibited medications; commonly systemic corticosteroids (8% and 11.5% for pirfenidone 2,403 mg and placebo respectively). No patients received incorrect study treatment and no patients who developed withdrawal criteria during treatment remained in the study.

7.1.1.11. Baseline data

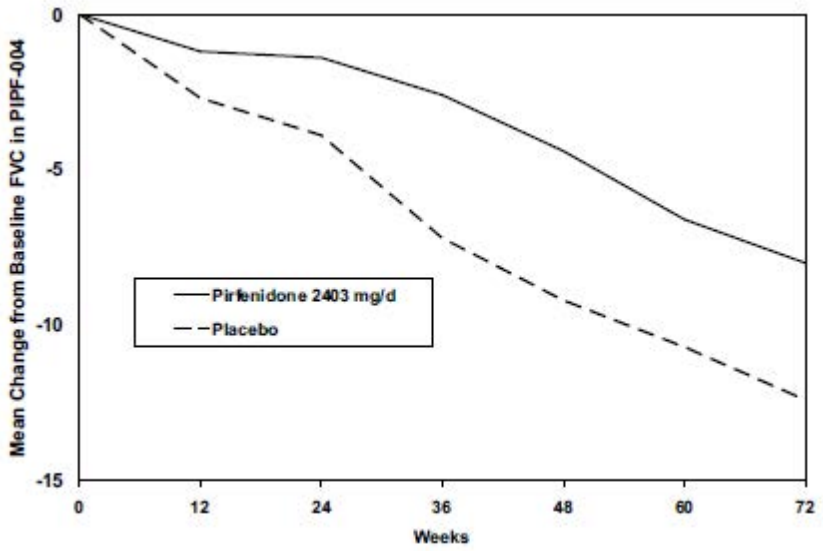
Demographic characteristics were comparable between treatment groups. Mean age was around 66 years in all groups (range 40 to 81 years); approximately 70% were male, at least 95% were White, and mean BMI was approximately 30 kg/m^2 in all groups. Approximately 66% were enrolled in the USA. Other baseline characteristics were comparable across groups.

Percent compliance per patient was 80% or more in 88.5%, 86.8% and 92.5% of the pirfenidone 1,197 mg, 2,403 mg, and placebo groups respectively.

7.1.1.12. Results for the primary efficacy outcome

The primary analysis was comparison of FVC mean change from baseline between pirfenidone 2,403 mg/day and placebo groups.

Figure 1: Mean change from baseline as a percentage predicted FVC (all randomised patients in Study PIPF-004)



The difference was statistically significant and reached a maximum absolute difference of 4.8% in favour of pirfenidone at 48 weeks.

Table 8. Mean change as a percentage predicted FVC (all randomised patients) in Study PIPF-004

Week	Mean Change[a]		Absolute Difference	Relative Difference	p-value[b]
	Pirfenidone 2403 mg/d (N = 174)	Placebo (N = 174)			
12	-1.2	-2.7	1.5%	55.6%	0.061
24	-1.4	-3.9	2.5%	64.1%	0.014
36	-2.6	-7.2	4.6%	63.9%	<0.001
48	-4.4	-9.2	4.8%	52.2%	<0.001
60	-6.6	-10.7	4.1%	38.3%	<0.001
72	-8.0	-12.4	4.4	35.5%	0.001

Source: Table 14-2.1.1

[a] For missing values if the patient was alive on the protocol-specified visit, the imputation was by the SSD method. If the patient died on or before the protocol-specified date, then 0 was imputed for the assessment. If the patient was not randomized early enough to have had a particular visit by the end of the study, no imputation was done.

[b] A rank ANCOVA, comparing pirfenidone 2403 mg/d vs. placebo, with standardized ranked change from Baseline as the outcome variable, treatment and geographic region (USA and ROW) as fixed effects, and standardized ranked Baseline as a covariate. Missing data due to a patient's death were ranked as worse than any nondeath and according to time until death.

7.1.1.13. Results for other efficacy outcomes

The categorical assessment of absolute change in % predicted FVC reflected the primary variable in showing evidence of treatment effect, as per Table 9. (see below).

Table 9. Change from Baseline to Week 72 in the pirfenidone (2,403 mg/day) versus placebo groups of Study PIPF-004.

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

Source: Table 14.2.2-5

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

[b] For missing values, if the patient was alive on a protocol-specified visit, the imputation was by the smallest SSD method. If the patient died on or before the protocol-specified date, then 0% was imputed for the assessment. If a patient was not randomized early enough to have had a particular visit by the end of the study no imputation was done.

The results for other pre-defined endpoints were provided. Progression free survival rate was higher for pirfenidone 2,403 mg than placebo (73.8%, (127 out of 172) versus 64.2% (111 out of 173); with 45 death or disease progression with pirfenidone 2,403 mg versus 62 for placebo, HR 0.64 (95% CI 0.44 to 0.95)). In the pirfenidone 2,403 mg group, 14.9% (26 out of 74) of patients experienced worsening of IPF compared with 17.2% (30 out of 174) of patients in the placebo group; HR 0.84 (0.50‑1.42).

At baseline, the mean 6MWT distance was 411.1 m in the pirfenidone 2,403 mg group and 410.0 m in the placebo group. At Week 72 the mean decline was -60.4 versus -76.8 m; at Weeks 48 and 60 the difference between groups was somewhat greater.

7.1.2. Study PIPF-006

This study of 2,403 mg/day was submitted to the EMA and with the initial application to FDA.

7.1.2.1. Study design, objectives, locations and dates

The study objective was to assess efficacy and safety of pirfenidone 2,403 mg/day compared with placebo in patients with IPF over 72 weeks. The Phase III multicentre randomised double blind study design was largely identical to that of Study PIPF-004 but with subjects randomised in a ratio of 1: 1 to two treatment arms (pirfenidone 2,403 mg/day n = 171, versus placebo n = 173). The study was conducted at 46 sites in the USA, Australia, Belgium, Germany, Ireland, Spain, and Switzerland from April 2006 to October 2008.

7.1.2.2. Inclusion and exclusion criteria

Criteria were identical to those for Study PIPF-004.

7.1.2.3. Study treatments

Patients who completed the washout period and met the screening criteria were randomised to receive pirfenidone 2,403 mg/day or placebo equivalent via oral administration in divided doses (3 capsules 3 times daily) with a meal. Study treatments were to be escalated as for Study PIPF-004. Treatments were supplied as visually indistinguishable hard white gelatin capsules, containing either pirfenidone 267 mg plus excipients, or excipients only.

There were pre-specified permitted therapies for IPF during the study period.

7.1.2.4. Efficacy variables and outcomes

The primary efficacy outcome variable was, as for Study PIPF-004, the absolute change in percent predicted FVC from Baseline to Week 72. Other efficacy outcomes included:

- time to worsening IPF
- Progression free survival
- Categorical assessment of absolute change from Baseline to Week 72 in % predicted FVC
- Change from Baseline to Week 72 in other pre specified assessments as for PIPF-004.

7.1.2.5. Statistical methods

Statistical methods were as for PIPF-004 for the comparison between the pirfenidone 2,403 mg/day versus placebo groups from Baseline to Week 72. The sample size was 320 and the duration 72 weeks. This assumed an absolute percent predicted FVC change between Baseline and Week 72 of 5.5% in the placebo arm and 2.75% in pirfenidone arm with a standard deviation of 6.0%.

7.1.2.6. Participant flow

Table 10 below follows the disposition of patients in Study PIPF-006.

Table 10. Disposition of patients in the study (all randomised patients, Study PIPF-006)

	Number of Patients, n (%)	
Disposition	Pirfenidone 2403 mg/d (N = 171)	Placebo (N = 173)
Patients who Completed the Study	139 (81.3%)	146 (84.4%)
Patients who Withdrew Early from the Study [a]	32 (18.7%)	27 (15.6%)
Reasons for Withdrawal from the Study		
Adverse event	5 (2.9%)	4 (2.3%)
Death	15 (8.8%)	14 (8.1%)
Lung transplantation	4 (2.3%)	4 (2.3%)
Sponsor decision	1 (0.6%)	0
Subject's personal decision	6 (3.5%)	5 (2.9%)
Other [b]	1 (0.6%)	0

7.1.2.7. Major protocol violations/deviations

There were no major imbalances between the treatment groups in the proportion of patients with important protocol deviations. A total of 17.5% (30 out of 171) and 21.4% (37 out of 174) in the pirfenidone 2,403 mg/day and placebo groups respectively reported an important protocol deviation, and most were related to the use of prohibited medications (16.4% in the pirfenidone treated group and 19.7% in the placebo treated group). Systemic corticosteroids (5.3% in the pirfenidone treated group and 11.6% in the placebo treated group) and drugs for obstructive airway disease (7.0% in the pirfenidone and 4.0% in the placebo treated groups) were the most common categories of prohibited medications reported in the pirfenidone and placebo groups, respectively.

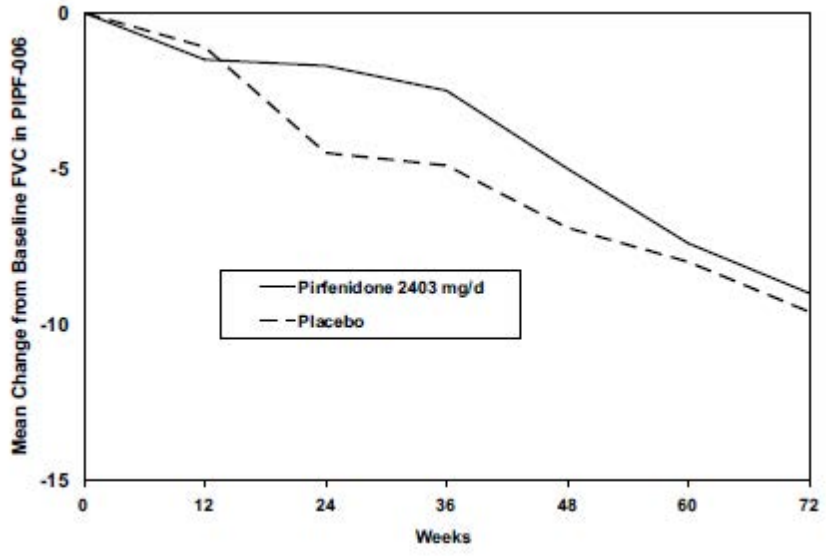
7.1.2.8. Baseline data

Demographic characteristics were comparable between groups. Most patients were White (98.8% and 98.8%), male (71.9%, 71.7%), and ≥ 65 years of age (59.0%, 64.8%). Mean age was 66.8 years (range: 45 to 80 years) and 67.0 years (range: 42 to 80 years) in pirfenidone and placebo groups, respectively. Mean weight was 95.4 and 93.2 kg for males and 76.6 and 77.5 kg for females; mean BMI was 31.1 and 30.4 kg/m^2 for males and 29.9 and 30.2 kg/m^2 for females. More than 80% were enrolled at sites in the USA. Other baseline characteristics were comparable. The prior use of systemic corticosteroids was reported in 12.9% pirfenidone and 9.8% of placebo patients. The number of patients who used selected CYP1A2 inhibitors was higher in the pirfenidone group (15.8% versus11.0%). Percent compliance per patient was 80% or more in 89% of pirfenidone patients and 94% placebo patients.

7.1.2.9. Results for the primary efficacy outcome

The primary analysis was comparison of FVC mean change from baseline between pirfenidone 2,403 mg/day and placebo groups.

Figure 2: Mean change from baseline in percent predicted FVC (all randomised patients Study PIPF-006)



This showed no significant difference between groups at 72 weeks. Between 12 and 48 weeks there was a difference between groups for this outcome variable, as shown in Table 11 below.

Table 11. Mean change in percent predicted FVC (all randomised patients Study PIPF-006)

Week	Mean Change[a]		Absolute Difference	Relative Difference	p-value[b]
	Pirfenidone 2403 mg/d (N = 171)	Placebo (N = 173)			
12	-1.5	-1.1	0.5%	27.7%	0.021
24	-1.7	-4.5	2.8%	62.2%	<0.001
36	-2.5	-4.9	2.4%	49.0%	0.011
48	-5.0	-6.9	1.9%	27.5%	0.005
60	-7.4	-8.0	0.6%	6.7%	0.172
72	-9.0	-9.6	0.6	6.3%	0.501

Source: Table 14.2.1-1

[a] For missing values if the patient was alive on the protocol-specified visit, the imputation was by the SSD method. If the patient died on or before the protocol-specified date, then 0 was imputed for the assessment. If the patient was not randomized early enough to have had a particular visit by the end of the study, no imputation was done.

[b] A rank ANCOVA, comparing pirfenidone 2403 mg/d vs. placebo, with standardized ranked change from Baseline as the outcome variable, treatment and geographic region (USA and ROW) as fixed effects, and standardized ranked Baseline as a covariate. Missing data due to a patient's death were ranked as worse than any nondeath and according to time until death.

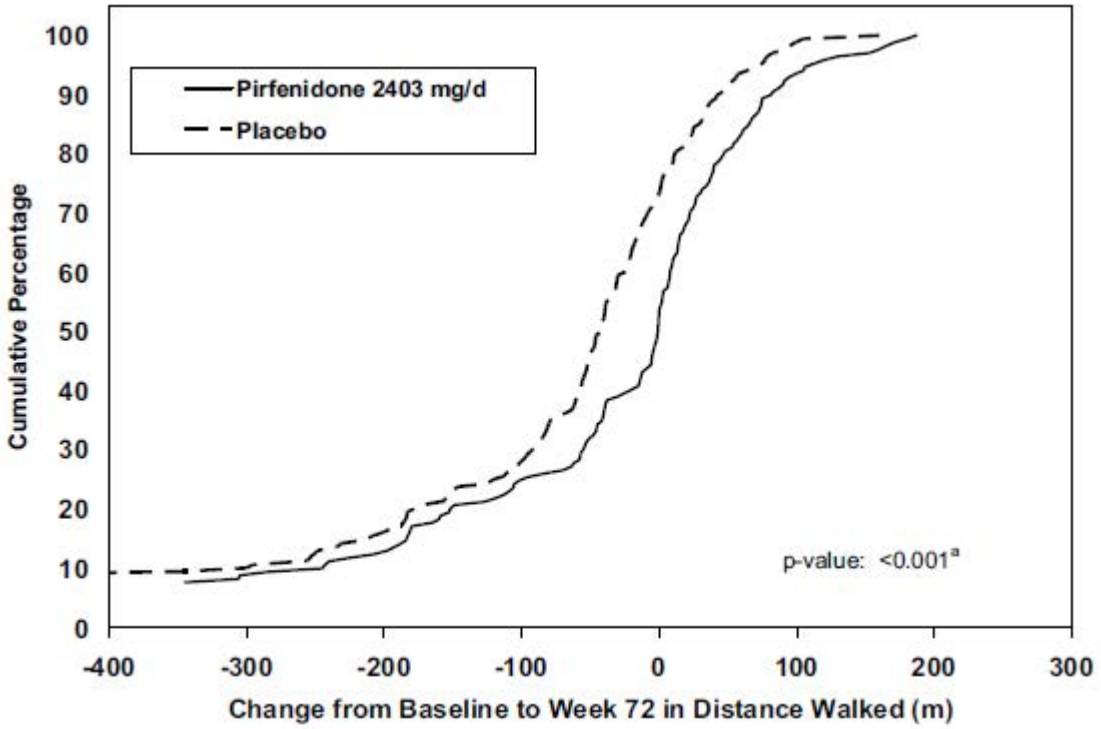
7.1.2.10. Results for other efficacy outcomes

For the categorical assessment of change in % predicted FVC, a lower proportion of patients receiving pirfenidone had a moderate or severe decline (that is, a decline of ≥ 10%) in percent predicted FVC at week 72 (22.8%, 39 out of 171 pirfenidone versus 26.6%, 46 out of 173 placebo) and a slightly higher proportion had mild or moderate improvement (25.8%; 44 out of 171 versus 22.0%, 38 out of 173), but differences were not statistically significant.

There were similar progression free survival rates (68.2%, 116 out of 170 versus 65.1%, 112 out of 172 for pirfenidone or placebo respectively).

The 6 MWT distance result was somewhat better for pirfenidone in this study (in comparison with PIPF-004) as seen in Figure 3 below.

Figure 3: Change from Baseline to Week 72 in Distance Walked (metres) using the 6MWT.



7.1.3. Study PIPF-016

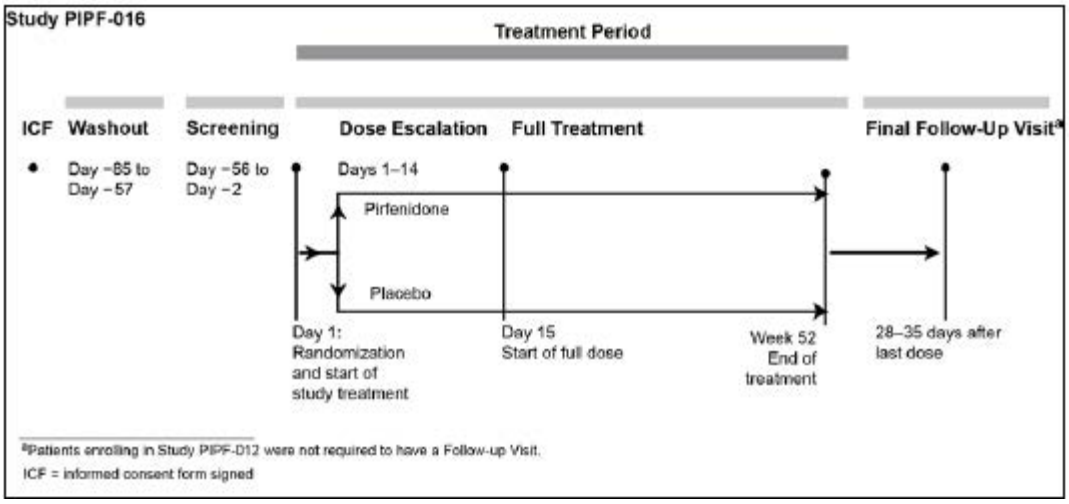
This 'confirmatory' efficacy and safety study was submitted to the FDA following initial rejection of the application for approval of pirfenidone in IPF, and published in 2014.[11] This study was not included in the initial CHMP Review provided by the sponsor because the EMA had already approved pirfenidone subject to post-market study requirements; however it was evaluated for subsequent inclusion into the Summary of Product Characteristics (SPC). Compared to Study PIPF-004 and Study PIPF-006 there were some modifications to eligibility, methodology and analyses.

7.1.3.1. Study design, objectives, locations and dates

PIPF-016 was a randomised double blind placebo controlled multinational study to evaluate efficacy and safety of pirfenidone in patients with IPF over 52 weeks. It was conducted in 127 sites in the USA, Australia, Brazil, Croatia, Israel, Mexico, New Zealand, Peru and Singapore between June 2011 and February 2014.

[11] King TE Jr et al. A Phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. N Engl J Med. 2014; 370 :2083-2092.

Figure 4: Flowchart for the timeline of Study PIPF-016



IPF patients were randomised in a ratio of 1: 1 to either pirfenidone 2,403 mg /day (n = 278) or matching placebo (n = 277) treatment for 52 weeks, with dose escalation over the first 14 days. An extension Study PIPF-012 was planned for eligible patients after the Week 52 visit. There was a data monitoring committee (DMC) for interim safety monitoring.

7.1.3.2. Inclusion and exclusion criteria

Eligible male and female patients aged 40 to 80 years must have had a confident diagnosis of IPF on clinical or radiologic data without evidence or suspicion of an alternative diagnosis and an IPF diagnosis at least 6 months before randomisation. The criteria for disease severity and progression were confirmed by central review. The eligibility criteria included patients with a greater risk of disease progression compared to PIPF-004 and PIPF-006.

7.1.3.3. Study treatments

Test group: Opaque hard white gelatin capsules; 2,403 mg/day of pirfenidone administered orally in 3 divided doses (three 267 mg capsules 3 times per day for a total of 9 capsules per day) with food.

Reference Group: matching white gelatin placebo capsules administered orally in 3 divided doses (3 placebo capsules 3 times per day for a total of 9 capsules per day) with food.

Study treatments were escalated over the first 14 days as for Study PIPF-004 and Study PIPF-006: 1 capsule 3 x daily for Days 1 to 7; 2 capsules 3 x daily for Days 8 to 14; 3 capsules 3 x daily from Day 15. Patients were to protect themselves from sunlight exposure and there were recommended procedures for dose modification, in particular for elevated LFTs.

Corticosteroids were used at the discretion of the investigator, without dose restriction, for up to 21 days in patients experiencing acute IPF exacerbation. The study drug was continued during this time if possible.

7.1.3.4. Efficacy variables and outcomes

The primary measure of lung function was FVC. Study measurements and assessments included spirometry for FVC and FEV1, DL_{CO}, 6MWT, UCSD SOBQ.[12]

The primary efficacy outcome was the change in % predicted FVC from Baseline to Week 52.

[12] UCSD SOBQ = University of California San Diego Shortness Of Breath Questionnaire. A validated assessment tool in both clinical practice and research in patients with moderate-to-severe lung disease. Eakin EG et al. Validation of a new dyspnea measure: the UCSD Shortness of Breath Questionnaire. University of California, San Diego. *Chest*. 1998; 113 :619-624.

In this study, presentation was by categorical assessment of change in % predicted FVC.

Two key secondary efficacy endpoints were different to PIPF-004 and PIPF-006:

- Change in 6 MWT distance from baseline to Week 52
- Progression free survival defined as time to first occurrence of any of the following; death, confirmed ≥ 10% absolute decline from baseline in % predicted FVC, or confirmed ≥ 50 m decline from baseline in 6MWT distance.

Additional secondary outcomes were:

- Change in dyspnoea measured by UCSD SOBQ score from baseline to Week 52
- Mortality including all cause and treatment emergent IPF related mortality.

7.1.3.5. Randomisation and blinding

Randomisation was by automated system using permuted block randomisation codes generated independently without stratification. Patients and study personnel/investigators were blinded and treatments were visually indistinguishable. Unblinded safety data were monitored independently for the DMC.

7.1.3.6. Analysis populations

The efficacy analysis population is the ITT population consisting of all patients who signed informed consent and were randomised to study treatment.

7.1.3.7. Sample size

Sample size estimates were based on the pooled data analysis of Studies PIPF-004/006. For the primary efficacy comparison 250 patients per group provided at least 90% power to detect a difference in normalized ranks of 0.08, with a standard deviation of 0.27.

7.1.3.8. Statistical methods

The change in percent predicted FVC from Baseline to Week 52 was analysed using a fixed effect rank ANCOVA comparing pirfenidone and placebo in the ITT population, with ranked baseline percent predicted FVC value as a covariate. This analysis was tested at an alpha level of 0.0498, adjusting for two interim mortality analyses.

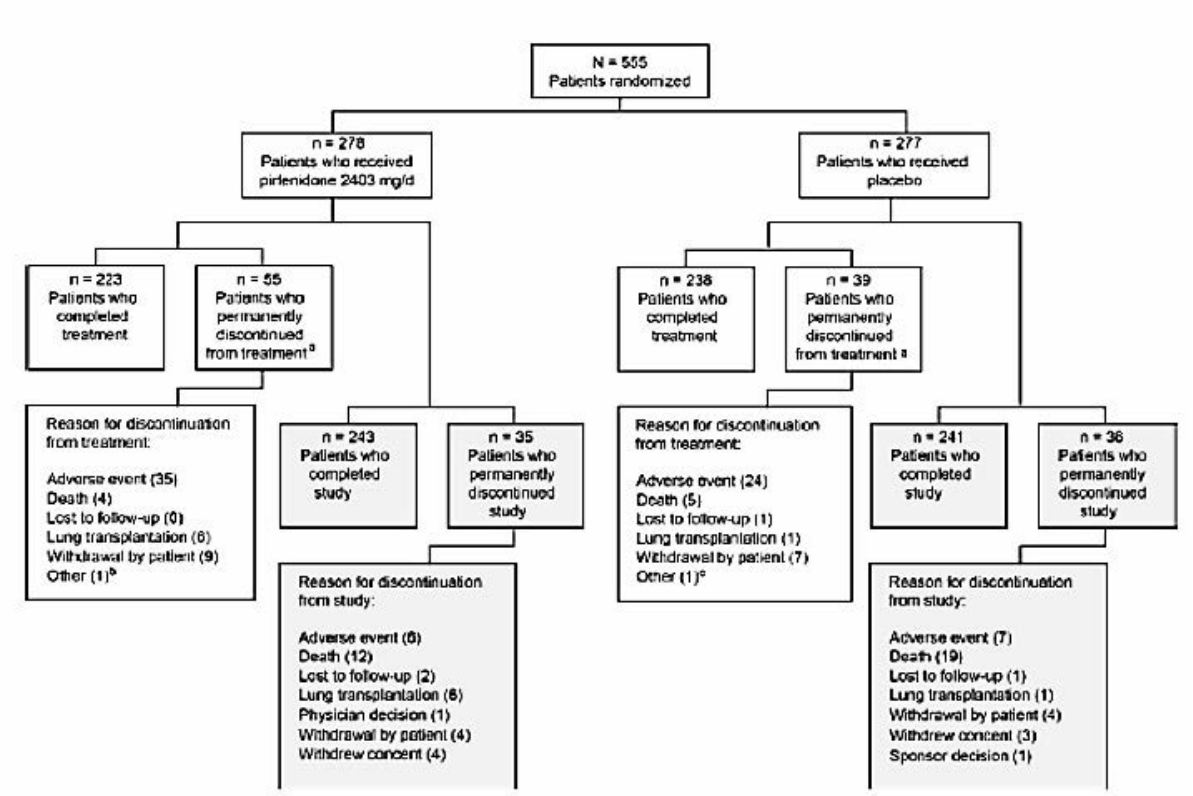
The magnitude of the treatment effect of pirfenidone was presented as the distribution of patients across the following categories of change from Baseline: decline in percent predicted FVC ≥ 10% or death; decline in percent predicted FVC < 10% to 0% or no decline in percent predicted FVC.

Change from baseline in 6MWT distance was analysed using a rank ANCOVA model, with ranked baseline 6MWT distance and ranked baseline DL_{CO} as covariates. Kaplan-Meier estimates were used to summarise progression free survival time.

7.1.3.9. Participant flow

See Figure 5 for a flow diagram taking into account those who 'completed treatment' and those who 'completed study'. Table 12 below details the disposition of patients according to study treatment.

Figure 5. Study PIPF-016 Disposition of patients by study treatment (randomised allocation to pirfenidone 2403 mg/day (n = 278) or placebo (n = 277)



[a] The numbers of patients reported as discontinuing from treatment due to a TEAE differs between Table 7 (Primary Reason For Discontinuation Of Treatment) and Table 38 (Study Treatment Discontinuation As An Action Taken For A TEAE). This figure represents data in Table 7 and Table 8.
[b] Other: Patient 15158522 "ran out of study medication" at the Week 52 visit.
[c] Other: Patient 10129612 "discontinued due to personal reasons" on Day 60.

Table 12. Disposition of patients in Study PIPF-016 according to study treatment

Disposition	Number of Patients, n (%)	
	Pirfenidone 2403 mg/d (N = 278)	Placebo (N = 277)
Completed study treatment	223 (80.2)	238 (85.9)
Discontinued study treatment early	55 (19.8)	39 (14.1)
Primary reason for early discontinuation of study treatment		
Adverse event	35 (12.6)	24 (8.7)
Withdrawal by patient	9 (3.2)	7 (2.5)
Death	4 (1.4)	5 (1.8)
Lung transplantation	6 (2.2)	1 (0.4)
Other[a]	1 (0.4)	1 (0.4)
Lost to follow-up	0	1 (0.4)

[a] Other reasons for discontinuation from study treatment were: "patient ran out of study medication" at the Week 52 visit (Patient 15158522, pirfenidone group); and "patient discontinued due to personal reasons" on Day 60 (Patient 10129612, placebo group).

7.1.3.10. Major protocol violations/deviations

There were no major imbalances between the treatment groups in the proportion of patients with protocol deviations.

7.1.3.11. Baseline data

Demographic characteristics were comparable between the treatment groups; most study patients were White (91.2%), male (78.4%), and ≥ 65 years of age (71.0%; overall mean 68.1 years). Two thirds (67.3% pirfenidone and 66.4% placebo) were enrolled in the USA. Baseline

disease characteristics were generally comparable between the treatment groups. Prior medications were generally comparable; systemic corticosteroids were used by a total of 2.2% and 0.7% of patients in pirfenidone and placebo groups, respectively. The frequency of concomitant use of systemic corticosteroids was lower in the pirfenidone group (29.5% versus 36.5%). The concomitant use of specific CYP1A2 inhibitors was pre-specified for analysis; use was lower in the pirfenidone group overall (8.3% versus 12.6%). Other use of interest included NAC (1.8% versus 2.2%).

The proportion of patients in the pirfenidone group who took ≥ 80% of their prescribed dose was lower than in the placebo group (85.3% versus 92.4%).

7.1.3.12. Results for primary efficacy outcome

The primary efficacy analysis of the change in the percent predicted FVC from Baseline at Week 52 demonstrated a statistically significant treatment effect of pirfenidone compared with placebo ($p < 0.000001$, rank ANCOVA).

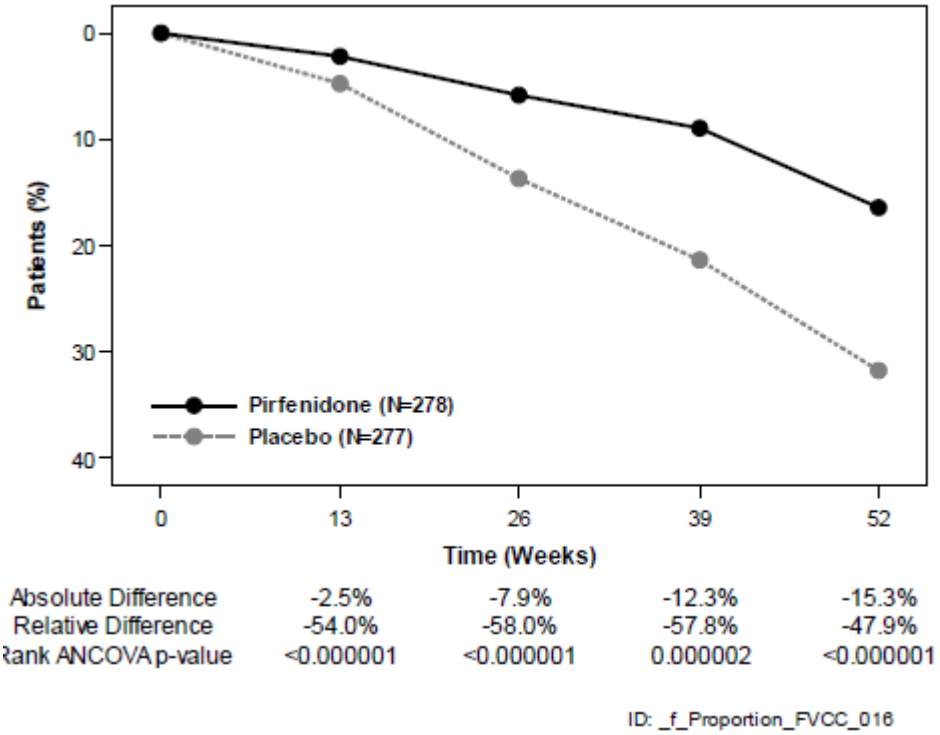
This is presented in Table 13 as the proportion of patients with change in pre-specified categories.

Table 13. Percent predicted FVC: change from baseline at week 52

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

[a] p-value by rank ANCOVA
FVC = forced vital capacity

Figure 6. Percent predicted FVC: proportion with decrease > 10% from baseline or death to Week 52 (all randomised)



There was an absolute mean difference of 192.8 mL in change from Baseline at Week 52 in FVC volume between the two treatment groups, favouring pirfenidone. The trend was supported by

linear slope analysis of the annual rate of decline in FVC volume. The SAP pre-specified analysis of ranked change from baseline in percent predicted FVC as a supportive analysis of the primary efficacy endpoint; the least square mean was -6.17 for pirfenidone versus -10.95 for placebo, a difference of 4.78 favouring pirfenidone.

7.1.3.13. Results for other efficacy outcomes

Change from baseline to week 52 in 6MWT distance

The proportion of patients having an absolute decline ≥ 50 metres at week 52 was 25.9% pirfenidone versus 35.7% placebo.

Progression free survival

Pirfenidone was associated with significant risk reduction; HR 0.57**,** 95% CI 0.43 to 0.77.

Dyspnoea

There was a reduction of in the proportion of patients with worsening dyspnoea as measured by the change from baseline in the UCSD SOBQ score of ≥ 20 points, favouring pirfenidone, but this did not reach statistical significance (p = 0.1577).

Mortality

Patients who discontinued study treatment before week 52 were to be followed for vital status to the week 52 time point. The mortality endpoint of all-cause mortality and the supportive mortality endpoint of IPF related mortality included all events occurring during this extended period. Treatment emergent IPF related deaths and the supportive mortality endpoint of treatment emergent all-cause mortality included all deaths occurring after the first dose of study treatment and up to 28 days after the last dose. 'IPF related' was defined as those deaths considered to be directly related to IPF by the Mortality Assessment Committee.

A smaller proportion of patients died in the pirfenidone group (4.0%) than the placebo group (7.2%). Analyses suggested a non-significant reduced risk of all-cause mortality through the Week 52 time point for pirfenidone compared with placebo (HR 0.55; 95% CI, 0.26 to 1.15; p = 0.1045, log rank test) however the study was not powered for this or other mortality endpoints.

7.2. TGA evaluator comment on pivotal trials

The Studies PIPF-004, PIPF-006 and PIPF-016 were well designed and conducted, considering the difficulties of testing treatments in this progressive and uncommon disease. The designs could reasonably be expected to minimise sources of bias and allow for adequate power to evaluate the primary efficacy outcome for pirfenidone 2,403 mg/day versus placebo. There was an adequate plan for attaining adequate clinical data quality and integrity of the studies.

FVC was used as a primary measure of lung function. (See Table 14 below for a tabulation comparing aspects of the three studies) Decrement in percent predicted FVC ≥ 10% in an individual patient is considered to be a clinically meaningful indicator of disease progression, and predictive of mortality, as supported by by publications such as Collard et al. 2003,[13] du Bois et al. 2011. [14] The estimated minimum clinically important difference was considered to be 2 to 6% in patients with IPF (du Bois R et al. 2011[15](9)).

[13] Collard et al. 2003 (7)
[14] du Bois et al. 2011 (8).
[15] du Bois R et al.(9) Am J Respir Crit Care Med 2011; 184; 1382–1389

The primary efficacy outcome, decline in percent predicted FVC over 12 to 18 months, is therefore accepted as clinically relevant, although an indirect indicator of mortality and morbidity.

Analyses and presentation were appropriate. The three individual trials appear to have a high quality rating for underlying methodology with no serious limitations due to bias.

However the absolute difference in treatment effect, namely the mean reduction in decline in percent predicted FEV, is small.

Trial results were inconsistent in that Study PIPF-004 and Study PIPF-016 showed a statistically significant effect of pirfenidone on the primary efficacy variable, but the result in PIPF-006 was not statistically significant.

The placebo group in Study PIPF-006 demonstrated a smaller decline in percent predicted FVC than placebo group in PIPF-004, consistent with variability in disease progression.

Table 14. Evaluator's tabulation of relevant differences between Study PIPF-004, Study PIPF-006 and Study PIPF-016. (n = ITT population)

Study ID Year	Population Age; Key IPF physiological characteristics; Study duration	Treatment Pirfenidone total dose (mg/day)	Comparator Placebo	Primary efficacy endpoint	Secondary endpoints
PIPF004 Nov 2008	40-80 yr, duration of diagnosis ≤ 48 months, FVC ≥ 50% and DLco ≥ 35% predicted; 72 weeks	2,403 mg N = 174 1,197 mg N = 87	N = 174	Change in % predicted FVC from baseline to week 72; Absolute difference 4.4% in favour of pirfenidone at week 72, significant	Time to worsening IPF, Progression-free survival, Change 6MWT, Categorical assessment of absolute change in % predicted FVC from baseline to week 72
PIPF-006 Nov 2008	As above	2,403 mg N = 171	N = 173	Change in % predicted FVC from baseline to week 72; Absolute difference 0.6% in favour of pirfenidone, non-significant	As above
PIPF - 016 Feb 2014	40-80 yr, duration of diagnosis ≥ 6 months to ≤ 48 months, FVC ≥ 50% DLco ≥ 30% and both ≤ 90% predicted and centrally reviewed; 52 weeks	2403 N = 278	N = 277	Change in % predicted FVC from baseline to week 52 by categorical assessment; difference 15.3% in favour of pirfenidone, i.e. decline FVC ≥ 10% or death 16.5% versus 31.8%; %predicted FVC LSM difference 4.8% in favour of pirfenidone*	Change in 6 MWT distance from baseline to week 52, Progression free survival (amended definition), Dyspnoea, Mortality

*LSM at week 52 change from baseline % predicted FVC (SE): pirfenidone -6.17 (0.875), placebo -10.95 (0.877), difference in LS mean 4.781, p < 0.0001.

Due to apparent heterogeneity of the IPF study population in the earlier studies, changes in study population selection in PIPF-016 were directed towards increasing the proportion at risk of progression from IPF (increased duration of diagnosis, reduction in lower limit of DL_{CO}), and reducing the proportion of subjects with significant co-existing COPD (FEV1/FVC ratio < 0.8 after administration of bronchodilator at screening, confirmed by central review) while enlarging the sample size. As demonstrated by the baseline data, overall the study populations were similar. No specific rationale was presented for widening the target population stated in the Indication from 'mild to moderate IPF', as approved in EU and Canada, to IPF generally, that is including severe grade IPF.

The decrement of ≥ 10% in percent predicted FVC was considered clinically relevant. The selection of the distribution of patients across pre-specified categories of change in percent predicted FVC was the primary presentation of treatment effect in Study PIPF-016. This did not change the underlying data collected or the primary efficacy variable that is change in percent predicted FVC. This is acceptable, although the treatment effect appears larger than when it is presented as mean difference in percent predicted FVC overall.

7.3. Other efficacy studies

7.3.1. PIPF-012

Study PIPF-012 is an ongoing, uncontrolled, open label extension study for eligible patients completing Studies PIPF-004 and PIPF-006 who receive treatment with pirfenidone 2,403 mg/day. The primary objective was to assess long-term safety and provide ongoing access to pirfenidone. Over the 180 week observation period, mean percent predicted FVC declined from 70.9% (n = 584) to 65.9% (n = 255). The Kaplan Meier estimate of survival, from the time of the first dose of pirfenidone in PIPF-012, was 69% (standard error (SE) = 2.4%) at Week 228. Large patient drop-out over time as well as open label and lack of control limit the interpretation with respect to efficacy.

7.3.2. PIPF-002

PIPF-002 was a long-term open label single arm study originally designed to assess the safety and efficacy of long-term pirfenidone treatment at doses up to 3,600 mg/day. A total of 83 patients were enrolled in Study PIPF-002, and 11 (13.3%) remained on study at 7 August 2013 with a median duration of pirfenidone exposure of 156 weeks (range 3 to 519). There was minimal change from baseline in key pulmonary function tests and the Kaplan-Meier estimated survival rate was 58%.

7.4. Analyses performed across trials (pooled analyses)

Results from patients in the pirfenidone 2,403 mg/day (n = 623) and placebo (n = 624) treatment groups from PIPF-004, PIPF-006, and PIPF-016 over 12 months were pooled for the resubmission integrated summary of efficacy for the FDA; referred to as '2014 RISE'. The groups were closely matched for baseline demographic characteristics; mean age 67.2 and 67.21 years, 74% male both groups, 95% White, mean weight 91 kg and 89 kg in pirfenidone and placebo groups respectively.

Other baseline characteristics were also well matched in the pooled dataset. As expected, the mean baseline percent predicted FVC was slightly lower in PIPF-016 compared with PIPF-004 and PIPF-006 (68.2% versus 75.4% and 74.0% respectively), however, the range of baseline values of percent predicted FVC was similar and overlapping across the three study populations.

There was a wide range around mean values for baseline lung function and exercise tolerance within each study and across studies, representing a range of presentations and disease

severity, including the gender/age/physiological variables (GAP index) staging for IPF (Ley 2012). [16]

The data for the change from baseline outcomes were analysed using a rank analysis of covariance (ANCOVA) model with rank change from baseline as the outcome and rank baseline value as a covariate. This allows weighting for the worst outcome, death, as well as non-normal distribution of the efficacy outcome. In all studies, 89.9% of patients in the pirfenidone 2,403 mg/day and 88.1% in the placebo groups completed 12 months of study procedures.

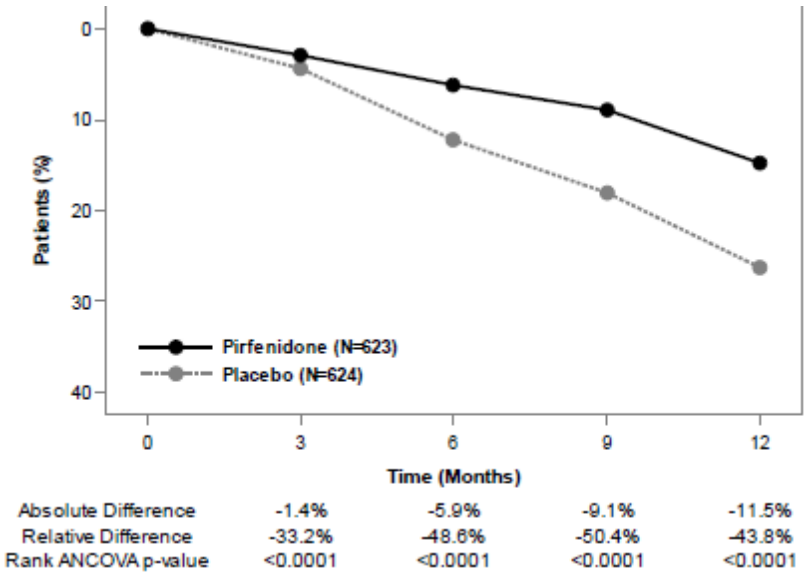
In the pooled analysis pirfenidone reduced the decline in percent predicted FVC compared with placebo over 12 months ($p < 0.0001$; rank ANCOVA). In the combined studies there was a relative reduction in the proportion of patients with a decline in percent predicted FVC $\geq$ 10% or death, and an increase in the proportion with no decline in percent predicted FVC, in those receiving pirfenidone compared with those receiving placebo as per 2014 RISE (Table 15).

Table 15. Categorical analysis of change from baseline to month 12 in % predicted FVC, pooled data

	Number of Patients, n (%)	
	Studies PIPF-016/004/006	
Change from Baseline to Month 12	Pirfenidone 2403mg/d (N = 623)	Placebo (N = 624)
Decline of ≥10% or Death	92 (14.8)	164 (26.3)
Decline of <10% to ≥0%	356 (57.1)	350 (56.1)
No decline (>0%)	175 (28.1)	110 (17.6)
p-value[a]	< 0.0001	

[a] p-value by rank ANCOVA.

Figure 7. Proportion of patients with decline > 10% in percent predicted FVC or death, pooled analysis



7.4.1. Mortality

In a pooled analysis of data from PIPF-016, PIPF-004, and PIPF-006 the risk of all-cause mortality within one year was reduced in the pirfenidone group compared with the placebo group (HR 0.52; 95% CI, 0.31 to 0.87; p = 0.0107, log-rank test), and the risk of treatment emergent IPF related death was also reduced (HR 0.32; 95% CI, 0.14 to 0.76; p = 0.0061,

[16] Ley B et al. A Multidimensional Index and Staging System for Idiopathic Pulmonary Fibrosis. *Ann Intern Med*. 2012; 156: 684-691.

log-rank test) in the pirfenidone group (see Table 16 below). Overall the number of IPF-related deaths on study was small.

Table 16. Overview of mortality endpoints at Month 12 (from 2014 RISE)

	Pirfenidone (N = 623)	Placebo (N = 624)	HR[a] (95% CI)	p-value[b]
All-cause mortality	22 (3.5%)	42 (6.7%)	0.52 (0.31, 0.87)	0.0107
Treatment-emergent all-cause mortality	14 (2.2%)	32 (5.1%)	0.45 (0.24, 0.83)	0.0094
IPF-related mortality	10 (1.6%)	28 (4.5%)	0.35 (0.17, 0.72)	0.0029
Treatment-emergent IPF-related mortality	7 (1.1%)	22 (3.5%)	0.32 (0.14, 0.76)	0.0061

[a] Hazard ratio (HR) was based on the Cox proportional hazard model.
[b] p-value was based on the log-rank test
IPF = idiopathic pulmonary fibrosis; CI = confidence interval.
Source: CSR PIPF-016 Tables14.2.2-10, 14.2.2-13, 14.2.2-12, 14.2.2-11

7.5. Evaluator's conclusions on clinical efficacy

PIPF-004 demonstrated statistically significant difference from placebo favouring pirfenidone in change from baseline in % predicted FVC, but in PIPF-006 no significant difference was shown.

Small adjustments in the inclusion criteria 'to increase the chances of disease progression' were made for PIPF-016. The study was larger, with changes in the definition for disease progression and clinically relevant secondary endpoints as well as the change in the presentation of the primary efficacy variable. PIPF-016 demonstrated a statistically significant difference in change from baseline percent predicted FVC decline ≥ 10% or death, favouring pirfenidone 2,403 mg/day over placebo.

As supportive evidence, in the pooled analysis the proportion of patients with FVC decline > 10% or death was significantly reduced over 1 year; pirfenidone 14.8% versus placebo 26.3%. Analyses for all-cause mortality were also supportive.

For regulatory purposes in the context of current international approval, efficacy of pirfenidone was satisfactorily demonstrated in a patient population with a clear diagnosis of idiopathic pulmonary fibrosis. However at Round 1 it was not clear whether this population included an appreciable number of patients with 'severe' disease or whether the indication should be restricted to 'mild to moderate' IPF, as for the EMA and Canadian approvals.

8. Clinical safety

8.1. Studies providing evaluable safety data

The following studies provided safety data:

- Pivotal studies:
  - Study PIPF-004
  - Study PIPF-006
  - Study PIPF-016;
- Studies PIPF-002 and PIPF-012 (cut-off 7/8/2013);
- 7 Phase I studies.

An Integrated Safety Summary submitted to the FDA as the 2014 Resubmission Safety Update ('2014 RSU') was a review of pooled safety data, focussed on analyses of safety data for

pirfenidone 2,403 mg/day versus placebo. It is the source of the information summarised in this section except where results from individual studies are mentioned.

Comment: The 2014 RSU referred to data sourced from the original 2009 ISS but the links were not active. These aspects could not be verified by the evaluator but are accepted as evaluated in the CHMP report.

8.1.1. Pivotal efficacy and safety studies

In the pivotal studies, safety data were collected as specified in study protocols:

- General adverse events AEs were recorded at every patient contact. Treatment emergent AEs (TEAEs) were defined as AEs that occurred after the first dose and within 28 days of the last dose of study treatment. AEs were classified as serious or non-serious, and graded as mild, moderate, severe or life-threatening (Grades 1 to 4)
- AEs of particular interest, including dermatologic AEs, were recorded at patient contacts
- Standard laboratory tests for haematology and chemistry. Liver chemistry tests were performed at pre-specified intervals according to the study protocol
- ECGs, physical examination, weight and vital signs.

8.1.2. Other studies

- Study PIPF-012: As this was an extension study, 'TEAEs' were defined as pre-existing AEs that worsened after the first dose in PIPF-012, or started after first dose in PIPF-012 until 28 days after last dose.
- Clinical pharmacology studies.

8.2. Patient exposure

Table 17. Summary of studies in pirfenidone IPF clinical development program

Study Number	Phase	Study Objective	Subject Status/ Patient Diagnosis	Number of Participants		Total Unique Patients/ Subjects
				Pirfenidone	Placebo/ Control	
InterMune-Sponsored Studies: Patients with IPF/PF in Phase 2 and 3 Studies						
PIPF-002	2	Safety and efficacy	IPF/PF	83	0	
PIPF-004	3	Safety and efficacy	IPF	261	174	
PIPF-006	3	Safety and efficacy	IPF	171	173	
PIPF-012	3	Safety and efficacy	IPF	274[a]	0	
PIPF-016	3	Safety and efficacy	IPF	278	277	
Total InterMune Phase 2 and 3 IPF/PF Patients:				**1067**	**624**	**1417[b]**
InterMune-Sponsored Studies: Subjects in Phase 1 Studies						
PIPF-005	1	Safety, PK	Healthy	41	0	
PIPF-007	1	Thorough QTc, PK	Healthy	81	81	
PIPF-008	1	Safety, MTD	Healthy	16	4	
PIPF-009	1	Safety, PK	Healthy or renal impairment	26	0	
PIPF-010	1	Safety, DDI, PK	Healthy	54	0	
PIPF-011	1	Safety, PK	Healthy or hepatic impairment	24	0	
PIPF-017	1	Safety, DDI, PK	Healthy	27	0	
Total InterMune Phase 1 Subjects:				**269**	**85**	**354**
Total InterMune Phase 2 and 3 IPF/PF Patients and Phase 1 Subjects:				**1336**	**709**	**1771[b]**
Marnac-Initiated Studies: Patients with IPF/PF in Phase 2 Studies						
PIPF-001	2	Safety and efficacy	IPF/PF	26	26	
PIPF-003	2	Safety and efficacy	IPF/PF	27	25	
Total Marnac Phase 2 IPF/PF Patients:				**53**	**51**	**104**
Grand Total Unique Phase 1–3 Participants:				**1382[c]**	**760**	**1865[b,c,d]**

[a] PIPF-012 treated 603 patients who enrolled from the Phase 3 Studies PIPF-004 and PIPF-006; 274 had received placebo and 329 had received pirfenidone in PIPF-004 or PIPF-006; thus, 274 of 603 patients received pirfenidone for the first time in PIPF-012.

[b] The 274 patients who received placebo in PIPF-004 or PIPF-006 and pirfenidone in PIPF-012 are included only once in this total.

[c] Seven patients who received pirfenidone in PIPF-001 and later entered PIPF-002 are counted only once in this total.

[d] Three patients who received placebo in PIPF-001 and pirfenidone in PIPF-002 are included only once in this total.

DDI = drug-drug interaction, IPF = idiopathic pulmonary fibrosis, MTD = maximum tolerated dose, PF = pulmonary fibrosis, PK = pharmacokinetics, QTc = corrected QT interval.

The Phase II Studies PIPF-001 (prednisolone control) and PIPF-003 (placebo control) were both terminated early. No data were located in the 2014 RISE but the sponsor included a brief summary.

Subjects contributing to pooled safety data from Phase II and III clinical studies had exposure as shown in Table 18.

Table 18. Pooled safety data (patient exposure) from Phase II and Phase III clinical studies

Study Number (Indication)	Total Number of Patients	Mean Duration of Treatment (Range)
Phase 3 placebo-controlled studies		
PIPF-004 (IPF)	Total: 435	
	Pirfenidone 2403 mg/d: 174	Pirfenidone 2403 mg/d: 70.7 weeks (2-104 weeks)
	Placebo: 174	Placebo: 71.4 weeks (<1-110 weeks)
	Pirfenidone 1197 mg/d: 87	Pirfenidone 1197 mg/d: 73.0 weeks (13-109 weeks)
PIPF-006 (IPF)	Total: 344	
	Pirfenidone 2403 mg/d: 171	Pirfenidone 2403 mg/d: 75.4 weeks (6-118 weeks)
	Placebo: 173	Placebo: 74.9 weeks (1-120 weeks)
PIPF-016 (IPF)	Total: 555	
	Pirfenidone 2403 mg/d: 278	Pirfenidone 2403 mg/d: 47.5 weeks (2–55 weeks)
	Placebo: 277	Placebo: 49.0 weeks (2–56 weeks)
Ongoing uncontrolled Phase 2 study		
PIPF-002 (IPF/PF) Cutoff: 07 August 2013	Total: 83	Pirfenidone: 167.1 weeks (3–519 weeks)
	Pirfenidone 2400 to 3600 mg/d: 83	
Ongoing uncontrolled Phase 3 extension study		
PIPF-012 (IPF) Cutoff: 07 August 2013	Total: 603	Pirfenidone: 149.4 weeks (1–257 weeks)
	Pirfenidone 2403 mg/d: 603	

Note: All patients had a diagnosis of IPF with the exception of 2 patients in PIPF-002.

The 'Randomised patient subset' was the 2,403 mg/day pirfenidone (n = 623) and the placebo groups (n = 624) from Studies PIPF-004, PIPF-006, and PIPF-016. Overall the demographics across treatment groups were well balanced. Most of the information below focuses on information from this subset.

The 'Pirfenidone patient subset' additionally included patients from PIPF-002 and PIPF-012, and those treated with pirfenidone 1,197 mg/day in PIPF-004 (total n = 1,067, n = 980 treated with 2,403 mg/day pirfenidone dose).

Long-term exposure in clinical studies included 172 patients treated for at least five years.

Table 19. Exposure to pirfenidone 2,403 mg/day in clinical studies, according to duration

Contributing Study	Randomized Patient Subset			Pirfenidone Patient Subset
	Pirfenidone 1197 mg/d	Pirfenidone 2403 mg/d	Placebo	
Phase 3 placebo-controlled studies				
PIPF-004	87[a]	174	174	261
PIPF-006	0	171	173	171
PIPF-016	0	278	277	278
Ongoing uncontrolled Phase 2 study				
PIPF-002	0	0	0	83
Ongoing uncontrolled Phase 3 extension study				
PIPF-012	0	0	0	274[b]
Total	**87[a]**	**623**	**624**	**1067**

[a] Pirfenidone 1197 mg/d group not included in Randomized Patient Subset, but included in Pirfenidone Patient Subset

[b] PIPF-012 includes 603 patients, but only 274 are newly exposed to pirfenidone, having been randomized to placebo in PIPF-004/PIPF-006

Duration on Study Treatment	2009 ISS		Additional Data		Cumulative Data	
	Pirfenidone (N = 345)	Placebo (N = 347)	Pirfenidone (N = 278)	Placebo (N = 277)	Pirfenidone (N = 623)	Placebo (N = 624)
Duration on study treatment (months)						
n	345	347	278	277	623	624
Mean	16.8	16.8	10.9	11.3	14.2	14.4
Standard deviation	5.19	4.94	2.65	2.29	5.15	4.85
Median	16.9	16.7	12.0	12.0	12.3	12.5
Min, Max	>0, 27	>0, 28	>0, 13	>0, 13	>0, 27	>0, 28
Number of patients on study treatment, n (%)						
>0 to <3	13 (3.8)	8 (2.3)	9 (3.2)	7 (2.5)	22 (3.5)	15 (2.4)
3 to <6	14 (4.1)	15 (4.3)	16 (5.8)	9 (3.2)	30 (4.8)	24 (3.8)
6 to <9	11 (3.2)	12 (3.5)	15 (5.4)	11 (4.0)	26 (4.2)	23 (3.7)
9 to <12	5 (1.4)	7 (2.0)	128 (46.0)	122 (44.0)	133 (21.3)	129 (20.7)
12 to <15	11 (3.2)	8 (2.3)	110 (39.6)	128 (46.2)	121 (19.4)	136 (21.8)
15 to <18	152 (44.1)	170 (49.0)	0	0	152 (24.4)	170 (27.2)
18 to <21	66 (19.1)	66 (19.0)	0	0	66 (10.6)	66 (10.6)
21 to <24	66 (19.1)	49 (14.1)	0	0	66 (10.6)	49 (7.9)
≥24	7 (2.0)	12 (3.5)	0	0	7 (1.1)	12 (1.9)
PEY[a]	482.7	486.7	253.0	260.1	735.7	746.8

[a] One person exposure year (PEY) is equal to 1 patient exposed to study drug for 1 year (ie, 365.25 days). The total of the PEYs is the sum of all patients' PEYs in that treatment group and data view.

The majority of patients (64%) had a mean daily dose of pirfenidone > 2,200 to ≤ 2,600 mg/day.

8.3. Adverse events

Almost all patients experienced a treatment emergent AE. In Studies PIPF-004, PIPF-006 and PIPF-016, the protocol included dose modification guidelines on the occurrence of selected AEs including GI events, hepatic events, photosensitivity or rash, and fatigue. While 42.7% of patients in the pirfenidone treatment group in the randomised patient subset had a TEAE that led to a dose reduction of any duration (compared with 16.2% for placebo) a lower percentage discontinued treatment early due to any TEAE (14.6% versus 9.6%).

Table 20 shows an overview of all adverse events in the randomised patient subset.

Table 20. Randomised patient subset: An overview of all adverse events in the randomised patient subset

	Number of Patients, n (%)	
	Randomized Patient Subset	
	Pirfenidone 2403 mg/d (N=623)	Placebo (N=624)
Any TEAE	617 (99.0)	611 (97.9)
Any treatment-related TEAE	556 (89.2)	424 (67.9)
TEAEs by maximum intensity		
Mild (Grade 1)	87 (14.0)	104 (16.7)
Moderate (Grade 2)	324 (52.0)	307 (49.2)
Severe (Grade 3)	175 (28.1)	155 (24.8)
Life-threatening (Grade 4)	31 (5.0)	45 (7.2)
Treatment-emergent deaths from any cause	27 (4.3)	44 (7.1)
Any TE SAE	168 (27.0)	178 (28.5)
Any treatment-related SAE	33 (5.3)	27 (4.3)
Any TEAE leading to early discontinuation of treatment	91 (14.6)	60 (9.6)
Any TEAE leading to dose reduction or interruption	266 (42.7)	101 (16.2)

TE=treatment-emergent; SAE=serious adverse event; TEAE=treatment-emergent adverse event

A table from 2014 RSU was provided that details by maximum intensity TEAEs occurring with a crude rate of 5% or more. For common TEAEs, compared to any TEAEs as tabulated above, a greater proportion were mild, and a lesser proportion severe or life threatening.

Comment: A high rate of AEs is not unexpected in patients with a progressive condition such as IPF. However there was clearly a higher rate of treatment related AEs in the pirfenidone group, including SAEs, and AEs leading to early discontinuation or dose interruption or adjustment.

8.3.1. All adverse events (irrespective of relationship to study treatment)

As above, overall AEs were reported for 99% of pirfenidone treated subjects and 97.9% in the placebo group. The most frequently reported events with incidence greater for pirfenidone were GI disorders (pirfenidone 72% versus placebo 52%); for example nausea 36% versus 15%, diarrhoea 26% versus 20%, dyspepsia 18% versus 7%, vomiting 13% versus 6%. This was followed by skin disorders (41% versus 15%); rash (30% versus 10%), photosensitivity (9% versus 1%), and pruritus (8% versus 5%). In other SOCs differences were seen in fatigue (26% versus 19%), dizziness (18% versus 11%), anorexia (13% versus 5%), insomnia (10% versus 7%), weight decreased (10% versus 5%) and hot flush (4% versus 2%).

In the randomised patient subset the proportions of patients with Grade 3 (severe) common TEAEs were pirfenidone (16.4%) versus placebo (15.5%); a smaller proportion of patients in the pirfenidone group experienced Grade 4 (life threatening) common TEAEs (1.9% versus 4.0%). All were respiratory events; IPF 8 versus 23 patients, pneumonia 3 versus 2, dyspnoea 1 versus 0. Hepatic treatment emergent adverse events were analysed by MedDRA SMQ; more pirfenidone treated patients had hepatic events than in placebo group (9.5% versus 4.3%).[17]

[17] MedDRA SMQ = Medical Dictionary for Regulatory Activities, Standardised MedDRA Queries are tools developed to facilitate retrieval of MedDRA coded data in the investigation of drug safety issues in Pharmacovigilance and clinical development.

In the pirfenidone patient subset almost every patient exposed over a longer duration had a TEAE (1064 out of 1067). The pattern was similar to the randomised subset. For common TEAEs (crude rate ≥ 5%) adjusted incidence/100 PEY was 27.5 for severe (Grade 3) events, 3.5 for life-threatening (Grade 4), 6.8 for deaths, 48.5 for SAEs, 14.7 for discontinuations due to AE and 53.7 for AE leading to dose reduction or interruption. Higher frequencies reflect longer exposure but exposure adjusted rates were stable over time. The GI events were reported for the majority of patients within the first 3 months, other AEs reported within the first 6 months.

8.3.1.1. Pivotal studies

Study PIPF-004

As noted in the Pharmacodynamics section, there appeared to be a dose response (1,197 mg/day versus 2,403 mg/day) in the reported incidence rate for some common TEAEs including rash (17% versus 30%), photosensitivity reaction (7% versus 14%), nausea (25% versus 34%), dyspepsia (14% versus 17%), headache (16% versus 21%) and dizziness (16% versus 19%) No dose response was apparent for many other common TEAEs.

8.3.1.2. Other studies

A total of 269 subjects were treated with pirfenidone in the Phase I trials. The adverse events of headache, nausea, and dizziness were the most frequently reported. The TEAEs were generally of mild to moderate severity. In PIPF-011 after a single dose there were more AE reports in patients with hepatic insufficiency.

In extension Study PIPF-012 there was long-term exposure (median 163 weeks). Severe or life threatening and serious AEs were mostly related to the underlying IPF. However, high rates of GI, dermatologic and hepatic events were also reported. Of note, 8 patients (1.3%) had a severe dermatologic TEAE including 2 patients with urticaria. Severe TEAEs based on liver test results included 2 patients with hepatic enzyme increased, 2 with liver function test abnormal, one patient with hyperbilirubinaemia and one with GGT increased.

8.3.2. Treatment-related adverse events (adverse drug reactions)

The Clinical Overview states that two analyses were conducted. In the first, a treatment related TEAE was defined according the opinion of the reporting investigator; the second method defined 'common and likely treatment related adverse events' on the basis of a frequency of ≥ 5% plus an incidence ≥ 1.5 times that observed with placebo. The tabulated summaries of ADRs in the proposed product labelling were derived using the first method. In the proposed Australian PI this section is referenced to 'EU SmPC'.[18]

The most commonly reported ADRs in the randomised patient subset (based on investigator assessment) in patients treated with pirfenidone compared to placebo respectively, were: nausea (32.4% versus 12.2%), rash (26.2% versus 7.7%), diarrhoea (18.8% versus 14.4%), fatigue (18.5% versus 10.4%), dyspepsia (16.1% versus 5.0%), anorexia (11.4% versus 3.5%), headache (10.1% versus 7.7%), and photosensitivity reaction (9.3% versus 1.1%).

The observed crude rates according to the second method are described in the 2014 RSU as follows:

- GI disorders:
  - Nausea (pirfenidone 36.1%, placebo 15.5%),
  - Dyspepsia (18.5%, 6.9%)
  - Vomiting (13.3%, 6.3%)

[18] SmPC = Summary of Product Characteristics

  - GORD (11.1%, 7.1%)
  - Stomach discomfort (8.5%, 2.9%)
  - Abdominal pain (6.3%, 2.9%)
- General Disorders and Administration Site Conditions:
  - Asthenia (6.4%, 3.8%)
- Investigations:
  - Decreased weight (10.1%, 5.4%)
- Metabolism and Nutrition Disorders:
  - Anorexia (13.0%, 5.0%)
  - Decreased appetite (8.0%, 3.2%)
- Nervous System Disorders:
  - Dizziness (18.0%, 11.4%)
  - Dysgeusia (5.8%, 2.2%)
- Psychiatric Disorders:
  - Insomnia (10.4%, 6.6%)
- Skin and Subcutaneous Tissue Disorders:
  - Rash (30.3%, 10.3%)
  - Photosensitivity reaction (9.3%, 1.1%)
- Vascular Disorders:
  - Hot flush (4.0%, 2.2%)

Treatment related SAEs (investigator assessment) occurred in 33 patients in the pirfenidone group (n =623) (5.3%) versus 27 patients (4.3%) in the placebo group (n = 624). The events by SOC were as follows:

- Cardiac disorders (4 versus 2)
- GI disorders (6 versus 4)
- General disorders (chest pain) (2 versus1)
- Hepatobiliary disorders (3 versus 2)
- Infections and infestations (6 versus 6)
- Abnormal investigations (4 versus 1)
- Neoplasms (3 versus 3)
- Nervous systems disorders (3 versus 2)
- Psychiatric disorders (1 versus 0)
- Renal (Acute renal failure) (1 versus 0)
- Respiratory (10 versus 8)
- Dermatological (2 versus 0)
- Vascular (Aortic aneurysm) 0 versus1.

8.3.2.1. Pivotal studies

The patterns of treatment-related AEs were similar in all the Phase III pivotal studies, as above.

8.3.2.2. Other studies

There were no notable deviations from the pooled data analyses in the ISS. In Phase I studies, drug related AEs were nausea, headache and dizziness**.** In the extension Study PIPF-012**,** 79.8% of patients had TEAEs that were considered by the investigator to be possibly or probably treatment related, including nausea 24.2%, diarrhoea 13.3%, rash 13.1%, dyspepsia 11.3%, and fatigue 10.4%. Of note, 8.5% of patients had weight decreased considered treatment related.

8.3.3. Deaths and other serious adverse events

8.3.3.1. Deaths

A total of 71 patients died within 28 days of last dose of study treatment, lower in the pirfenidone than placebo group (4.3%, 27 patients versus 7.1%, 44 patients). IPF was the most common cause of death (10 pirfenidone, 1.6% versus 21 placebo, 3.4%). Other causes of death in more than 2 patients were respiratory failure (5 patients, 0.8%, in both groups) and pneumonia (3 patients, 0.5%, in both groups. The number of deaths per 100 patient exposure years (PEY) was lower in the pirfenidone group than placebo (3.7 versus 5.9). Adjusted mortality incidence rates were stated to be slightly higher in the 2014 RSU pirfenidone patient subset compared with the 2009 ISS (6.8 versus 5.1 per 100 PEY), reflecting disease progression with increased person exposure years; the causes of death were consistent with those in the randomised patient subset.

8.3.3.2. Serious adverse events

TE SAEs were reported in 168 (27%) and 178 (28.5%) patients in pirfenidone and placebo groups respectively in the cumulative randomised patient subset. IPF, pneumonia, and respiratory failure occurred in fewer patients in the pirfenidone group. The most frequently reported (≥ 1% in either group) were as shown in Table 21.

Table 21. Treatment emergent serious adverse events in pirfenidone versus placebo randomised groups

TE SAE	Pirfenidone n (%)	placebo
IPF	33 (5.3)	58(9.3)
Pneumonia	22(3.5)	27(4.3)
Respiratory failure	7(1.1)	9(1.4)
Coronary artery disease	7(1.1)	3(0.5)
Angina pectoris	6 (1.1)	2(0.3)
Prostate cancer	4 (0.9% M)	6(1.3% M)
Acute respiratory failure	5 (0.8)	7(1.1)
Bronchitis	3(0.5)	9(1.4)

Incidence of TE SAEs by baseline percent predicted FVC (< 70%, 70 to 80%, and ≥ 80%) were pirfenidone 31.1%, 23.4%, 23.2% versus placebo 34.0%, 23.4%, 22.4% respectively. Treatment

related (investigator assessed causality) SAEs occurred 5.3% in the pirfenidone group versus 4.3% in the placebo group.

Hepatic events were analysed. TE SAEs including hepatitis and abnormal LFTs occurred in more pirfenidone patients 6 (1%) versus placebo 1 (0.2%). Pirfenidone was discontinued in 5 cases. In the other case pirfenidone was interrupted due to moderate ALT/AST elevations that resolved upon study drug cessation; LFTs remained normal or mildly elevated throughout the rest of the study after treatment was restarted. There were no reported cases of liver failure or death.

In the pirfenidone patient subset TE SAEs occurred in 52.4%, an adjusted event rate of 45/100 PEY. Considering the longer duration of treatment the conditions were as expected and similar to those in the randomised subset.

8.3.3.3. Pivotal studies

Cause of death was assessed by principal investigators in Studies PIPF-004 and PIPF-006 and by an independent Mortality Assessment Committee (MAC) in PIPF-016.

See section 'cardiovascular safety' below for cardiac deaths. Of the hepatic SAEs, one case in PIPF-016 met Hy's law criteria.[19] In this case, following non-serious 'hepatic enzyme increased' from days 35 to 104, pirfenidone was discontinued at the onset of hepatitis on day 105. LFTs decreased to near normal by day 182; the patient was unable to return for testing subsequently due to progression of respiratory disease.

8.3.3.4. Other studies

No TE SAEs or deaths were reported in Phase I studies. In PIPF-012, 141 deaths of 603 enrolled had occurred by the cut-off date, 4.5 years after the last patient enrolled. As expected, the majority were due to IPF (78) and respiratory failure (13).

8.3.4. Discontinuation due to adverse events

In the randomised patient subset discontinuations were 5% higher for pirfenidone than placebo (14.6% versus 9.6%). Rates were stated to be higher in the 2014 pirfenidone patient subset (38.5%) than in the 2009 ISS (16.3%), consistent with longer duration. Adjusted event rates are more comparable (14.7 versus 12.6 per 100 PEY). In the ISS 2009 rates of TE AEs leading to study drug discontinuation were higher for those with hepatic abnormality at baseline than without (17.6% versus 14.2%).

Overall rates of patients who had a TEAE leading to dose reduction or treatment interruption were higher in the pirfenidone group than in the placebo group: 42.7% versus 16.2%. The rates were highest in patients with TEAEs in the SOCs of GI disorders (18.5% versus 5.8%) and skin and subcutaneous tissue disorders (17.5% versus 1.8%). The common TEAEs (≥ 5% of patients) reported as leading to dose modification by a higher proportion for pirfenidone than placebo were rash (9.8% versus 1.0%) and nausea (7.5% versus 1.6%).

8.3.4.1. Other studies

Discontinuations in Phase I studies PIPF-005 and PIPF-008 were associated with higher doses. In extension Study PIPF-012, 2% of patients discontinued due to GI TEAES of interest (nausea 8, diarrhoea 3, vomiting 1) and 3.3% for dermatologic TEAEs. Elevated LFT TEAEs overall were reported for 9.8% of patients and four patients discontinued due to elevated liver test results.

[19] Hy's Law = Based on observations by Hy Zimmerman (scholar in drug-induced liver injury) Hy's law suggests that a drug is at high risk of causing a fatal drug-induced liver injury when given to a large population if changes in laboratory parameters according to specific criteria are seen when the drug is given to a smaller population.

8.4. Laboratory tests

Marked laboratory abnormalities (Grade 4 toxicity or change in toxicity of 3 grades from baseline) in cumulative data were infrequent and similar between groups except for LFTs, lymphocytes, and hyponatraemia.

8.4.1. Liver function

Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations ≥ 3 x upper limit of normal (ULN) occurred in a larger proportion of pirfenidone treated patients than placebo treated patients. Most of these elevations were mild (3 to 5 x ULN), 2.4% versus 0.5%.

8.4.1.1. Pivotal studies

All instances of ALT or AST elevation ≥ 3 x ULN in the three studies were reversible upon discontinuation of pirfenidone. As noted above one patient treated with pirfenidone 2,403 mg/day in PIPF-016 had concurrent elevations in ALT or AST > 3 x ULN and total bilirubin > 2 x ULN and met Hy's law criteria.

8.4.1.2. Other studies

Increased GGT was seen in Phase I multiple dose Study PIPF-005.

8.4.2. Kidney function

Cumulative shift data did not indicate differences between treatment groups for markedly abnormal laboratory measurements for creatinine.

8.4.3. Other clinical chemistry

Hyponatraemia was reported for 0.8% of pirfenidone patients and 0.3% of placebo patients. In shift data marked sodium (hyponatremia) abnormalities (from Grade 0 to Grade 3) were reported in 9 pirfenidone patients (1.5%) and 1 placebo patient (0.2%).

8.4.3.1. Pivotal studies

In Study PIPF-006, one pirfenidone patient had a Grade 4 SAE of hyponatraemia considered unrelated to study treatment.

8.4.4. Haematology

Reductions in lymphocyte count from Grade 0 to Grade 3 were seen for 6 (1.0%) pirfenidone patients versus 1(0.2%) placebo. Lymphocyte abnormalities were not associated with AEs in clinical studies.

8.4.4.1. Pivotal studies

In Study PIPF-004, one pirfenidone patient had a post baseline Grade 4 lymphocyte abnormality at Week 4, which was resolved at Week 6, Grade 2 at Weeks 12, 24, and 36, and resolved thereafter. One patient in the pirfenidone group was reported to have bone marrow failure, considered unrelated to study treatment by the investigator. The narrative for this patient [information redacted] shows that the patient was a 46 year old male with pre-existing macrocytic anaemia who developed thrombocytopenia after treatment with pirfenidone for more than a year, and on biopsy had markedly hypocellular bone marrow with hypoplasia.

8.4.5. Electrocardiograph

In PIPF-004 and PIPF-006 no formal ECG analysis was completed. In PIPF-016 ECGs were evaluated centrally by a cardiologist blinded to treatment.

8.4.5.1. Pivotal studies

In Studies PIPF-004 and PIPF-006 after unblinding, an imbalance in cardiac arrhythmia events was noted. All ECGs collected between baseline and 28 days after end of treatment were

retrospectively analysed. This was reported to show no clear evidence of a pirfenidone related effect on heart rate, cardiac depolarization, QT prolongation, or electrocardiographic morphology.

In PIPF-016 one patient in each treatment group had an isolated instance of QTcB > 500 ms.[20] on routine post randomisation ECG, not reported as AE and no change in dose. One TEAE of QTcB prolongation was reported in the pirfenidone group, mild and possibly related; no QTcB value was > 500 ms and the patient had RBB reported the same day and no dose change was made.

8.4.5.2. Other studies

In the non-pivotal StudyPIPF-007, results suggested pirfenidone had no effect on QT interval and other ECG parameters in healthy subjects.

8.5. Vital signs

Mean results for the pirfenidone and placebo groups were similar. In the randomised patient subset weight loss of ≥ 10% occurred in 17.7% and 26.9% for males and females respectively in the pirfenidone group compared to 9.2% and 11.3% in the placebo group. In the pirfenidone patient subset with longer exposure, the proportion with weight loss ≥ 10% was 35.2% for men and 44. 4% for women respectively.

8.5.1.1. Pivotal studies

There were a few cases of marked weight loss. In pivotal Study PIPF-016 maximum weight loss was pirfenidone 27 kg versus placebo 22 kg; there were two weight loss TEAEs described as severe in the pirfenidone group but none in the placebo group. One withdrew from study.

8.6. Post-marketing experience

Post Market Safety Update Reports (1 to 7) were provided. The cumulative post-marketing exposure as of 27 February 2014 was estimated to be 13,191 patient years, a total of approximately 15,000 patients.

PSUR 4 included the case of elevated bilirubin in PIPF-016 that triggered review of hepatic events. Three other cases of Hy's law were found as described below. Increased total serum bilirubin in conjunction with elevated AST and ALT was added to the SPC.

Based on reports in PSUR 5 and PSUR 6, as of 28 February 2014, two new TEAEs of interest were identified in post-marketing experience, added to the SPC and assessed as safety signals for pirfenidone:

- Agranulocytosis (3 cases)
- Angioedema (14 cases identified).

These were also added to the SPC.

According to PSUR 7, to 27 August 2014 the estimated cumulative exposure in clinical trials was 1,574 patients, and total post-marketing exposure was estimated to be 16,634 patient-years. There are named patient programmes and patient assistance programmes in Europe and patient registries in both Canada and in Belgium-Netherlands-Luxembourg. A post-authorisation safety Study PIPF-025 has enrolled approximately 1,000 participants. Since the international birth date (IBD) of 28 February 2011, a total of 8,185 suspected ADRs have been reported in the post-marketing surveillance period. This included 1,931 (23.6%) from

[20] QTcB = QT-interval corrected for heart rate using Bazett's correction formula

spontaneous reporting, literature, or regulatory authorities; 190 (2.3%) from clinical trials; and 6,064 (74.1%) from solicited reporting. The majority (7,161) were non-serious. The total number of ADRs increased from 5,525 in PSUR 6 to 8,185 in PSUR 7. This is stated to be largely due to solicited reporting and spontaneous post-marketing reports from Europe and Canada.

Overall the pattern of the post-marketing AEs is similar to that observed in clinical trials. In PSUR 7 a series of cases of thrombocytopenia were reported in post-marketing surveillance. These cases lead to an investigation of thrombocytopenia as a safety signal. The MAH concluded that current information was not sufficient to propose any current changes to the reference safety information and that more monitoring of this signal would be required. Additionally there was mention of a potential warfarin-pirfenidone interaction.

8.7. Safety issues with the potential for major regulatory impact

Several issues identified during drug development and with subsequent experience have implications for safe use.

8.7.1. Liver toxicity

Pirfenidone has a known association with liver toxicity. Hepatic events were analysed in the cumulative datasets as adverse events of interest, for example through SMQ 'possible drug related hepatic disorders comprehensive search'. Liver related laboratory outcomes were categorised according to specified test range values, as described in the 2012 Safety Update SAP for the assessment of potential hepatotoxicity.

In the randomised patient subset 9.5% pirfenidone patients reported hepatic TEAEs versus 4.3% for placebo. There were 6 pirfenidone patients with hepatic TE SAEs versus 1 placebo patient. Three pirfenidone patients had moderate to severely abnormal LFTs judged probably related and 2 had severe hepatitis, judged probably or possibly related. One was discontinued because of persistent GGT elevation and diagnosed with malignant hepatic neoplasm. Overall LFT elevations were more frequent and severe with pirfenidone treatment.

Notable elevations in AST/ALT tended to occur early in therapy; of 21 patients with an ALT /AST > 3 x ULN, 14 first had ALT/AST > 3 x ULN in the initial 6 months of treatment. Of 7 pirfenidone patients with ALT/AST > 5 x ULN, 5 patients first had that elevation in the first 6 months; 2 patients had smaller elevations (Grade 1, mild, up to 3 x ULN) at baseline and during the initial 6 months of treatment. For ALT/AST >3 and < 5 x ULN (in the absence of symptoms or bilirubin > 2 x ULN), the protocols allowed dose reduction or interruption if clinically appropriate, with subsequent re-titration to full dose, as tolerated. Of 15 patients in this category 12 were on pirfenidone at completion of study, 7 on full dose.

Data from the pirfenidone patient subset indicated that adjusted incidence rates did not increase with longer term exposure.

In the combined database, including Japanese Phase II studies, PIPF-016 and 2 post-market reports (total exposure approximately 15,000 patients), 4 patients met Hy's law criteria of concomitant elevations in ALT or AST > 3 x ULN and total bilirubin > 2 x ULN in the absence of alternate explanations. In all 4 cases, liver test elevations occurred early after first exposure to pirfenidone (that is ALT > 5 x ULN by Week 13), and all showed reversal after discontinuation of pirfenidone.

Regular LFT monitoring was useful for early identification and new onset symptoms such as nausea, abdominal discomfort or malaise should be considered as a warning for potentially serious LFT elevations. LFT evaluation is therefore recommended prior to initiation of therapy and then monthly for the first 6 months and 3 monthly thereafter.

Comment: Advice from the Phase III study protocols is the basis of the PI recommendations for managing drug dosage with elevation of LFTs. The sponsor's recommendation in 2014 RSU are:

- LFTs 3 to 5 x ULN, bilirubin normal; cease confounding medications and monitor closely, and interrupt or reduce and titrate pirfenidone as necessary
- LFTs 3 to 5 x ULN with symptoms or elevated bilirubin; permanently discontinue
- ALT/AST > 5 x ULN; permanently discontinue.

8.7.2. Haematological toxicity

There were occasional reports of haematological abnormalities in the clinical development program. There were 3 reports of SAE of agranulocytosis in the post-marketing experience (as of 28 February 2014). Each event occurred within 2 months after the start of pirfenidone treatment. Each patient's neutrophil count normalized when pirfenidone was discontinued.

8.7.3. Serious skin reactions

Photosensitivity reaction was reported for 9.3% of pirfenidone patients and 1.1% of placebo patients in the randomised patient subset, most within the initial 6 months. In the pirfenidone group, one patient had a TE SAE. Rash was reported for 30.3% of pirfenidone patients (1 patient had SAE) and 10.3% of placebo patients. The narratives for patients with individual skin SAEs were not accessible. The PI notes that patients must be protected from sunlight.

8.7.4. Cardiovascular safety

In cumulative data for the randomised patient subset there was an imbalance in cardiac arrhythmias (SMQ) (pirfenidone14.4% versus 8% placebo) and valvular incompetence (1.1% versus 0.6%; 1 SAE of mitral valve incompetence in a patient on pirfenidone). Types of arrhythmia events were diverse and numbers were low for specific events. The pirfenidone group recorded 1 death (myocardial infarction) versus 4 deaths from cardiac disorders in the placebo group, with an additional death in the placebo group assessed by MAC as sudden cardiac death. In the cumulative pirfenidone patient subset 13 additional cardiac deaths were identified in the long-term safety studies PIPF-002 and PIPF-012, all with a medical history of cardiac disease or risk factors prior to pirfenidone treatment.

Review by independent cardiology experts concluded that there was no clear evidence of an effect of pirfenidone on heart rate, cardiac depolarization, QT prolongation, or electrocardiographic morphology.

8.7.5. Unwanted immunological events

There were 14 reports of angioedema in the post-marketing experience (as of 28 February 2014). All occurred within 3 months after the start of pirfenidone treatment. A majority of the cases were considered serious but each patient improved when pirfenidone was discontinued.

8.8. Safety in special populations

8.8.1. Hepatic impairment

In the randomised patient subset, the proportion of patients with baseline hepatic impairment was relatively low, about 10 % in the Phase III studies. Data submitted stated there overall there were no consistent differences in AEs between patients with normal and impaired hepatic function at baseline, although source tables show increases in some patients and increased discontinuations with baseline hepatic abnormality. Although no dose adjustment is proposed in mild to moderate hepatic impairment, it is proposed that pirfenidone 'should be used with caution'.

8.8.2. Renal impairment

Patients with mild to moderate renal impairment were well represented in the randomised patient subset. While the frequency of AEs was slightly higher in these patients compared to those with normal renal function, a similar pattern was observed in both the pirfenidone and placebo treated patients.

8.8.3. Safety related to drug interactions

As mentioned in reference to PK data (see section: Pharmacokinetics above) it is proposed to contraindicate use with fluvoxamine, and recommend dose modification with ciprofloxacin.

8.8.4. Other events identified as of special interest

As noted, GI symptoms were common and more frequent compared to placebo, mostly within first 3 months. Events generally were mild to moderate, without clinically significant effects following dose modification. The cause is not fully understood; a possible effect on gastric and intestinal motility was suggested.

Dizziness was observed more frequently with pirfenidone treatment than placebo (18.0% versus 11.4%). The majority of patients who reported dizziness first did so within the initial three months of treatment. Falls were infrequent but more common in pirfenidone patients (2.4% versus 1.4%). Of the pirfenidone treated patients who reported dizziness, 5.4% experienced a fall at some time after the first report of dizziness.

Fatigue was more common with pirfenidone (26% versus 19%), however generally benign and reported in the first 9 months. It is identified in the PI under Adverse events. Of note, in the EU EMA SPC, dizziness and fatigue are mentioned as potentially influencing ability to drive or operate machinery.

Anorexia was more common with pirfenidone (13% versus 5% for likely drug related events).

Weight loss was also more frequent in the pirfenidone groups compared to placebo.

8.8.5. Other safety issues

There is little if any experience with high doses or overdose in the clinical setting.

The last part of the trade name is the same as registered product rabeprazole 10 mg or 20 mg trade name, 'Pariet'. However 'Esbriet' 267 mg appears unlikely to be associated with a high risk of errors in transcription, prescribing or dispensing.

8.9. Evaluator's overall conclusions on clinical safety

Overall the data indicated a well characterised and acceptable safety profile for IPF patients, although monitoring and effective management of adverse events will be required.
Dose adjustments may be needed soon after initiation and this is important for the proposed usage.

Occurrence of common AEs such as GI and CNS responses may be amenable to measures to improve tolerability, such as dose escalation and dosing with food as recommended in the PI. Dose reduction or interruption might be required to allow recovery and subsequent dose titration. Some AEs require prompt assessment to avoid serious clinical consequences. The onset of an adverse event needs to be recognised as a potential reaction to pirfenidone that might require discontinuation or dose reduction.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

The benefits of pirfenidone in the proposed usage in patients with IPF include:

- reduction in the decline of percent predicted FVC
- increased proportion of patients with improved exercise tolerance, (for example 6 MWT)
- in pooled analyses, suggestion of reduction in mortality.

9.2. First round assessment of risks

The risks of pirfenidone in the proposed usage are:

- Well characterised GI, CNS and hepatic adverse events that can generally be managed in clinical practice
- drug interactions.

9.3. First round assessment of benefit-risk balance

The benefit-risk balance of pirfenidone, given the proposed usage, is favourable at Round 1.

10. First round recommendation regarding authorisation

According to the clinical evaluator, at Round 1, recommendation for registration of pirfenidone for IPF is expected, subject to responses to questions and satisfactory amendments to the PI.

10.1. First round comments on clinical aspects of the Safety Specification in the draft RMP

The Safety Specification in the draft Risk Management Plan is essentially based on the same information as described in the Clinical Safety section, the Integrated Safety Summary submitted to the FDA as the 2014 Resubmission Safety Update ('2014 RSU'). The safety specification is satisfactory at Round 1.

Of note, 'missing information' in the Safety Specification includes 'patients suffering from severe stages of IPF'. According to the Safety Specification this is because these patients were excluded from the clinical trial population. However the indication proposed in Australia is non-specific as to severity of IPF (see section: Clinical questions (below))

11. Clinical questions

11.1. Additional expert input

The following aspects are inconsistent across international regulatory agencies and need resolution prior to Australian approval:

- Is the narrower Indication for the treatment of 'mild to moderate' IPF appropriate, as per the SPC?
- Should use be contraindicated in severe hepatic and renal disease as in the SPC?

11.2. Clinical questions for the sponsor

1. The Indication approved by the EMA is for the treatment of *'mild to moderate Idiopathic Pulmonary Fibrosis*'.Please provide the location of the justification for the widening the target population for the Australian submission to treatment of all stages of IPF severity.

   Please provide any available information on clinical efficacy outcomes in Australian patients provided with pirfenidone 'Esbriet' through the SAS.

2. The proposed Indication does not specify *'mild to moderate IPF*'. However, use of pirfenidone in severe stage IPF is described as '*missing information'* in the Safety Specification in the draft RMP.

   Please clarify this inconsistency.

3. Please provide PSUR 8 which should be available, covering the period to August 2014 to February 2015.

4. Have there been regulatory actions with respect to thrombocytopenia or warfarin interaction signals?

5. Please provide any available information on safety in Australian patients provided with pirfenidone 'Esbriet' through the SAS.

12. Second round evaluation of clinical data submitted in response to questions

1. '*The Indication approved by the EMA is for the treatment of 'mild to moderate Idiopathic Pulmonary Fibrosis'.Please provide the location of the justification for the widening the target population for the Australian submission to treatment of all stages of IPF severity.*

Please provide any available information on clinical efficacy outcomes in Australian patients provided with pirfenidone 'Esbriet' through the SAS.'

Evaluator's comment

No new efficacy data were provided.

In reply to the first part of the question, the sponsor confirmed that the widening of the indication to all stages of IPF severity is consistent with the data provided for FDA approval, due to the modification of the entry criteria in Study PIPF-016 to favour enrolment of patients with a greater likelihood of disease progression. These are the same data provided with this submission.

In reply to the second efficacy question the sponsor replied that information collected in association with supply under SAS does not include efficacy data.

This is acceptable.

2. *The proposed indication does not specify 'mild to moderate IPF'. However, use of pirfenidone in severe stage IPF is described as 'missing information' in the Safety Specification in the draft RMP. Please clarify this inconsistency.*

Evaluator's comment

In response regarding inconsistency between the proposed indication RMP description of use in severe stage IPF as 'missing information', the sponsor explained further that this was due to the indication approved in EU. A post-authorisation commitment to address the potential risk of missing data, approved by EMA CHMP, was undertaken by conducting the post-authorisation

safety study, the registry study 'PASSPORT' (PIP-025) to evaluate the long-term safety profile. The approximately 1000 patients already registered have a baseline FVC range from 21% to 121%, median 64.7% and 143 patients have baseline FVC < 50%.

3. *Please provide PSUR 8 which should be available, covering the period to August 2014 to February 2015.*

Evaluator's comment

As of this PSUR reporting period, estimated cumulative patient exposure to pirfenidone in clinical trials was 1574 patients. Cumulative post-marketing exposure was estimated to be 20,368 patient years. During this six month reporting period, the total worldwide post-marketing exposure to pirfenidone was estimated to be 3743 patient years. In this PSUR reporting period, 7651 suspected ADRs were received. A total of 591 (7.7%) were from spontaneous or literature reports, 47 (0.6%) were from clinical trials, and 7013 (91.7%) were from solicited reporting. The total (cumulative) number of ADRs has nearly doubled from 8185 in PSUR 7 to 15,827 in PSUR 8 largely due to solicited reporting from patient support programme reporting originating in the US.

In PASSPORT to December 2014 there were 670 of 1006 (66.6%) patients who experienced a total of 1790 ADRs of special interest. The safety profile was comparable to the label with the most frequent adverse reactions including gastrointestinal (34.4%) and skin (25.1%) SOCs. Also common was the category 'other clinically significant ADR (28.9%) which included decreased appetite (11%) cough (2.5%) dyspnoea (2.2%) and headache (2.1%).

In PASSPORT there were 55 (5.5%) patients who experienced 77 SADRs. Fifteen of 55 patients (1.5 %) had gastrointestinal disorders, such as diarrhoea, nausea, or vomiting. Ten patients (1.0%) reported a skin or subcutaneous tissue disorder, such as photosensitivity, erythema, or rash; 5 reported weight decreased, 1 of which was fatal with no information to suggest cause of death other than IPF.

Abnormal LFTs. dizziness, fatigue and weight loss are addressed in the PI.

One 18 year old patient who was given Esbriet for lung fibrosis after a double lung transplant developed angioedema and pirfenidone was ceased.

4. *Have there been regulatory actions with respect to thrombocytopenia or warfarin interaction signals?*

Evaluator's comment

The sponsor stated that these remain as open signals with continued monitoring. There has been no update to CDS or EU SmPC. A summary of the PRAC assessment was provided.

It noted 7 reports of thrombocytopenia, potentially confounded, and none in clinical studies.

For warfarin-pirfenidone interaction the EMA rapporteur assessment was no change in relative frequency, and ongoing monitoring was required. The FDA has also asked about this and the sponsor is preparing a draft report. A tabular overview of regulatory actions was provided.

A detailed response is provided in answer to the RMP evaluation.

5. *Please provide any available information on safety in Australian patients provided with pirfenidone 'Esbriet' through the SAS.*

Evaluator's comment

The Roche SAS safety database identified 2 patients who received Esbriet and experienced adverse events.

AER 1630959 concerned an 81yeear old woman who developed nausea and vomiting after staring pirfenidone 2,403 mg daily total in 3 separate doses. Vomiting ceased when she ceased

the capsules and re-occurred after re-introduction. Nausea and vomiting are known AEs for Pirfenidone and listed in the proposed PI in Table 4 as 'occurring in ≥10% Pirfenidone treated patients and more commonly than placebo'.

One AER concerned a 77 year old man who developed shingles around 300 days after initiating treatment, with concurrent conditions including osteoarthritis, hypertension and prostatitis, with concomitant medications treating these conditions. The physician assessed the relationship as unrelated to pirfenidone.

12.1. Evaluators conclusions to clinical data submitted for second round evaluation

The responses to the safety questions were acceptable to the clinical evaluator.

The inconsistency between the EU RMP 'missing information' and the proposed Indication in Australia may have implications for prescriber education. This is drawn to the attention of the RMP evaluator and the Delegate.

13. Second round benefit-risk assessment

13.1. Second round assessment of benefits

The benefits of pirfenidone are unchanged from those identified in the First Round assessment of benefits.

13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of pirfenidone are unchanged from those identified in the First Round assessment of risks.

13.3. Second round assessment of benefit-risk balance

The clinical evaluator considers that based on the available data the benefit-risk balance of pirfenidone 'Esbriet, given the proposed usage, is favourable.

14. Second round recommendation regarding authorisation

The clinical evaluator considers that the data provided support registration of pirfenidone for the proposed Indication:

'Esbriet is indicated for the treatment of idiopathic pulmonary fibrosis (IPF)'.

15. References

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Form for Australian PI ARGPM Guidance 8 Product information 8.3

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