16 December 2010

EMA/CHMP/115147/2011
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Esbriet

International Nonproprietary Name: pirfenidone

Procedure No. EMEA/H/C/002154

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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Table of contents

List of abbreviations

AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC	area under the curve (specifically area under the concentration versus time curve)
CI	confidence interval
CL_t/F	apparent total plasma clearance
C_{max}	maximum concentration
CNS	central nervous system
CYP	cytochrome P450
DL_{CO}	carbon monoxide diffusing capacity
ERS	European Respiratory Society
FVC	forced vital capacity
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GI	gastrointestinal
HPS	Hermansky-Pudlak syndrome
IL-1β	interleukin-1-beta
IV	intravenous
Hgb	haemoglobin
HR	hazard ratio
HRCT	high-resolution computed tomography
IPF	idiopathic pulmonary fibrosis
ITT	intention to treat
LFT	liver function test
6MET	6-minute exercise test
LPS	lipopolysaccharide
6MWT	6-minute walk test
PD	pharmacodynamic(s)
PF	pulmonary fibrosis
PFS	progression-free survival
PK	pharmacokinetic(s)
SAE	serious adverse event
SD	standard deviation
SpO_2	oxygen saturation by pulse oximetry
SmPC	Summary of Product Characteristics
$t_{1/2}$	terminal half life
t.i.d.	three times daily (= *ter id die*)
TK	toxicokinetic(s)
TLC	total lung capacity
T_{max}	time to maximum plasma concentration
TNF	tumor necrosis factor
UCSD SOBQ	University of California at San Diego Shortness-of-breath Questionnaire
ULN	upper limit of normal
USA	United States of America
VC	vital capacity

1. Background information on the procedure

1.1. Submission of the dossier

The Applicant InterMune Europe Ltd. submitted on 26 February 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Esbriet, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 February 2009.

Esbriet was designated as an orphan medicinal product EU/3/04/241 on 16 November 2004 in the following indication: the treatment of idiopathic pulmonary fibrosis (IPF). IPF is estimated to affect not more than 3 in 10,000 persons in the EU population. The Applicant applied for the following indication: Treatment of Idiopathic Pulmonary Fibrosis (IPF).

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Esbriet as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website:

ema.europa.eu/Find medicine/Human medicines/Rare disease designations.

The legal basis for this application refers to:

A - Centralised / Article 8(3) / New active substance.

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on Applicants' own tests and studies and bibliographic literature supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/129/2008 for the following condition:

- Idiopathic Pulmonary Fibrosis (IPF)

on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable

Protocol Assistance:

The Applicant received Protocol Assistance from the CHMP in 2005, 2007 and 2008. The Protocol Assistance pertained to non-clinical and clinical aspects of the dossier.

Licensing status

Pirfenidone under the tradename Pirespa Tablets 200 mg has been given a Marketing Authorisation in Japan in October 2008 for the treatment of IPF.

A new drug application for Esbriet was filed in the US where the product received a complete response letter.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Ian Hudson** Co-Rapporteur: **David Lyons**

- The application was received by the EMA on 26 February 2010.
- The procedure started on 24 March 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 June 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 June 2010.
- During the meeting on 22 July 2010, the CHMP agreed on the consolidated List of Questions to be sent to the Applicant. The final consolidated List of Questions was sent to the Applicant on 22 July 2010.
- The Applicant submitted the responses to the CHMP consolidated List of Questions on 12 October 2010.
- The Rapporteurs circulated the Joint Assessment Report on the Applicant's responses to the List of Questions to all CHMP members on 29 November 2010.
- During the meeting on 13-16 December 2010, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Esbriet on 16 December 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 15 December 2010.

2. Scientific discussion

2.1. Introduction

Problem statement

Idiopathic pulmonary fibrosis (IPF) is a rare disease of unknown etiology that is characterised by progressive fibrosis of the interstitium of the lung, leading to decreasing lung volume and progressive pulmonary insufficiency. IPF is a well-recognised and distinct interstitial lung disease with unique histopathologic, clinical and prognostic characteristics (American Thoracic Society/European

Respiratory Society (ATS/ERS), 2000; ATS/ERS, 2002). IPF is most prevalent in middle aged and elderly patients, and usually presents between the ages of 40 and 70 years (ATS/ERS 2000). Many patients experience long periods of relative stability but acute episodes of rapid respiratory deterioration may result in death. Most patients die of respiratory failure. Median survival, as described across a range of studies, is only 2 to 5 years after diagnosis. Despite continued improvement in the understanding of the pathogenesis of IPF, there remain no approved therapies or medications in the European Union, nor has the prognosis been substantially altered over the last two decades.

About the product

Pirfenidone (5-methyl-1-phenyl-2-[1H]-pyridone) is an immunosuppressant (ATC code L04AX05). The mechanism of action has not been fully established. However, existing data suggest that pirfenidone exerts both antifibrotic and anti-inflammatory properties.

The proposed indication for pirfenidone is for the treatment of adult patients with IPF. The finally approved indication is as follows: "Esbriet is indicated in adults for the treatment of mild to moderate Idiopathic Pulmonary Fibrosis (IPF)."

The drug product is an immediate release hard capsule containing 267 mg of pirfenidone drug substance. The recommended daily dose is three 267 mg capsules three times a day with food for a total of 2403 mg/day. The posology stated in the SmPC requires dose titration to the MDD over two weeks: days 1 to 7 – 801 mg/day, days 8 to 14- 1602 mg/day, and day 15 onwards – 2403 mg/day.

Type of Application and aspects on development

This application has been submitted as complete and independent application according to Article 8.3 of Directive 2001/83/EC meaning that it includes complete quality data, non-clinical and clinical data based on applicants' own tests and studies and bibliographic literature supporting certain tests or studies.

Pirfenidone was designated as an orphan medicinal product in the following indication: the treatment of idiopathic pulmonary fibrosis (IPF). IPF is estimated to affect not more than 3 in 10,000 persons in the EU population.

With regard to the paediatric development, a product specific waiver for all subsets of the paediatric population has been granted on the grounds that the disease or condition, Idiopathic Pulmonary Fibrosis, for which the specific medicinal product as intended, occurs only in the adult population.

For the development of pirfenidone Protocol Assistance was received from the CHMP pertaining to non-clinical and clinical aspects of the dossier.

2.2. Quality aspects

2.2.1. Introduction

Esbriet is presented as hard gelatin capsules containing 267 mg of pirfenidone as the active substance. The capsules have a blue opaque body and gold opaque cap imprinted with "InterMune 267 mg" in brown ink and contain a white to pale yellow powder.

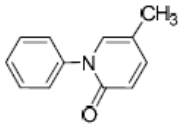
Excipients used in the preparation of Esbriet are well known excipients used in capsule preparations such as microcrystalline cellulose, croscarmellose sodium, povidone, magnesium stearate (present in

capsule content); gelatin and titanium dioxide (E 171) and indigo carmine (E132) (present in capsule shell: body); gelatin, titanium dioxide (E171), yellow iron oxide (E172), red iron oxide (E172) (present in capsule shell: body) and shellac, iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172) (present in brown ink S-1-16530).

The capsules are packed in polyvinyl chloride / polyethylene / polychlorotrifluoroethylene / aluminium foil (PVC/PE/PCTFE/alu) blisters or in white high density polyethylene (HDPE) bottles (250 ml) with child - resistant closure system.

2.2.2. Active Substance

Pirfenidone is chemically designated as 5-Methyl-1-phenyl-2-1(*H*)-pyridone and has the following structure:



Pirfenidone is white to pale yellow powder. It is freely soluble in methanol, ethyl alcohol, acetone, and chloroform, sparingly soluble in 1.0 N HCl, water and 1.0 N NaOH. Dissolution in water is pH independent. Pirfenidone does not possess any chiral centres and therefore is not subject to stereoisomerism. The acid dissociation constant, pKa, was calculated to be (-0.2 ± 0.6) and is consistent with the observation that pirfenidone behaves as a neutral compound in aqueous environment. The substance is not hygroscopic. Melting range is between 106°C and 112°C.

Pirfenidone primarily exists in a single stable crystalline form designated as Form A. Sufficient evidence was provided to prove that the form A is obtained by the utilised manufacturing process.

Particle size distribution of the active substance is controlled.

Manufacture

Information about manufacturing process of pirfenidone has been provided using Active Substance Master File (ASMF) procedure. The synthesis is simple and consists of two steps. Sufficient information regarding the manufacturing process, materials, critical steps and intermediates, process validation and manufacturing process development have been provided in the restricted part of the ASMF.

Confirmation of the chemical structure of pirfenidone was provided by UV, IR, ^{1}H-NMR, ^{13}C-NMR as well as by mass spectral analysis. The IR, NMR and MS spectrum assignations were consistent with the declared chemical structure.

In addition the potential for polymorphism and other solid-state forms of pirfenidone has been investigated. The pirfenidone drug substance was characterised by Raman spectroscopy, X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), dynamic vapour sorption (DVS), and thermogravimetry coupled with Fourier-transformed infrared spectroscopy (TG-FTIR). Particle size distribution profile was also investigated. Laser diffraction particle size distribution analysis and data for various particle sizes for a representative batch of pirfenidone was provided.

Potential impurities have been well discussed in relation to their origin (raw material, manufacturing process and degradation products) and potential carry-over into the final drug substance. A very detailed investigation has been carried out in all possible related substances and inorganic impurities that may be present in the drug substance.

The possibility of genotoxic impurities has been considered. Results of structural alert screening and genotoxicity testing confirm that potential genotoxicity of impurities in pirfenidone was not a concern.

Specification

The drug substance specification includes tests for physical appearance, identification (IR and UV), water content (Karl Fisher), residue on ignition, sulphated ash, heavy metals, related substances (HPLC), assay (HPLC), loss on drying, particle size distribution and microbiological purity (total aerobic microbiological count, total combined yeast and mould count, specified microorganisms: *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella spp*.).

A detailed description for all analytical methods was provided. Some of the proposed methods are in accordance with the Ph Eur. Complete method validation data was provided for the non compendial (in-house) analytical methods. Appropriate HPLC methods are used for assay and related substances and they have been appropriately validated.

The assay analysis is performed by an HPLC method with UV detection at the maximum absorption of the defined pirfenidone peak. The method has been validated with regard to specificity, linearity, range, accuracy, precision, robustness, system suitability and stability of solutions. All chromatograms were presented including standard, sample and stress chromatograms

Related substances are determined by an HPLC method with UV detection. The results for known impurities are calculated relative to the response of the impurities reference standards and unknown impurities are calculated to the response of pirfenidone reference standard peak.

The method has been validated with regard to specificity, linearity, range, limit of quantification (LOQ), limit of detection (LOD), accuracy, precision, robustness, system suitability and stability of solutions. All chromatograms are presented including standard, sample and stress chromatograms. The results indicate that impurities in pirfenidone can be determined accurately over the range evaluated.

Particle size is measured by laser diffraction and it has been validated for repeatability and ruggedness to confirm its suitability.

In general specification limits and analytical methods proposed are suitable to control the quality of the drug substance.

Batch analysis results for pirfenidone have been presented. All batches were manufactured by the proposed commercial manufacturer according to the process described in the ASMF. All batches show the same impurity profile. It can be concluded that the batch analysis results indicate that the process is under control. Active substance of a high purity is consistently produced.

Stability

Stability studies were performed according to ICH requirements. Sixty months long term stability data (25°C ± 2°C / 60%RH ± 5%) and 6 months accelerated data (40°C ± 2°C / 75%RH ± 5%) were presented for four batches. These batches were representative of the commercial drug substance. The stability samples were packaged in a container closure system which mimicked the one which will be used for the commercial drug substance. All results of the key parameters tested show no or a very slight change vs. the initial time point testing. This was also the case for the batches stored at accelerated conditions. It can be concluded that the drug substance manufactured by the described process is very stable over a proposed re-test period.

Forced degradation studies have also been performed in order to further characterise the drug substance. In the solid state, no degradation products have been found under stress conditions such as acid, base, oxidation, heat or light. In the photostability study conducted in accordance with ICH Q1B guideline conditions, good stability of pirfenidone in the solid state when exposed to light was confirmed. Degradation has only been observed under light exposure of pirfenidone in solution.

It has been confirmed that the first three production-scale batches will be tested according to the protocol, and thereafter one batch per year will be tested for stability. In accordance with EU GMP guidelines[1], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The aim of pharmaceutical development program was to obtain a hard gelatin capsule dosage form that would deliver a daily dose of 2400 mg in a 3 divided doses (800 mg per dose). To facilitate swallowing, this 800 mg dose was subdivided into three fractions considering that idiopathic pulmonary fibrosis occurs generally in an older population who may have difficulty in swallowing large oral dosage forms. Each capsule therefore contains 266.66 mg (267 mg) pirfenidone, giving a daily dose of 2403 mg. Small (size 1) hard gelatin capsules have been chosen.

The formulation and general manufacturing process for the capsules has been consistent throughout the clinical development programme and 267 mg capsules were used in a safety and pharmacokinetic phase 1 and phase 3 clinical trials.

Standard manufacturing processes have been developed. The proposed final dosage form is an immediate release capsule. Compatibility with excipients was evaluated by preparing mixtures of pirfenidone with proposed excipients. The mixtures were stored under accelerated conditions and evaluated. The mixtures were also evaluated by x-ray powder diffraction (XRPD) to monitor structural changes of pirfenidone. Analysis indicated that there was no chemical or structural incompatibility between pirfenidone and the tested excipients. Based on the data submitted a filler (microcrystalline cellulose), a binder (povidone), a disintegrant (croscarmellose sodium), and a lubricant (magnesium stearate) were considered appropriate and determined to be compatible with the drug substance.

Various variations of the final formulation were investigated in order to achieve the desired dissolution profile. Further amendments to the manufacturing process and processing were made in order to optimise the manufacturing process.

The in vitro dissolution method was developed to monitor consistency of drug release. The discriminatory power of the method has been appropriately demonstrated.

Manufacturing process development has been well documented. The manufacturing process used for the clinical trials and commercial batches has not substantially changed. It has been shown that the manufacturing process is robust and it does influence the polymorphic form. Choice of the process was considered justified and the critical process parameters and process equipment are generally satisfactorily identified.

It can be concluded that the formulation development of the product was generally described satisfactorily. The key critical parameters were identified and successfully evaluated. The formulation

[1] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

and choice and optimisation is satisfactory. The proposed dissolution method was considered acceptable.

Adventitious agents

Among excipients used in the drug product only gelatin (component of the capsule shell) is of animal origin. For gelatin Ph Eur TSE Certificates of Suitability were provided.

Magnesium stearate used in the formulation is of vegetable origin.

Manufacture of the product

The manufacturing process is sufficiently described as well as a process flow diagram provided. The process comprises a standard series of steps followed by encapsulation. Critical steps have been identified and relate to the established in-process controls. The Applicant has set the ranges and target values for critical process parameters based on experience of manufacturing similar products, but more importantly based on experimental data for the manufacture of a range of batches of the finished product.

The Applicant has provided process parameters and batch data for two full scale batches as well as for two final blend and finished product testing pilot scale clinical and one pilot scale stability batches. The data shows consistent manufacture and is considered sufficient for this standard manufacturing process.

The utilised manufacturing process is considered standard and at the time of submission only process validation protocol was provided. This was considered acceptable. The protocol includes suitable tests to monitor the steps of the process and includes homogeneity testing of the. Formal full scale validation of the commercial process will be conducted in accordance with the agreed process validation protocol.

Product specification

The drug product specifications include tests for appearance, identity (UV and HPLC), uniformity of dosage units (mass variation), dissolution (with UV detection), water content (Karl Fisher), assay (HPLC), related substances (HPLC), microbiological purity (total aerobic microbiological count, total combined yeast and mould count, specified microorganisms: *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Salmonella spp*.) and identity tests for the capsule colourants: iron oxides, titanium dioxide, indigo carmine.

The proposed specifications are in line with the ICH 6A and the Ph Eur monograph for capsules.

Analytical methods have been sufficiently described, some of them are compendial methods described in the Ph Eur. Adequate validation data have been provided for non-compendial methods.

Assay and related substances are determined by an HPLC method with UV detection. System suitability criteria were appropriately investigated and set in line with standard requirements. The procedure has been validated for specificity, limit of detection (LOD), limit of quantification (LOQ), linearity, accuracy/recovery, precision, range, robustness and stability of solutions. The method has been demonstrated to be capable of providing accurate results, with satisfactory precision over an appropriate range for quantification of pirfenidone and related substances.

Dissolution is determined using Ph Eur method. Pirfenidone content is measured by UV using pirfenidone reference standard. The procedure for the determining dissolution rate has been validated

for specificity, linearity, accuracy, precision and intermediate precision, range, stability and robustness. Effect of filtration was also investigated for both sample and standard solution. The method is adequately described and it has been demonstrated to be capable of providing accurate results, with satisfactory precision over an appropriate range. The validation has been carried out in accordance with ICH.

The Applicant has submitted batch analyses data all manufactured at the proposed manufacturing site.. Batch analysis results demonstrated compliance with the proposed specification and confirmed consistency and uniformity of the product. The results were consistent from batch to batch and proved that the product can be manufactured reproducibly according to the agreed specifications.

Stability of the product

Stability studies were performed on 3 batches manufactured at the proposed manufacturing site and packed in the container closure systems (bottles and blisters) proposed for the commercial product.

Studies were carried out in accordance with current ICH/CHMP guidelines. Stability data submitted covers long-term 24 months at 25°/60%, 30°/65% and 30°/75% RH and 6 months accelerated at 40°/75% RH for both packaging materials.

Photostability testing was carried out on one batch. The capsules are not sensitive to light.

Furthermore the Applicant has committed to monitor the primary stability batches through the proposed shelf-life. The first three commercial scale batches of the product packaged in HDPE bottles will be placed on long-term stability at 25°C/60% RH conditions and on accelerated stability at 40°C/75% RH in accordance with the agreed stability protocol. For the blister packaging a bracketing approach was proposed. The stability blisters will be placed on long-term stability at 25°C/60% RH conditions and on accelerated stability at 40°C/75% RH conditions. In addition, one batch of each packaging of the drug product will be placed annually on long-term stability study.

The overall stability data showed that Esbriet is chemically, physically and microbiologically stable. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

In accordance with EU GMP guidelines[2], any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information about the active substance, pirfenidone, has been provided using the Active Substance Master File Procedure. The chemical-pharmaceutical documentation was of acceptable quality.

The active substance is relatively simple and has been satisfactorily characterised, the synthesis is well controlled. The designated starting material is considered acceptable and does not employ any potentially hazardous reagents, or catalysts.

Known and potential impurities have been satisfactorily addressed. The drug substance is stable under stressed conditions, except when in solution and exposed to light.

The control tests and specifications for drug substance product are in line with the requirements of ICH Q6A and Ph Eur requirements for substances for pharmaceutical use and considered satisfactory.

[2] 6.32 of Vol. 4 Part I of the Rules Governing Medicinal Products in the European Union

A retest period was supported by satisfactory stability studies that show that the drug substance is stable, when in solid form.

The drug product is an immediate release hard capsule containing 267 mg of pirfenidone. The composition of the finished product has been described, and all excipients have been fully characterised.

The development pharmaceutics has been satisfactorily described. The excipients are well established and used in acceptable quantities. Their function has been satisfactorily described.

The formulation is considered satisfactorily justified.

The method of manufacture is considered standard and has been satisfactorily described, including hold times and in-process tests. The scale of manufacture is supported by batch data. The Applicant has provided process parameters and batch data for two full scale batches as well as for pilot scale batches. The data shows consistent manufacture and is considered sufficient for this manufacturing process. A satisfactory validation protocol for three commercial scale batches has been provided.

Specifications are provided for the excipients, which include appropriate functional tests, where appropriate. Compliance with current TSE requirements is satisfactory. The gelatin excipient is supported by EDQM TSE certificates of suitability.

The scope of the finished product specification complies with ICH Q6A and the Ph Eur requirements for hard capsules, limits comply with regulatory requirements and are in line with batch data. The analytical methods and validation data are satisfactory. The batch data demonstrate consistent manufacture.

The stability programme is considered satisfactory. The batches placed on stability are considered representative of the product to be marketed. The results generated during the stability studies support the proposed shelf life and storage conditions as defined in the SmPC.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The drug substance and the drug product have been appropriately characterised and generally satisfactory documentation has been provided. The results indicate that the drug substance and the drug product can be reproducibly manufactured and therefore the product should have a satisfactory and uniform performance in the clinic.

2.3. Non-clinical aspects

2.3.1. Introduction

The Applicant has conducted non-clinical programme that is generally acceptable and in line with the advice given by the CHMP.

The pivotal toxicology and safety pharmacology studies were reported to be GLP-compliant. The main bioanalytical validation and toxicokinetic bioanalyses were also GLP-compliant.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The primary pharmacodynamic actions of pirfenidone are suggested to relate to its anti-fibrotic and anti-inflammatory actions and were characterised in in vitro experiments and in vivo models.

In vitro, pirfenidone suppressed the proliferation of fibroblasts, inhibited lipopolysaccharide (LPS)-stimulated release of platelet-derived growth factor AB and of transforming growth factor (TGF-β1), inhibited collagen synthesis in fibroblast cultures and promoted the release of collagenase from fibroblasts over the concentration range 5.5 to 185 µg/mL. Concentration-dependent inhibition of the release of LPS-induced tissue necrosis factor-α (TNF-α) was observed with respective median (50%) inhibitory concentration (IC50) values of 48.3 and 30 µg/mL in THP-1 (human monocytic leukaemia cells) and RAW264.7 cells (mouse peritoneal macrophage cell line). These in vitro effects were seen at clinical concentrations or low multiples of clinical concentrations; a daily clinical dose of 2403 mg resulted in a C_{max} of 14.7 µg/mL and AUC_{0-24} of 180 µg·h/mL.

In vivo, a range of studies was conducted in models of fibrosis in mice, rats, hamsters and dogs. Relevant pharmacodynamic activity was found in:

- a mouse model of bleomycin-induced lung fibrosis (investigating treatment and prophylaxis via oral administration)
- a mouse heterotropic tracheal allograft model (investigating prophylaxis via dietary administration)
- a rat model of bleomycin-induced lung fibrosis (investigating prophylaxis via dietary administration)
- a rat orthotopic left lung transplant model (investigating treatment via dietary administration)
- a hamster model of bleomycin-induced lung fibrosis (investigating prophylaxis via dietary administration)
- a canine model of congestive heart failure

Primary in vitro and in vivo pharmacodynamics studies were conducted with the major metabolite in animal and human plasma, 5-CA pirfenidone, and 5-OH pirfenidone (present in mouse and rat plasma but not detectable in dog or human plasma). 5-CA pirfenidone did not exhibit any pharmacological activity in vitro or in vivo. 5-OH pirfenidone was pharmacologically active in vivo and in vitro and was approximately 50% as active as pirfenidone.

Secondary pharmacodynamic studies

Pirfenidone demonstrated anti-inflammatory effects in rat models of induced edema and adjuvant-induced arthritis. No effects on humoral or cellular immunity were observed in mice.

Safety pharmacology programme

A comprehensive receptor and enzyme screening battery did not reveal any binding that was likely to have any appreciable effects at clinical exposures.

Pirfenidone demonstrated minimal hERG inhibition (16%) at concentrations of 185 µg/mL, with an IC_{50} of 925 µg/mL (5000 µM) and had no effect on action potentials in guinea pig ventricular papillary muscle. In anaesthetised rats, decreased blood pressure was seen at ≥30 mg/kg and increased heart rate at 100 and 300 mg/kg. Premature ventricular contractions occurred continuously in 2/6 rats at 300 mg/kg. Similar effects were seen in conscious rats, although decreased blood pressure was only seen at 300 mg/kg, and AV block was observed in some animals at 100 and 300 mg/kg. Similar effects were not observed in dogs.

No consistent effects on blood pressure or ECG were seen in dogs at 300 mg/kg. Although prolongation of QT and QTc intervals was seen at 100 mg/kg, apparent shortening of QT interval was seen in the

same study at 300 mg/kg; there was also an increase in heart rate. A single oral dose of 100 or 300 mg/kg gives C_{max} values approximately 3 and 6.5 times the clinical C_{max}. In a follow-up study in anaesthetised dogs dosed by the intraduodenal route, no effect on ECG was observed, whilst an increase in heart rate and decrease in blood pressure were seen at 100 and 300 mg/kg. Measured C_{max} values at 100 and 300 mg/kg were approximately 7 and 14 times the clinical C_{max}.

No consistent effects on blood pressure or ECG were seen in dogs given intravenous (IV) pirfenidone.

5-CA pirfenidone had no effects on hERG channel inhibition or action potential at 1000 µM (215 µg/mL).

No consistent effects on the respiratory system were seen following single-dose intraduodenal administration up to 300 mg/kg in anaesthetised rats apart from increased respiratory volume. No consistent effects on the respiratory system were seen following single-dose oral (up to 300 mg/kg) or IV (5-minute bolus dose of 0.9, 3.1 or 6.1 mg/kg/5 min followed by 1-hour infusion with 8.8, 29.3 or 58.7 mg/kg/h) administration in dogs.

Transient neurobehavioural effects including sedation, abnormal posture, abnormal limb position, staggering gait, ptosis and hypothermia were seen in mice given single oral doses of 30 to 300 mg/kg. At an oral dose of 300 mg/kg, pirfenidone caused a prolongation of pentobarbital-induced sleeping time; the electro-shock and pentylenetetrazole-induced convulsion thresholds were significantly higher.

Decreased gastric emptying and decreased small intestinal transport were seen in rats given a single oral dose of up to 300 mg/kg.

Pharmacodynamic drug interactions

The absence of studies on pharmacodynamic interactions was justified as no specific potential interactions were identified from the nonclinical data which were considered relevant for further nonclinical investigation. The potential for relevant drug interactions was evaluated clinically.

2.3.3. Pharmacokinetics

Pharmacokinetic results were similar for unlabelled material from PK and TK studies in mice, rats, guinea pigs and dogs. Pirfenidone is rapidly absorbed with t_{max} of 0.5 hour, and extensively metabolised in all species examined with terminal elimination half-life ranging between 1.6 to 4.8 hours in mice, rats and dogs and similar to the half-life in humans. Bioavailability was high at 97% in rats and 79% in dogs. In mice and rats at 30 to 2000 mg/kg, pirfenidone showed an approximately dose-proportional increase in absorption. No meaningful changes in pharmacokinetic indices were seen with repeated dosing.

Tissue distribution studies provided little evidence to suggest accumulation of pirfenidone and its metabolites in any tissues; adequate exposure was shown in the presumptive target organ, the lung. In mice, peak tissue radioactivity occurred within 5 minutes of dosing and well-perfused tissues, such as kidney>liver>lung, had the highest levels of radioactivity.

Total radioactivity was widely distributed following oral administration to rats and was eliminated from the majority of tissues at a similar rate to that from plasma. The highest initial levels were seen in the pancreas, spleen and adrenal glands. High levels were later seen in the kidney, probably reflecting its role in. In pigmented rats, no selective distribution or retention of radioactivity was noted in melanin-containing tissues. Overall, there was no selective distribution of radioactivity in tissues recognised as potential targets for clinical adverse effects.

In vitro, protein binding at a concentration of 100 µg/mL approximated 30% in the mouse and the rat while in the dog and human it approximated 50%. In the human, binding was predominantly to albumin. In humans in vivo, serum protein binding ranged from 54% to 62%. It is unlikely that there will be any clinically significant protein binding-based drug-drug interactions. Little or no effect of pirfenidone on the P-gp transporter system was observed. Therefore, it is unlikely that clinically relevant drug-drug interactions will occur. In rats, approximately 11% of pirfenidone-associated material underwent entero-hepatic recirculation.

Following a single oral dose of [14C]-pirfenidone to rats on Gestation Day 19, the maximum concentration of radioactivity in the uterus and mammary gland (21 to 26 µg Eq/g) and fetal organs/tissues (16 to 21 µg Eq/g) was seen 30 minutes after dosing. Disappearance of radioactivity from fetal tissues and blood was rapid but the concentration ratios of radioactivity in the amniotic fluid relative to the maternal plasma were 0.09, 0.38, 0.46 and 9.44 at 5 and 30 minutes and 8 and 24 hours respectively. The 9-fold increase at 24 hours at the top dose indicates the potential for accumulation and recirculation in the fetus; it is noted however that material in the amniotic fluid is likely to represent metabolites rather than the parent compound. These findings are adequately reflected in the SmPC.

In lactating rats given [14C]-pirfenidone orally at 100 mg/kg on Postpartum Day 12, plasma radioactivity reached a peak concentration of 35.9 µg Eq/mL by 0.3 hours with an elimination half-life of 3.4 hours. The radioactivity was rapidly transferred into the milk with a peak concentration of 31.3 µg Eq/mL by 0.4 hours with an elimination half-life of 4.7 hours. These findings are adequately reflected in the SmPC.

The metabolism of pirfenidone was rapid in rats and dogs and was mediated predominantly by CYP1A2 in humans. Clinical co-administration of fluvoxamine, a strong inhibitor of CYP1A2, was associated with markedly increased pirfenidone exposure and its concomitant use is contraindicated in the SmPC.

The metabolite profile of pirfenidone was qualitatively similar between laboratory species and humans with the major circulating metabolite being 5-CA pirfenidone. In rats and mice, the plasma levels of the 5-CA pirfenidone metabolite were substantially higher than that of the parent pirfenidone while the plasma levels of 5-CA pirfenidone approximated 50% of pirfenidone levels in dogs and humans. The elimination of pirfenidone was rapid and occurred primarily via metabolism. The primary route of excretion of pirfenidone was via the urine as the 5-CA pirfenidone metabolite and appeared to be independent of the dosing route in rats and dogs. Little or no parent compound was found in the urine of rats, dogs, mice and humans. About 5 to 10% in rats and about 10 to 15% in dogs were excreted faecally via biliary excretion. The faecal radioactivity was associated with 5-CA pirfenidone in rats and 5-CA pirfenidone and the aglycon of 3-O-glucuronide in dogs, accounting for 29% and 25% of radioactivity respectively.

2.3.4. Toxicology

Rats and dogs were shown to have similar metabolic profiles to humans and were thus selected as suitable species for toxicology studies. Pirfenidone has been studied in single-dose studies in mice, rats and dogs, in repeat-dose studies in mice and rats by the dietary route, by oral gavage and by intravenous infusion in rats and by oral capsule in dogs. Carcinogenicity studies by the dietary route were conducted in mice and rats. Reproductive toxicity studies were conducted in rats and rabbits and a battery of genotoxicity studies has been performed. Because pirfenidone absorbs light in the visible

range, phototoxicity and photogenotoxicity studies were also conducted with both pirfenidone and the 5-CA metabolite.

Single dose toxicity

Eleven single-dose oral toxicity studies were conducted; three studies, including toxicokinetics, were conducted and are considered pivotal: a mouse study (NCR001), a rat study (NCR140) and a dog study (PCLN-PIRF-088).

Hypoactivity, prone position and abnormal gait were observed in mice at all dose levels, with lateral recumbency and dyspnoea at 1000 mg/kg and above with 4/4 males and 3/4 females dying at 2000 mg/kg (NCR001). At 2000 mg/kg, the C_{max} of pirfenidone was 554.6 (males) and 488.4 (females) µg/mL; the C_{max} of 5-CA pirfenidone was 841.9 µg/mL in males.

In rats, abnormal gait, reduced activity, lateral recumbency, respiratory depression and pupil dilation were observed at all dose levels, with reduced body temperature at 1000 mg/kg in fasted rats with 1/6 males and 3/6 females dying (NCR140). Because of the high death rate, no TK indices were determined in fasted rats given 1000 mg/kg. In fed animals at 1000 mg/kg, the C_{max} of pirfenidone was 202.3 (males) and 196.7 (females) µg/mL and the AUC_{0-24h} was 600.6 (males) and 1042.1 (females) µg·h/mL.

In dogs, emesis, weakness of limbs, decreased activity and salivation were observed at both dose levels with mydriasis, vocalisation, and tremors at 1000 mg/kg (PCLN-PIRF-088). There were no deaths and no effects on body weight, food consumption or urinalysis attributable to pirfenidone. Transient effects on haematology and serum chemistry were observed; these were not considered to be biologically meaningful in that the findings were not necessarily seen in both animals at a given dose level or were not dose-related. A decrease in thymus weight was seen in both animals at 1000 mg/kg which was accompanied by very slight cortical atrophy in the male only. At 1000 mg/kg, the pirfenidone C_{max} values were 117.0 (male) and 167.3 (female) µg/mL and the AUC_{0-24h} values were 220.4 (male) and 509.7 (female) µg·h/mL.

Repeat dose toxicity

The predominant observation in repeat-dose toxicology studies up to 6/9 months in duration included altered posture, hypoactivity, altered gait and sedation. These signs coincided with plasma t_{max} and were mitigated by lowering C_{max} such as through dosing via the diet or by dividing the daily dose. The most consistent target-organ effect seen across all species was increased liver weight. This increase in liver weight was often accompanied by hepatic centrilobular hypertrophy. Except for a 3- to 4-fold increase in alkaline phosphatase in dogs, there were no remarkable changes in markers of liver function or injury such as ALT, AST and bilirubin. Therefore, the hepatic effects appear not to represent specific hepatotoxicity caused by pirfenidone but rather a consequence of hepatic metabolism of pirfenidone and induction of CYP enzymes. The pattern of CYP enzyme induction observed in rodents resembled that of phenobarbital.

The exposure at the highest doses evaluated in chronic toxicology studies in rats and dogs were 6 times and 12 times, respectively, the C_{max} in IPF patients and 2 times and 4 times, respectively, the AUC. In repeat-dose chronic toxicity studies in rats and dogs, only unchanged pirfenidone was analysed. However, based on metabolic data in PK studies and shorter-term toxicology studies, the multiples of exposure in toxicology species for the 5-CA pirfenidone metabolite would be equal to or higher than the exposure to that metabolite in humans. These margins have been calculated without taking account of plasma protein binding.

Given the difficulty in achieving sustained large exposure multiples in animals, because of the severity of the physical signs, a study in rats was performed using continuous IV administration. Similar adaptive changes to those seen in oral studies, but no other anatomical pathology findings, were associated with the continuous infusion of pirfenidone to SD rats at doses up to 1625 mg/kg/day for 4 weeks. This dose resulted in the death of four females; one female at 1000 mg/kg also died.

All the findings in the repeat-dose toxicity studies were found to be either wholly or partially reversible, and there was no evidence of delayed toxicity. The NOAELs in the 3- and 9-month studies in terms of systemic toxicity were 200 mg/kg/day which correlates with $AUC_{0\text{-}24h}$ values of 535.1/488.3 and 660.6/479.1 µg·h/mL (male/female animals) in the 3- and 9-month studies, respectively.

Genotoxicity

The potential for genotoxicity has been evaluated in several studies: in vitro (Ames tests and chromosome aberrations) and in vivo (micronucleus test in mice and unscheduled DNA synthesis (UDS) test in rats). 5-CA pirfenidone has been shown to be present in in vitro studies with rat liver microsomes and also in vivo and thus has also been implicitly evaluated in these studies. All these genetic toxicology studies were negative and neither pirfenidone nor the 5-CA metabolite is genotoxic.

Carcinogenicity

Oral administration of pirfenidone via the diet to B6C3F1 mice at doses of 800, 2000 or 5000 mg/kg/day for 104 weeks resulted in an increase in liver tumours. Similarly, oral administration of pirfenidone via the diet to F344 rats at doses of 375, 750 or 1500 mg/kg/day for 104 weeks resulted in increases in liver tumours in both sexes and uterine tumours in females. The pirfenidone-related liver tumours in rats and mice, and uterine tumours in rats, appear to be rodent- and species-specific and of questionable clinical relevance.

In hepatic assays in rats and mice, a significant induction of CYP enzymes was observed in both species treated with pirfenidone. The hepatic CYP induction, pattern of isoenzymes induced, absence of mutagenicity/clastogenicity, and the nature of hepatic and thyroid pathological changes (rat) that are seen with pirfenidone are similar to those seen with phenobarbital. Phenobarbital is a prototype rodent hepatocarcinogen that induces tumours through a non-genotoxic mechanism involving liver hyperplasia. Hepatic tumours produced by this mechanism in rodents are not considered to be relevant to humans. Mechanistic studies in female rats showed a pirfenidone treatment-related increase in extra-cellular dopamine in the hypothalamus. In this respect, pirfenidone appears to behave like dopamine agonists or dopamine releasers.

In another study, it was also noted that there was a trend for higher oestradiol levels and lower progesterone and prolactin levels, and higher oestradiol to progesterone ratio after pirfenidone administration. These combined results indicate that the uterine tumours in the rat carcinogenicity study are probably related to a chronic dopamine-mediated sex hormone imbalance. It is suggested that the prolactin-inhibiting action of dopamine may result in a high oestrogen/progesterone ratio that could cause uterine neoplasms. These endocrine mechanisms believed to be involved in the rodents are not present in humans.

Reproduction toxicity

Two combined fertility and embryofetal toxicity studies were performed in rats, one by the dietary route and the second by oral gavage. An embryofetal toxicity study was conducted in rabbits and a pre- and post-natal study in rats, both by oral gavage.

In the dietary study, significant decreases in body weight and food consumption were observed in males and females; in females, these correlated with depressed gravid uterine weights and fetal body weights. These findings are adequately described in the SmPC. There were no effects on fertility and fetal morphological development was unaffected. The NOAEL for fertility and fetal development was concluded to 900 mg/kg/day.

In the study by gavage, females receiving 450 or 1000 mg/kg/day exhibited a dose-related prolongation of the oestrous cycle and a high incidence of irregular cycles. There were no gross, skeletal or visceral variations, malformations or ossification changes attributable to pirfenidone. There was no evidence of any adverse effects on male (including sperm counts and motility) and female fertility, increased embryolethality or teratogenicity in rats. The NOAELs were concluded to be 50 mg/kg/day in males, and in pregnant rats and <50 mg/kg/day in females before mating for general toxicity, and 150 mg/kg/day for reproductive toxicity in females and 1000 mg/kg/day for treated males and developmental toxicity.

In an embryo-fetal developmental toxicity study in rabbits, lower food intake was noted at 100 and 300 mg/kg/day with lower body weight gain at 300 mg/kg/day. There were no effects on fetal or placental weights and there was no evidence of increased embryolethality or of teratogenicity: the NOAEL was concluded to be 30 mg/kg/day for general and reproductive toxicity in dams and 300 mg/kg/day for developmental toxicity in fetuses.

In a pre-and post-natal study in rats, deaths occurred in F0 animals at 1000 mg/kg/day and a statistically significant prolongation of gestation period was noted (22.7 days versus 22.2 days in control). Also at 1000 mg/kg, there was a reduction in the total numbers born and of live pups born. The available data supports the conclusion that the causative factors in the prolonged gestation and reduced offspring viability are likely to be operating in the peri-natal period. It is not possible to identify these factors, however, the possibility that direct fetotoxicity is involved cannot be discounted. Therefore, the SmPC advises that treatment should be avoided during pregnancy. Except for reduced body weights during the lactation period at doses ≥300 mg/kg/day, there were no changes in F1 pup survival, physical development and sexual maturity milestones, behavioural tests, fertility or F2 litter size.

Toxicokinetic data

In repeat-dose oral toxicology studies in mice, rats and dogs, there was an increase in systemic exposure to pirfenidone that was approximately dose-proportional. Levels of pirfenidone and the 5-CA pirfenidone metabolite measured in dietary studies in mice and rats showed that metabolite levels were up to 2- to 7-fold higher than the parent pirfenidone levels. There was no evidence of a gender difference, or evidence of accumulation of pirfenidone or the 5-CA pirfenidone metabolite after daily repeat dosing. In mice and rats, oral gavage dosing resulted in substantially higher C_{max} values of pirfenidone compared with after dietary administration.

Local tolerance

No local tolerance studies were performed since the oral route is the intended method of administration in humans.

Other toxicity studies

Antigenicity and immunotoxicity

Pirfenidone was not antigenic in guinea pigs and was not immunotoxic.

Phototoxicity

There was no evidence of photosensitivity with pirfenidone but transient phototoxic effects were noted in the skin of guinea pigs and these were mitigated with topical application of sunscreen agents. No systemic toxicity was noted in hairless mice with concomitant oral administration of pirfenidone and exposure to UVA/UVB daily for 1 month. Reversible local toxicity of the skin characterised as mild acanthosis and mild single-cell necrosis was observed in the epidermis of the auricle and the dorsal skin. The SmPC contains advice for the protection of the skin.

5-CA-pirfenidone was negative in a bacterial test for photomutagenicity and for photoclastogenicity in Chinese hamster lung cells. Pirfenidone was negative for photomutagenicity but positive for photoclastogenicity. The photoclastogenicity assay has not been formally validated and it has been argued that the assay lacks specificity and might not be relevant for predicting the risk for DNA damage. Thus, the clinical implication of the pirfenidone finding is unknown.

Based on a request from the CHMP to further discuss the potential for photoclastogenicity, the applicant provided additional data including data from an assay using photodegraded material (PCLN-PIRF-108) confirming that the photodegraded material was not clastogenic, and from a comparison of photodegraded material with pirfenidone solution exposed to UVA as for the original photoclastogenicity study (NCR303). The findings support that the photodegradation products of pirfenidone (solid and aqueous states) are unlikely to be a biologically significant factor in the observed photoclastogenicity of pirfenidone. It is also noted that the reported skin reactions seen in the clinical studies so far support the conclusion that the skin rashes seen are more likely to be a manifestation of phototoxicity than photoallergy. Overall, it is considered that the issue is adequately addressed in the SmPC and the Risk Management Plan.

Impurities

The specified impurities do not appear to represent any particular toxicological hazard, were present in the drug material used in all toxicity studies and thus were qualified as part of these studies.

2.3.5. Environmental risk assessment

The worst case Predicted Environmental Concentration (PEC) for pirfenidone, assuming no degradation or removal in sewage treatment, is 0.36 µg/L and the $PEC_{FRESHWATER\ SEDIMENT}$, 0.323 µg/Kg. The worst case PEC/PNEC ratios for pirfenidone to surface water, groundwater, micro-organisms and sediment organisms (3 x 10-4, 1 x 10-5, 3.6 x 10-5 and 6.5 x 10-5) are all well below the respective trigger values indicating that it does not present a risk in these compartments. The inclusion of the estimated level of excretion of pirfenidone in the calculation of $PEC_{SURFACE\ WATER}$ and $PEC_{FRESHWATER\ SEDIMENT}$ further increases the safety margin for these compartments.

2.3.6. Discussion on non-clinical aspects

In general, the design of the nonclinical programme is acceptable and there is no need for any additional studies.

The single-dose studies are adequate. In fasted animals, the toxic effects were greater than in fed animals. In rodents, signs of effects on the central nervous system, including hypoactivity, respiratory effects, abnormal gait and recumbency were noted. In dogs, emesis, salivation and vocalisation were recorded.

The duration of repeat-dose studies is adequate to support this application.

The main physical signs in the oral subchronic and chronic toxicology studies of pirfenidone were similar to those seen acutely and included altered posture, hyopactivity, altered gait and sedation. These could be mitigated by dividing the daily dose or by dietary administration. The main systemic effect was an increase in liver weight, often in conjunction with hepatic centrilobular hypertrophy. There was no increase in ALT, AST or bilirubin, suggesting that the hepatic effects are not a manifestation of toxicity but are the result of enzyme induction. The findings were all wholly or partially reversible. The Applicant has conducted supplementary studies to investigate this question and the data support the proposed mechanism. There was no evidence of delayed toxicity.

Because the doses were limited by the physical signs, the margins of exposure to pirfenidone in animals over humans are not very large. The exposure to the main metabolite was around unity or slightly greater than the human exposure. An additional study with dosing by intravenous infusion was conducted to address this point. Although some deaths occurred, there were no additional findings or irreversible toxicity identified in the infusion study compared with the gavage or dietary studies. Overall, there are no concerns over the degree of exposure in the toxicity studies.

The findings in the carcinogenicity studies are compatible with the Applicant's hypothesis that the liver tumours found were related to enzyme induction. Pirfenidone and the major metabolite were not genotoxic and there was no early development of tumours compared with the controls. The arguments advanced in respect of the thyroid, uterine and Leydig cell tumours are also plausible and support the view that the tumours are not relevant to humans. The proposed mechanism is considered plausible.

There were no effects on fertility in either gender but there was an effect on the oestrous cycle. There were also prolongation of gestation and a reduction in viability in the neonates in animals dosed in the peri-natal period. The effect on the oestrous cycle is consistent with the hormonal disturbances seen in the mechanistic studies. It is possible that the prolongation of gestation is also mediated via hormonal disturbances, but other mechanisms might be involved in this effect and in the reduction in viability.

Pirfenidone was shown to cause phototoxicity and photoirritation when dosed concomitantly with exposure to UV light. In hairless mice, there was no systemic toxicity but effects on the skin were noted. The proposed SmPC includes instructions for the protection of the skin.

The impurities listed in the specification are considered to be adequately qualified.

The Applicant has conducted an acceptable programme of work to investigate the potential for ecotoxicity. It is concluded that pirfenidone will not constitute a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

In the toxicity studies, pirfenidone had effects on the central nervous system that precluded the administration of high doses. The main target organ was the liver, but the changes were considered to be adaptive and there was no irreversible or delayed toxicity. Tumours were found in the carcinogenicity studies, but those in the liver were deemed to result from the adaptive changes and not indicative of a risk for humans. Hormonally-mediated mechanisms have been proposed for tumours in the uterus of rats and these are considered plausible; the findings are not considered to represent a risk to patients.

Overall, the nonclinical programme is appropriate and there are no remaining issues. The nonclinical findings are adequately reflected in the SmPC.

2.4. Clinical aspects

2.4.1. Introduction

Overall, pirfenidone has been evaluated and characterised in 1345 healthy subjects and patients at doses ranging from 801 mg/day to 4806 mg/day. Of these, 770 patients have received the proposed recommended dose of 2403 mg/day, or greater, in the Applicant-sponsored Phase 2 or Phase 3 studies.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Applicant. The Applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A tabular overview of clinical studies is provided below in Table 1.

Table 1 Overview of clinical studies of pirfenidone in IPF

Table 5-1 Tabular Listing of Efficacy Studies of Pirfenidone in IPF

Study No.	Study Design	Study Treatment Daily Dose (Dosage Form)	No. of Patients Treated	Median Duration of Treatment, (min, max)	Primary Efficacy Analysis
InterMune Phase 3 Studies					
PIPF-004	Randomized, double-blind, placebo-controlled	Pirfenidone 2403 mg/d Placebo Pirfenidone 1197 mg/d	174 174 87	75.1 weeks (13–109 weeks)	Absolute change in percent predicted FVC from Baseline to Week 72[a]
PIPF-006	Randomized, double-blind, placebo-controlled	Pirfenidone 2403 mg/d Placebo	171 173	72.7 weeks (6–118 weeks)	Absolute change in percent predicted FVC from Baseline to Week 72[a]
Shionogi Phase 3 Study					
SP3	Randomized, double-blind, placebo-controlled	Pirfenidone 1800 mg/d Placebo Pirfenidone 1200 mg/d	110 109 56	52 weeks (planned)	Change in VC from Baseline to 52 weeks[b]
Shionogi Phase 2 Study					
SP2	Randomized, double-blind, placebo-controlled	Pirfenidone 1800 mg/d Placebo	72 35	325 days (29–359 days)	Change in 6MET SpO_2 from Baseline to 48 weeks[c]
InterMune Open-Label Study					
PIPF-002	Open-label	2403 mg/d or 40 mg/kg/d (to a maximum of 3600 mg/d)	83	106 weeks[d] (3–251 weeks)	NA[e]

Table 5.2-1 Listing of Clinical Studies

Type of Study	Study No.	Location of Study Report	Objectives of the Study	Study Design and Type of Control	Test Product(s); Route of Administration	Number of Subjects (Sex, M/F)	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Pharmacokinetics – Healthy Subject PK and Initial Tolerability									
PK	PIPF-005	5.3.3.1	To characterize the single dose food or antacid PK effect and the multiple dose PK profile	Open-label	267-mg Pirfenidone capsules: Single Dose (801 mg), Multiple Dose (801, 1602, 2403, 3204, and 4005 mg/d); Oral	Single Dose, 16 (9 M/7 F); Multiple Dose, 25 (14 M/11 F)	Healthy adults	Single Dose and Multiple Dose, 15 days	Complete; Full
MTD, Dose-escalating, Safety	PIPF-008	5.3.3.1	To determine the maximum tolerated dose of pirfenidone for use in PIPF-007	Randomized, double-blind, placebo-controlled	267-mg Pirfenidone capsules (801, 1602, 2403, 3204, 4005 and 4806 mg/d); Oral	20 (10 M/10 F)	Healthy adults	12 days [20 days planned]	Complete; Full
Pharmacokinetics – Intrinsic Factors									
PK, Safety	PIPF-009	5.3.3.3	To determine PK and safety in patients with renal insufficiency	Open-label	267-mg Pirfenidone capsules (801 mg); Oral	26 (16 M/10 F) [24 planned]	Patients with mild, moderate, or severe renal insufficiency	Single Dose	Complete; Full
PK, Safety	PIPF-011	5.3.3.3	To determine PK and safety in patients with hepatic insufficiency	Open-label	267-mg Pirfenidone capsules (801 mg); Oral	24 (13 M/11 F)	Patients with moderate hepatic insufficiency	Single Dose	Complete; Full
Pharmacokinetics – Extrinsic Factors									
PK, Safety	PIPF-010	5.3.3.4	To determine the impact of a strong CYP1A2 inhibitor and a CYP1A2 inducer on PK and safety; to compare safety of pirfenidone in smokers vs. nonsmokers	Open-label	267-mg Pirfenidone capsules: 2 single doses (801 mg), fluvoxamine (50, 100 or 150 mg/d); Oral	54 (23 M/31 F)	Healthy adults	11 days	Complete; Full
Pharmacodynamics – Healthy Subjects and PK/PD									
PK/PD, Thorough QT	PIPF-007	5.3.4.1	To evaluate the ECG (QT interval) effects of pirfenidone and the relationship between PK and QTc change	Double blind, randomized, parallel, placebo & open-label positive control	267-mg Pirfenidone capsules (2403, 4005 mg/d), Moxifloxicin single dose (400 mg), Placebo; Oral	162 (81 M/81 F) [160 planned]	Healthy adults	10 days	Complete; Full

Cross reference: Table 2.7.6-1 in Module 2
IPF = Idiopathic Pulmonary Fibrosis; PF = Pulmonary Fibrosis; IPP = Individual Patient Protocols; PK = pharmacokinetics; PD = pharmacodynamics; M= male; F = female; ECG = electrocardiogram; QTc = corrected QT interval; MTD= maximum tolerated dose

2.4.2. Pharmacokinetics

The pharmacokinetics (PK) of pirfenidone and its major metabolite, 5-carboxy-pirfenidone has been evaluated in five Phase 1 (PIPF-005, PIPF-007, PIPF-008, PIPF-009, PIPF-010). It should be noted that non-clinical studies suggest that 5-carboxy-pirfenidone has limited biological activity and no TNF-inhibitory effects have been identified at clinically relevant concentrations.

Absorption

Pirfenidone is absorbed slowly, with a mean peak plasma concentration of 7.87 µg/mL, occurring approximately 3–4 hours after ingestion of a single dose of 801 mg (PIPF-005). The slow absorption rate maybe one of the reasons for the increase in gastric irritancy as noted in the increase in gastric adverse events.

Compared to the fasted state, administration after food slows the rate of absorption and reduces peak plasma concentrations of pirfenidone. Since the frequency of GI AEs appears related to higher Cmax values (PIPF-005) and GI or CNS AEs are less frequent when pirfenidone is administered with food, a recommendation that pirfenidone be taken with food is warranted. This effect does not appear to have an impact on steady state serum levels. The benefit of ingestion with food is the reduction in GI side-effects.

Distribution

The in vitro human serum protein binding of [14C]-pirfenidone was investigated at concentrations 1, 10, and 100 µg/mL (PCLN-PIRF-110). The in vitro serum protein binding of pirfenidone in humans was approximately 58% at a concentration of 10 µg/ml which approximates to the observed C_{max} in healthy volunteers and patients with IPF. The amount of protein binding was similar over the concentration range of 1-10 µg/mL but decreased slightly at the highest concentration tested, 100 µg/ml (PCLN-PIRF-110). The ex vivo serum protein binding of pirfenidone was also investigated at 1 and 3 hours after oral administration of 600 mg in healthy male volunteers. Serum protein binding rates ranged from 54% to 62%.

Based on the results of the pooled population PK analysis (PIPF-ORD1), the mean apparent oral steady-state volume of distribution for pirfenidone is approximately 70 L indicating that distribution to tissues is modest.

The CHMP noted that the dose of pirfenidone used in the ex vivo measurements is slightly lower than the dose recommended for treatment of IPF but is sufficiently close to represent what could be expected with the slightly higher recommended dose.

Metabolism

Two in vitro studies to characterise the enzymes responsible for the metabolism of pirfenidone were conducted using human liver microsomes (PCLN-PIRF-111 and PCLN-PIRF-112). A third study was conducted using cryopreserved human hepatocytes and extrahepatic microsomes of the kidney and the small intestine of humans (PCLN-PIRF-114). In human liver microsomes pirfenidone was primarily metabolised by CYP1A2 (approx. 48%) and multiple other CYPs (each <13%). There was a negligible contribution to the metabolism of pirfenidone by microsomes from the kidney and small intestine. In healthy human volunteers significant decreases and increases in pirfenidone clearance were observed secondary to concomitant administration of CYP1A2 inhibitors and inducers (PIPF-010), respectively, which supports this as the primary route of metabolism.

Elimination

Following single-dose administration of pirfenidone in healthy older (50 to 66 years) adults, the mean apparent terminal elimination half-life was 2.4 hours (PIPF-005). Pirfenidone is predominantly (80-85%) excreted via the urine with 95% as the primary metabolite, 5-carboxy-pirfenidone (PIPF-005). This is consistent with findings from mass balance studies in rats and dogs after oral or IV

administration. While the oral clearance of pirfenidone appears modestly saturable this does not appear likely to be clinically relevant at the proposed therapeutic dose of 801 mg t.i.d.

The CHMP stated that the excretion data regarding pirfenidone clarifies that this is primarily through one of the main metabolites 5-carboxy-pirfenidone.

Dose proportionality and time dependencies

Dose-dependency was assessed by normalising all C_{max} and trough concentrations to a dose of 100 mg and applying ANOVA; no significant dose-dependency was identified suggesting linear pharmacokinetics up to a dose of 600 mg three times daily.

Special populations

The pooled population PK analysis incorporated an evaluation of the influence of a range of subject demographic and disease characteristics on the pharmacokinetics of pirfenidone. Differences in the PK of pirfenidone that reached statistical significance were identified for age, gender, race and obesity although the magnitude of the differences was small. The predicted AUC for pirfenidone was approximately 23% higher in 80 year old compared to 50 year old patients. In females, the C_{max} of pirfenidone was approximately 10% higher than in males, which was probably related to a smaller body size in the former. When analysed as an independent factor, the predicted AUC_{0-24} of pirfenidone was 21% lower in white compared with black subjects. Obese subjects had higher exposure than either normal or overweight subjects but the former were older and had worse renal function.

The data submitted by the Applicant indicates that when taking pirfenidone patients who have mild to moderate hepatic impairment may have increased pirfenidone exposure and patients who have mild to moderate renal impairment may have increased metabolite exposure. In these cases where increased exposure is seen there is a higher risk of seeing the most frequent, dose dependant adverse events. In the case of hepatic impairment the rate of pirfenidone metabolisation is reduced which will lead to an increase in serum levels. The SmPC contains an appropriate precaution statement also particularly addressing concomitant use of CYP1A2 inhibitors, a contra-indication in patients with severe hepatic impairment or end stage liver disease, as well as information on monitoring of patients with moderate liver disease. In the case of renal impairment there is an increase in 5-carboxy-pirfenidone serum levels. However, 5-carboxy-pirfenidone seems to have a low biological activity and is excreted well and should not cause any untoward effects in patients with moderate to severe renal impairment. It does not seem to have any effect of adverse event rates. Therefore the contra-indication in the SmPC regarding severe renal impairment or end stage renal disease requiring dialysis is considered a sensible precaution.

Pharmacokinetic interaction studies

Since the primary route of pirfenidone metabolism is via CYP1A2 the potential for inhibitors or inducers of this enzyme to affect its PK has been evaluated. Co-administration of fluvoxamine, a strong inhibitor of this enzyme was associated with markedly increased pirfenidone exposure with a statistically significant approximately six-fold increase in $AUC_{0-\infty}$ of pirfenidone and a doubling of C_{max} (PIPF-010). While fluvoxamine is a strong inhibitor of CYP 1A2, it also inhibits other enzymes involved in pirfenidone metabolism e.g.CYP2C9 and 2C19.

Based on in vitro studies, the potential for pirfenidone to be impacted by inhibitors of other CYP enzymes is unlikely. Cigarette smoking induces CYP1A2 and its effects on pirfenidone pharmacokinetics were also evaluated in this study (PIPF-010). The $AUC_{0-\infty}$ was higher in non-smokers than smokers

(mean 46.7 versus 25.5 mg.h/L), as was C_{max} (mean 8.82 versus 6.25 µg/mL), while clearance was lower (mean 18.1 versus 41.3 L/h).

By contrast, evaluation of potential PK interactions in a subset of patients enrolled in the Phase 3 study PIPF-004 revealed no significant effect of inhibitors or inducers of CYP1A2 or CYP3A4 (PIPF-ORD1). Despite this latter finding, pirfenidone should be used with caution in patients treated with inhibitors or inducers of CYP1A2. Given the magnitude of the effect observed specifically with fluvoxamine, it would be appropriate to contra-indicate its concomitant use as indicated in the proposed product labelling. Special care should also be exercised if patients are treated with therapies that are inhibitors of both CYP1A2 and other CYP isoenzymes (e.g. CYP2C9, 2C19, and 2D6), or if CYP1A2 inhibitors are being used concomitantly with inhibitors of other relevant enzymes such as CYP2C9, 2C19, and 2D6. Given the lower pirfenidone exposure seen in smokers, patients should be advised to stop smoking although this is likely to be routine advice for patients with IPF.

There have been no clinical studies to evaluate the potential for pirfenidone to affect the metabolism of other drugs. However, in vitro studies to investigate the potential of pirfenidone to induce/inhibit drug metabolising enzymes have been conducted in human hepatocytes and microsomes. No relevant inhibition or induction of drug metabolism via cytochrome P450 enzymes CYP1A2, CYP2C9, CYP2C19, CYP3A4/5, CYP2A6, CYP2C8/9, CYP2D6 or CYP2E1 was observed at clinically relevant concentrations of pirfenidone. There was also little effect on monoamine oxidase (MAO) enzymes A and B. In addition, no effect on P-gp mediated digoxin efflux was observed in vitro with Caco-2 cell monolayers. On the basis of these findings, the potential for pirfenidone to impact the PK of other medicinal products appears to be low.

Pharmacokinetics using human biomaterials

Human biomaterials have been used to investigate the protein binding, metabolism, and inhibition/induction potential of pirfenidone in several in vitro studies.

Regarding the extent of serum protein binding of pirfenidone the overall mean protein binding was approximately 58% at 1 and 10 µg/mL but decreased slightly to approximately 50% at the highest concentration tested, 100 µg/mL. Ex vivo serum protein binding rates ranged from 54% to 62%.

Based on in vitro studies sought to characterise the enzymes responsible for the metabolism of pirfenidone the substance was found to be primarily metabolised by CYP1A2 (approximately 48%) with other CYPs contributing (each <13%).

Four studies investigated the potential for pirfenidone to induce or inhibit several CYP enzymes (CYP1A, CYP1A2, CYP2A6, CYP2C9, CYP2C8/9, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A4/5). The results of these studies indicated no appreciable induction and little or no inhibition of any of the CYP enzymes by pirfenidone or 5-CA pirfenidone.

Little or no effect was detected regarding the inhibition potential of pirfenidone at concentrations ranging from 10 to 1000 µM in vitro in human hepatocyte mitochondrial preparations for monoamine oxidase (MAO) enzymes A and B (MAO-A and MAO-B).

The potential for pirfenidone to be a substrate of P-glycoprotein (P-gp) mediated transport was concluded to be unlikely using Caco-2 cell monolayers (human adenocarcinoma colonic cell line Caco-2) at concentrations ranging from 10 to 1000 µM. The potential for pirfenidone to inhibit P-gp mediated digoxin efflux at concentrations ranging from 1 to 1000 µM was examined using Caco-2 cell monolayers. The IC_{50} value of pirfenidone for P-gp inhibition was determined to be greater than 1000 µM.

2.4.3. Pharmacodynamics

Mechanism of action

The mechanism of action of pirfenidone has not been fully established. However, existing data suggest that pirfenidone exerts both antifibrotic and anti-inflammatory properties in a variety of in vitro systems and animal models. In cell-based systems, pirfenidone has been shown to suppress the proliferation of fibroblasts; attenuate the production of profibrotic cytokines including platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) from human macrophage cell lines; inhibit release of collagenase from fibroblasts; and reduce the accumulation of extracellular matrix components, particularly collagen. Pirfenidone is also capable of reducing the synthesis and release of proinflammatory cytokines, including tumor necrosis factor-alpha (TNF-α) and interleukin-1–beta (IL-1β), and has been shown to reduce the accumulation of inflammatory cells in response to various stimuli.

Primary and Secondary pharmacology

Study PCLN-PIRF-010 investigated the anti-fibrotic activity of pirfenidone on untreated and PDGF-stimulated proliferation of human dermal fibroblasts and found a statistically significant effect at all concentrations in untreated cultures and at 30 and 1000 µM in stimulated cultures.

The Applicant has conducted a single study to measure the QTc pharmacodynamic potential of pirfenidone in healthy subjects (PIPF-007). The results indicate that the placebo and positive control arms behaved in the expected manner; neither of the pirfenidone arms met the criterion of a prolongation of QTC of >10 ms and the study can be interpreted as indication that pirfenidone does not adversely influence the cardiac conduction system. The PK/PD interaction analysis is presented in the ECG analysis report and does not indicate a signal of a positive interaction.

2.4.4. Discussion on clinical pharmacology

The Applicant has presented some in vitro modelling which could potentially explain the mode of action of pirfenidone as an anti-fibrotic and anti-inflammatory agent. This in vitro data however has not been substantiated with in vivo pharmacodynamic models therefore the proposed views can only be hypothetical and must be viewed as such. The Applicant has conducted a QTc prolongation study to investigate if pirfenidone has the potential to alter cardiac electrophysiology. The study results presented would indicate that pirfenidone is devoid of this pharmacodynamic activity.

2.4.5. Conclusions on clinical pharmacology

Pirfenidone appears to have anti-fibrotic and anti-inflammatory properties but these have not been clearly shown in man. Therefore the mode of action remains not fully established. Pirfenidone does not seem to alter cardiac conductance when used alone.

2.5. Clinical efficacy

2.5.1. Dose response studies

The Applicant has not conducted formal dose response studies. The Phase III Studies SP3 and PIPF-004 investigated a lower and higher dose; the data as well as a discussion of the dose/response are included in the respective sections below.

2.5.2. Main studies

The Applicant has submitted two Phase III studies PIPF 004 and PIPF 006 which were regarded pivotal by the CHMP and are summarised in the table below. It should also be noted that the Applicant has also submitted a pooled analysis of these two studies due to the great similarity in design and aims of these two trials.

Table 2 Summary of InterMune phase 3 studies

Table 4-1 Summary of InterMune Phase 3 Studies

Study No., No. of Centers, Location	Study Start and End Dates	Study Design	Study Treatment Regimen[a]	No. of Patients Treated	Median Duration of Treatment, (min, max)	Patient Sex (No.), Mean Age (Range), Race (No.)	Study Population	Primary Efficacy Outcome Variable and Analysis[b]
PIPF-004 64 sites USA and ROW (Canada, Mexico, UK, France, Italy, Poland, and Australia)	14 Jul. 2006 through 28 Oct. 2008	Phase 3, randomized, double-blind, 3-arm, placebo-controlled	Randomization: 2:2:1	435	75.1 weeks (13–109 weeks)	Male: 311 Female: 124 66.4 years (40–81 years) White: 419 Nonwhite: 16	Patients with a confident diagnosis of IPF	Absolute change in % predicted FVC from Baseline to Week 72 Rank ANCOVA
			Pirfenidone 2403 mg/d (3 × 267-mg capsules) PO TID	174				
			Matching placebo capsules	174				
			Pirfenidone 1197 mg/d (3 × 133-mg capsules) PO TID	87				
PIPF-006 46 sites USA and ROW (Australia, Belgium, Germany, Ireland, Spain, Switzerland)	27 Apr. 2006 through 24 Oct. 2008	Phase 3, randomized, double-blind, placebo-controlled	Randomization: 1:1	344	72.7 weeks (6–118 weeks)	Male: 247 Female: 97 66.9 years (42–80 years) White: 168 Nonwhite: 6	Patients with a confident diagnosis of IPF	Absolute change in % predicted FVC from Baseline to Week 72 Rank ANCOVA
			Pirfenidone 2403 mg/d (3 × 267-mg capsules) PO TID	171				
			Matching placebo capsules	173				

Source: CSR PIPF-004 and CSR PIPF-006

6MWT = Six-minute walk test, ANCOVA = Analysis of covariance, DL_{CO} = Carbon monoxide diffusing capacity, FVC = Forced vital capacity, HRCT = High-resolution computed tomography, PO = By mouth, ROW = Rest of world, SpO_2 = Oxygen saturation by pulse oximetry, TID = Three times daily, UK = United Kingdom, USA = United States of America

[a] The dose of study treatment was escalated over a 14-day period from 1 capsule TID on Days 1–7, to 2 capsules TID on Days 7–14, to a full maintenance dose of 3 capsules TID on Day 15 and continuing, as tolerated.

[b] Secondary efficacy outcome variables are described in Section 4.1.2.8 and include the time to worsening of IPF, progression-free survival, categorical assessment of the absolute change in percent predicted FVC, changes in dyspnea, percent predicted DL_{CO}, worst SpO_2 during the 6MWT distance, HRCT assessment (Study PIPF-006 only), and 6MWT distance. Exploratory efficacy outcome variables, described in Section 4.1.2.9, include all-cause mortality, time to first requirement for prescribed oxygen, number of days without respiratory hospitalizations, and changes in other clinical, physiologic, and quality of life measurements.

Study PIPF-004 A randomised, double-blind, placebo-controlled, phase 3, three-arm study of the safety and efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis.

Methods

This study was a randomised, double-blind, placebo-controlled, 3-arm study in patients with idiopathic pulmonary fibrosis. Patients were randomised 2:2:1 to receive pirfenidone 2403 mg/day, placebo, or pirfenidone 1197 mg/day, respectively. They were to remain in blinded study treatment from randomisation until approximately 72 weeks after the last patient had been randomised. The study included a wash-out period (for patients to discontinue all prohibited medication before screening), a screening period, a study treatment period and a final follow-up visit. All patients were required to have a final follow-up visit 3 to 4 weeks after the treatment completion visit.

Figure 1 Study flow diagram

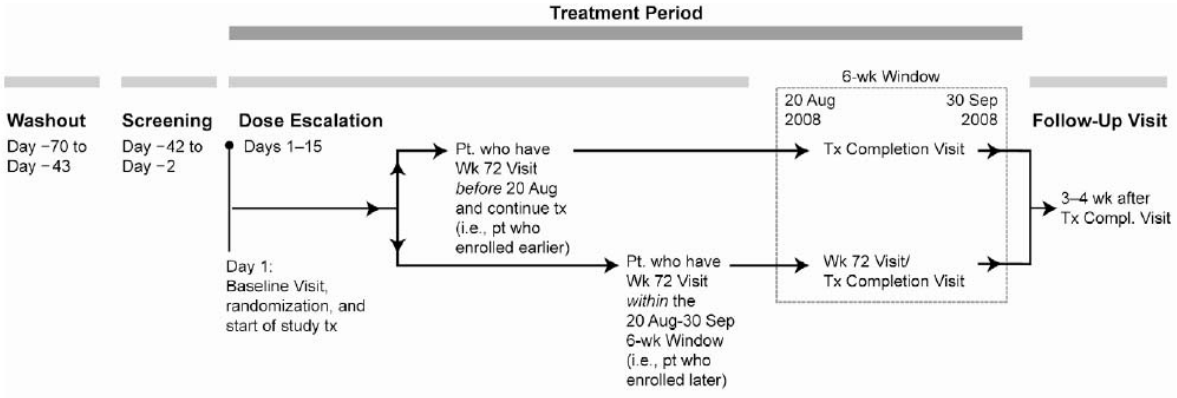


Figure 9-1 Study Flow Diagram

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

Study participants

Eligible patients 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:

- 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 randomisation.
- 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 <50yrs 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 ≥50yrs 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:
    - Percentage 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 (DLco)≥35% of predicted value at screening.
    - Either FVC or Hgb-corrected DLco ≤90% of predicted value at screening.
    - No evidence of improvement in measures of IPF disease severity over the year preceding study entry.
    - Distance walked ≥150 meters with O_2 saturation ≥83% on ≤6L/minute of O_2 during the 6-minute Walking Test (6MWT) oxygen titration procedure performed at screening.

The inclusion criteria presented for study PIPF 004 cover the heterogeneity of this condition. Lung biopsy confirmation of IPF was sought before enrolling the patient in the study. This is in accordance with the current recommendations.

Treatments

- 1197 mg/day of pirfenidone administered orally (PO) in 3 divided doses (three 133-mg capsules PO 3 times per day [TID] for a total of 9 capsules per day) with food.
- 2403 mg/day of pirfenidone administered orally in 3 divided doses (three 267-mg capsules PO TID for a total of 9 capsules per day) with food.
- Placebo capsules administered orally in 3 divided doses (3 placebo capsules PO TID for a total of 9 capsules per day) with food.

Objectives

- To assess the safety and efficacy of treatment with pirfenidone 2403 mg/day compared with placebo in patients with idiopathic pulmonary fibrosis (IPF)
- To assess the safety and efficacy of treatment with pirfenidone 1197 mg/day in patients with IPF.
- To characterise the pharmacokinetic (PK) disposition of pirfenidone in patients with IPF.

Outcomes/endpoints

- Primary efficacy outcome variable: absolute change in percent predicted FVC from Baseline to Week 72.

- Secondary efficacy outcome variables:

- 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 percent predicted FVC, a 15% absolute decline from Baseline in percent predicted Hgb-corrected DLco, or death)
- Categorical assessment of absolute change in percent predicted FVC from Baseline to Week 72
- Change in dyspnoea from Baseline to Week 72 based on the University of California at San Diego Shortness-of-Breath Questionnaire (UCSD SOBQ)
- Absolute change in the percent predicted Hgb-corrected DLco from Baseline to Week 72.
- Change in the worst oxygen saturation by pulse oximetry (SpO_2) observed during the 6MWT from Baseline to Week 72
- Change in distance walked in 6MWT from Baseline to Week 72

- Exploratory efficacy outcome variables:

- Overall survival time
- Change in respiratory status from Baseline to Week 72 as measured by St. George's Hospital Respiratory Questionnaire (SGRQ)
- Change in resting alveolar-arterial gradient (A-a gradient) from Baseline to Week 72
- Absolute change in percent predicted total lung capacity (TLC) from Baseline to Week 72
- Time from randomisation to first requirement for prescribed outpatient use of supplemental oxygen for patients not on supplemental oxygen at Baseline
- Change in quality of life from Baseline to Week 72 as measured by the World Health Organisation Quality-of-Life (WHO QOL) Questionnaire
- Change in biomarkers from Baseline to Week 24 (this analysis has not been conducted and is not part of this clinical study report [CSR])
- Change in Borg scale difference before and after 6MWT from Baseline to Week 72
- Number of days alive without a respiratory hospitalization through Week 72

Sample size

The original sample size was 325 patients to be randomised 2:2:1 to receive pirfenidone 2403 mg/day, placebo, or pirfenidone 1197 mg/day.

During the study enrolment period, based on emerging data, the sponsor decided to increase the sample size and extend the duration of treatment to provide appropriate powering for evaluating

primary and secondary efficacy outcome measures. These changes increased the power of the study to demonstrate statistically significant effects on the primary and secondary endpoint analyses.

A total of 75 patients were added to the previously planned 325 patients and the treatment duration was increased by 12 weeks, from 60 to 72 weeks.

The primary efficacy endpoint remained the change in forced vital capacity (FVC) but was now to be assessed at Week 72. The increased sample size and treatment duration provided approximately 97% power to detect a 50% reduction in the rate of FVC progression after 72 weeks of treatment with pirfenidone compared to placebo and also increased the power on the various secondary endpoints.

Randomisation

Patients were randomised 2:2:1 to receive pirfenidone 2403 mg/day, placebo, or pirfenidone 1197 mg/day, respectively.

Blinding (masking)

This was a randomised, placebo-controlled, double-blind study. A Data Monitoring Committee (DMC) was chartered to review unblinded safety and efficacy data at regular intervals during the trial and to evaluate the conduct and integrity of the study.

Statistical methods

The intent-to-treat (ITT) population was defined to include all randomised patients who received any amount of study treatment. This was the primary population for efficacy analysis.

The primary efficacy endpoint was the absolute change from baseline to week 72 in percent predicted forced vital capacity (FVC).

FVC was assessed at screening, day 1 (before randomisation), week 12 and every 12 weeks thereafter until the end of the study. Patients were scheduled to remain on blinded study treatment from randomisation until approximately 72 weeks after the last patient had been randomised into the study.

At each visit at least three acceptable FVC measures were to be recorded.. Baseline percent predicted FVC was defined as the mean of the maximum acceptable measurements obtained at screening and Day 1. The week 72 percent predicted FVC was defined as the mean of the maximum acceptable measurements obtained at each of the week 72A and 72B visits (two separate days on the week 72 visit).

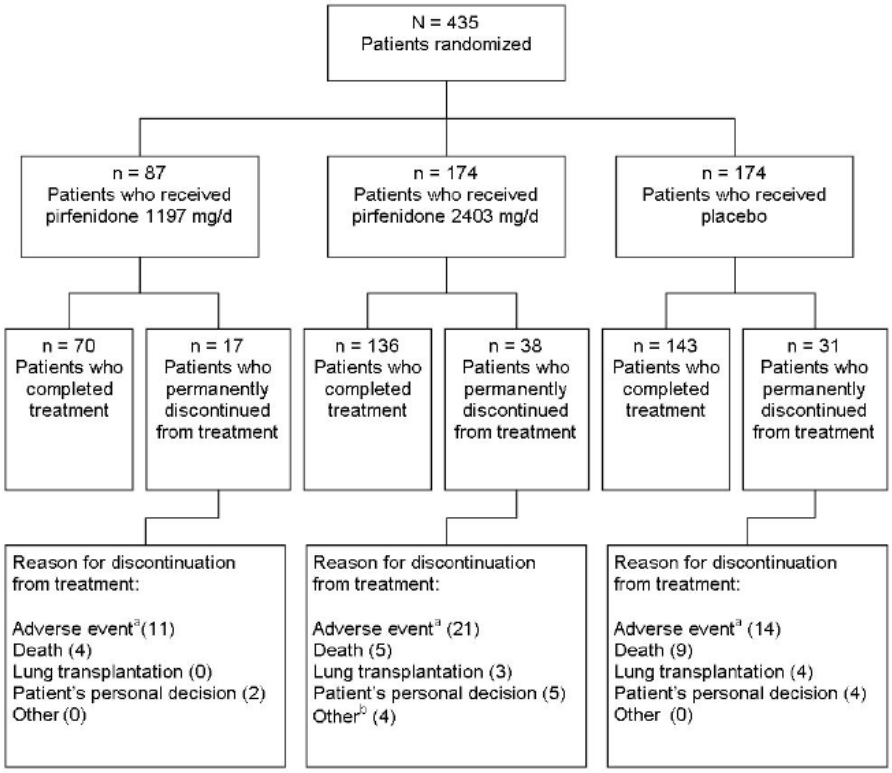
Differences between the treatment groups and placebo were analysed using rank analysis of covariance (the Mantel-Haenszel mean score chi-square test) stratified by geographic region (US or ROW). Rank baseline percent predicted FVC value was included as a covariate. Data for patients who died (imputed as percent predicted FVC = 0%) were ranked according to time to death, with the shortest time receiving the worst rank.

To be included in the study, patients had to have a 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).

Results

Participant flow

Figure 2 Participant flow



As seen above, the study shows an increase in adverse event drop outs in patients using the higher dose of pirfenidone. Death rate was higher in the placebo group than in the treated groups.

Recruitment

Date of First Patient Visit: 14 July 2006; date Last Patient Completed Study: 07 November 2008.

Conduct of the study

The most important protocol amendment concerned the increase of the sample size and the extension of the duration of the study to 72 weeks to increase the power and broaden the clinical experience. Additional changes to the study conduct based on protocol amendments are described.

Baseline data

Table 3 Patient demographics (all randomised patients)

Table 11-1 Patient Demographics (All Randomized Patients)

Demographic Parameter	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 174)	Placebo (N = 174)
Geographic Region, n (%)			
USA	58 (66.7%)	114 (65.5%)	114 (65.5%)
ROW	29 (33.3%)	60 (34.5%)	60 (34.5%)
Age (years)			
N	87	174	174
Mean ± SD	68.0 ± 7.63	65.7 ± 8.15	66.3 ± 7.53
Median	69.0	66.0	67.0
Range (Min, Max)	45, 81	45, 80	40, 79
Age Distribution (years), n (%)			
<55	5 (5.7%)	16 (9.2%)	10 (5.7%)
55–64	23 (26.4%)	59 (33.9%)	63 (36.2%)
65–74	39 (44.8%)	72 (41.4%)	69 (39.7%)
≥75	20 (23.0%)	27 (15.5%)	32 (18.4%)
Sex, n (%)			
Male	65 (74.7%)	118 (67.8%)	128 (73.6%)
Female	22 (25.3%)	56 (32.2%)	46 (26.4%)
Primary Race, n (%)			
White	83 (95.4%)	168 (96.6%)	168 (96.6%)
Black or African American	1 (1.1%)	2 (1.1%)	2 (1.1%)
Asian	3 (3.4%)	2 (1.1%)	4 (2.3%)
American Indian or Alaska Native	0	2 (1.1%)	0
Ethnicity, n (%)			
Hispanic or Latino	10 (11.5%)	13 (7.5%)	13 (7.5%)
Not Hispanic or Latino	77 (88.5%)	161 (92.5%)	161 (92.5%)
Weight (kg)			
Male			
n	65	118	128
Mean ± SD	88.4 ± 13.49	91.3 ± 15.92	88.9 ± 16.10
Median	84.8	89.8	87.5
Range (Min, Max)	64, 129	64, 148	56, 147
Female			
n	22	56	46
Mean ± SD	72.8 ± 12.98	77.0 ± 13.17	77.0 ± 14.61
Median	69.5	79.7	80.3
Range (Min, Max)	55, 105	40, 107	48, 107

Demographic Parameter	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 174)	Placebo (N = 174)
BMI (kg/m^2)			
Male			
n	65	118	128
Mean ± SD	29.4 ± 4.07	29.8 ± 4.10	29.8 ± 4.47
Median	29.5	29.7	29.1
Range (Min, Max)	21, 45	22, 44	22, 48
Female			
n	22	56	46
Mean ± SD	28.5 ± 4.43	30.6 ± 4.35	30.3 ± 5.10
Median	27.1	30.9	30.0
Range (Min, Max)	22, 37	21, 41	20, 42

Source: Table 14.1-1, Table 14.1-5
BMI = body mass index; SD = standard deviation; ROW = rest of the world; Max = maximum; Min = minimum

Table 4 Other baseline characteristics (all randomised patients)

Table 11-2 Other Baseline Characteristics (All Randomized Patients)

Baseline Characteristic	Pirfenidone 1197 mg/d (N = 87)	Pirfenidone 2403 mg/d (N = 174)	Placebo (N = 174)
FVC (% predicted)[a]			
n	87	174	174
Mean ± SD	76.4 ± 14.38	74.5 ± 14.47	76.2 ± 15.51
Median	75.8	73.0	73.6
Range (Min, Max)	52, 116	52, 124	48, 136
DL_{CO} (% predicted)[b]			
n	87	174	172
Mean ± SD	47.2 ± 8.22	46.4 ± 9.49	46.1 ± 10.24
Median	47.3	45.4	43.7
Range (Min, Max)	34, 71	30, 81	30, 90
UCSD SOBQ (total score)			
n	85	171	169
Mean ± SD	30.0 ± 20.09	33.1 ± 21.65	30.4 ± 20.61
Median	27.0	29.0	27.0
Range (Min, Max)	0, 81	0, 94	0, 81
6MWT Distance (m)			
n	87	170	170
Mean ± SD	417.5 ± 112.83	411.1 ± 91.87	410.0 ± 90.93
Median	420.0	421.0	415.5
Range (Min, Max)	151, 685	145, 692	178, 637
Worst SpO_2, 6MWT (% saturation)			
n	87	171	170
Mean ± SD	89.4 ± 3.86	89.2 ± 4.34	89.5 ± 3.66
Median	89.0	89.0	89.0
Range (Min, Max)	79, 98	78, 98	81, 98
Supplemental Oxygen Use, n (%)			
Yes	15 (17.4%)	29 (16.7%)	25 (14.4%)
No	71 (82.6%)	145 (83.3%)	149 (85.6%)
Time Since IPF Diagnosis to Randomization (years)			
n	87	174	174
Mean ± SD	1.4 ± 1.16	1.3 ± 0.96	1.4 ± 1.12
Median	0.9	1.0	1.1
Range (Min, Max)	>0, 4	>0, 4	>0, 4
IPF Diagnosis by HRCT, n (%)			
Definite IPF	83 (95.4%)	159 (91.4%)	164 (94.3%)
Probable IPF	4 (4.6%)	14 (8.0%)	10 (5.7%)
Uncertain IPF	0	1 (0.6%)	0

Numbers analysed

Table 5 Patient disposition – study PIPF-004

	1197mg/day	2403 mg/day	Placebo
Randomised	87	174	174
Treated	87	174	174
ITT population	87 (100%)	174 (100%)	174 (100%)
Completed study	73 (84%)	146 (84%)	144 (83%)
Discontinued because of death	9 (10%)	12 (7%)	18 (10%)
Discontinued for reason other than death	5 (6%)	16 (9%)	12 (7%)
Adverse Event	3	8	3
Lung transplantation	0	3	4
Patient's personal decision	2	4	5
Other*	0	1	0

*deportation

Outcomes and estimation

Table 6 Change from baseline to week 72 in FVC (% predicted) – PIPF-004

	1197mg/day		2403 mg/day		Placebo	
Baseline						
Mean (sd)	76.4 (14.38)		74.5 (14.47)		76.2 (15.51)	
Median	75.8		73.0		73.6	
Week 72						
N observed	76		154		150	
N imputed due to death	6		8		16	
N imputed, other	5		12		8	
	Value	Change	Value	Change	Value	Change
Mean	66.4	-10.0	66.6	-8.0	63.9	-12.4
SD	24.60	16.68	21.77	16.47	26.31	18.45
25^{th} percentile	55.9	-10.2	57.4	-9.4	53.6	-12.5
Median	69.1	-5.6	66.7	-5.8	67.0	-6.9
75^{th} percentile	82.1	-2.9	78.9	-0.2	82.9	-3.2
p-value*				p=0.0010		

*From ranked analysis of covariance – test for 2403 mg vs. placebo only

There is a highly statistically significant difference seen between the 2403 mg/day group and placebo. The level of significance (p=0.0010) is of the level which would be acceptable for a single pivotal trial. It is more extreme than the p=0.00125 that is derived from two studies successful at p=0.05.

In terms of mean changes there is a clear dose response. However the mean values could be a little misleading, as they can be skewed by the 0% scores being included for patients who died. Therefore looking at the median and the quartiles is also important, as the p-values are derived from a non-parametric method which can handle appropriately the 0% imputations.

The median change at week 72 was -6.9 on the placebo group compared to -5.6 and -5.8 on the active groups. The 1197 mg/day group actually has the slightly better median (though two active groups are

very similar) but when looking at the quartiles the advantage for the higher dose is clear, as it has a much better 75th percentile.

Table 7 Change from baseline in FVC (% predicted) – PIPF-004

	1197mg/day	2403 mg/day	Placebo
Week 12			
Mean (sd)	-1.2 (3.91)	-1.2 (6.80)	-2.7 (9.52)
Median	-0.7	-0.6	-1.3
p-value		p=0.0610	
Week 24			
Mean (sd)	-2.5 (8.61)	-1.4 (7.51)	-3.9 (12.09)
Median	-1.3	-0.7	-2.1
p-value		p=0.0139	
Week 36			
Mean (sd)	-3.8 (10.39)	-2.6 (9.08)	-7.2 (15.57)
Median	-2.5	-1.6	-3.8
p-value		p=0.0001	
Week 48			
Mean (sd)	-6.4 (14.23)	-4.4 (12.06)	-9.2 (17.18)
Median	-2.6	-3.0	-4.6
p-value		p=0.0009	
Week 60			
Mean (sd)	-8.6 (15.30)	-6.6 (15.49)	-10.7 (17.58)
Median	-4.4	-3.7	-5.9
p-value		p=0.0002	

Looking at the changes over time, the difference between 2403 mg/day was evident from the first assessment (week 12) and achieved statistical significance by the second (week 24). The graph below plotting the median changes shows clear separation from placebo for both groups, but both active doses seem fairly similar to each other. The subsequent graph which plots the upper and lower quartiles makes the difference between the active doses clearer. In the high dose group almost 25% of patients experience no decline from baseline by week 72. Overall this evidence clearly demonstrates the efficacy of pirfenidone in terms of % predicted FVC, and provides evidence that 2403 mg/day does better than 1197 mg/day.

Figure 3 Median change from baseline over time – PIPF-004

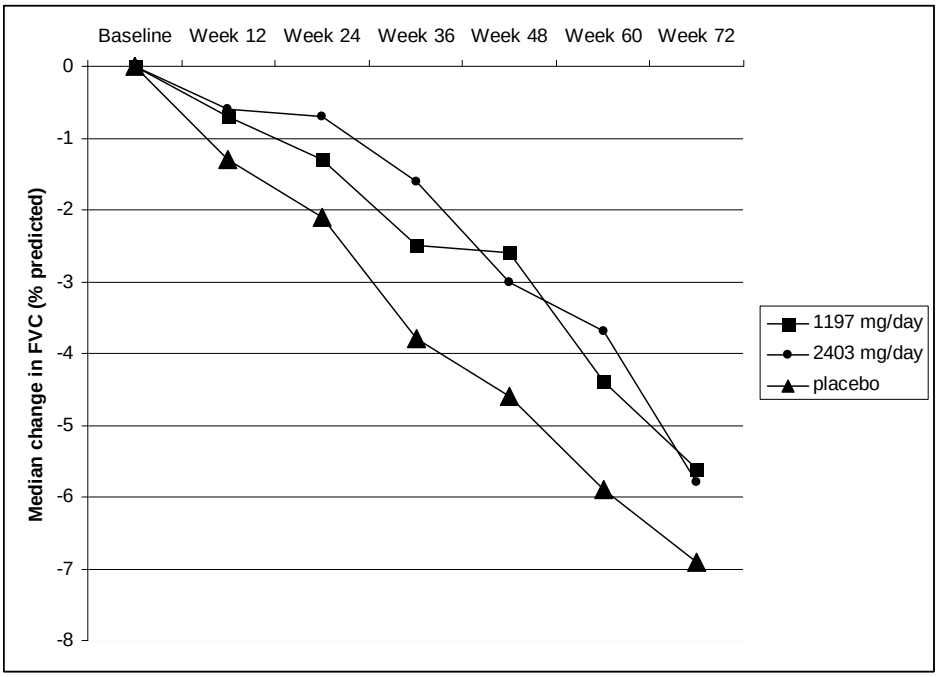
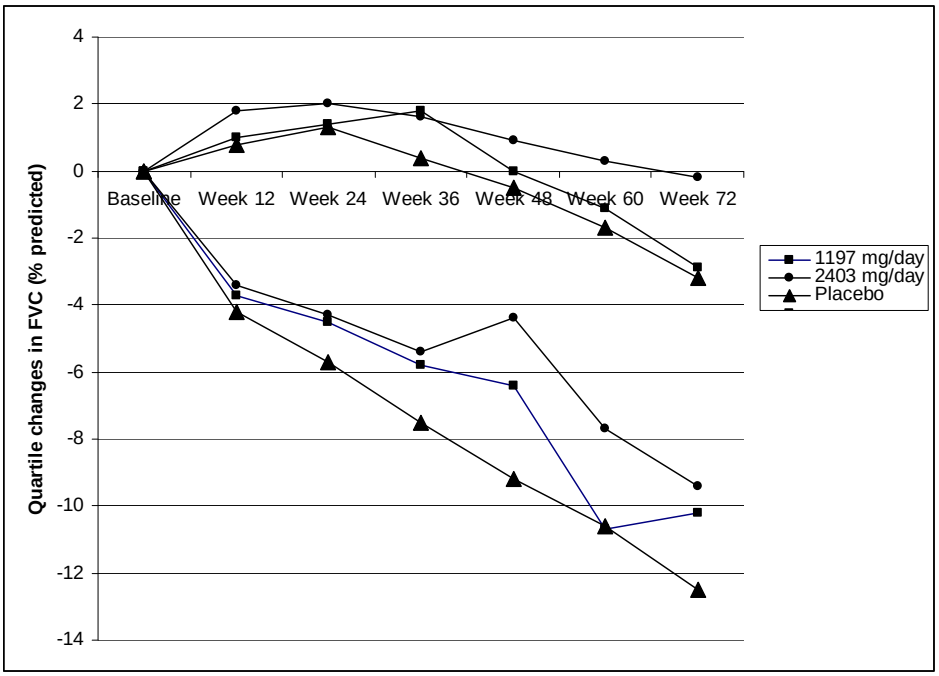


Figure 4 Lower and upper quartile changes from baseline over time – PIPF-004



Ancillary analyses

In PIPF-004 none of the secondary or exploratory parameters were statistically significant when compared with the control group. There were favourable trends for the $Sp0_2$ (p=0.087) and A-a gradient (p= 0.065).

Study PIPF-006 A randomised, double-blind, placebo-controlled, phase 3, two-arm study of the safety and efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis.

Methods

This study was a randomised, double-blind, placebo-controlled study in patients with IPF. Patients were randomised 1:1 to receive pirfenidone 2403 mg/day or placebo, and were to remain on blinded study treatment from randomisation until approximately 72 weeks after the last patient had been randomised in the study. The primary efficacy parameter was the absolute change in percent predicted forced vital capacity (FVC) from Baseline to Week 72. The study included a Washout Period (for patients to discontinue all prohibited medications before screening), a Screening Period, a Study Treatment Period, and a Final Follow-up Visit. All patients were required to have a Final Follow-up Visit 3 to 4 weeks after the Treatment Completion Visit.

Figure 5 Study flow diagram

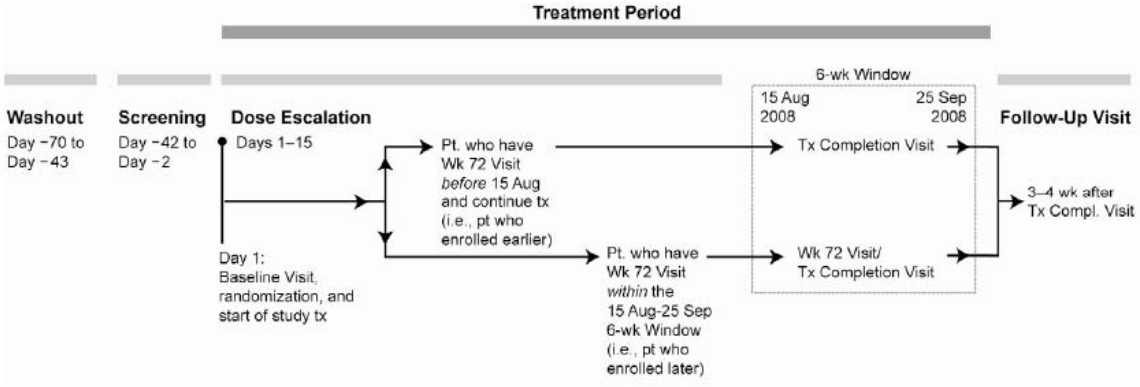


Figure 9-1 Study Flow Diagram

Compl. = Completion; pt = patient(s); tx = treatment; wk = week(s)
Note: Actual Visit windows varied from planned windows as follows: 1st Treatment Completion Visit occurred 12 August 2008; last Treatment Completion Visit occurred 3 October 2008; 1st Final Follow-Up Visit occurred 2 September 2008; last Final Follow-Up occurred 31 October 2008.

Study participants

Eligible patients 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, as follows:

• Clinical symptoms consistent with IPF, including insidious onset of otherwise unexplained dyspnoea on exertion of 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 randomisation

• 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: open or video-assisted thoracoscopic surgical (VATS) lung biopsy showing definite or probable UIP findings, as well as the absence of any features on specimens resulting from these procedures, which supported an alternative diagnosis within 48 months of randomization:

  - Open or VATS lung biopsy that showed definite or probable UIP
  - Transbronchial biopsy that 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}) ≥35% of predicted value at screening only
  - Either FVC or Hgb-corrected DLco ≤90%screening
  - No evidence of improvement in measures of IPF disease severity over the year preceding study entry
  - Distance walked ≥150 m (with O_2 saturation ≥83% on ≤6L/minute of O_2 during the 6-Minute Walk test (6MWT) oxygen titration procedure performed at screening.

Treatments

- 2403 mg/day of pirfenidone administered orally (PO) in 3 divided doses (three 267-mg capsules PO 3 times per day [TID] for a total of 9 capsules per day) with food.
- Placebo capsules administered orally in 3 divided doses (3 placebo capsules PO TID for a total of 9 capsules per day) with food.

Objectives

- To assess the efficacy of treatment with pirfenidone 2403 mg/day compared with placebo in patients with idiopathic pulmonary fibrosis (IPF).
- To assess the safety of treatment with pirfenidone 2403 mg/day compared with placebo in patients with IPF.

Outcomes/endpoints

- Primary efficacy outcome variable: absolute change in percent predicted FVC from Baseline to Week 72.

- Secondary efficacy outcome variables:

  - 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 percent predicted FVC, a 15% absolute decline from Baseline in percent predicted Hgb-corrected DLco, or death)
- Categorical assessment of absolute change in percent predicted FVC from Baseline to Week 72
- Change in dyspnoea from Baseline to Week 72 based on the University of California at San Diego Shortness-of-Breath Questionnaire (UCSD SOBQ)
- Absolute change in the percent predicted Hgb-corrected DLco from Baseline to Week 72
- Change in the worst oxygen saturation by pulse oximetry (SpO_2) observed during the 6MWT from Baseline to Week 72
- Change in the HRCT assessment of lung fibrosis from Baseline to Week 72
- Change in distance walked in 6MWT from Baseline to Week 72

- Exploratory efficacy outcome variables:

- Overall survival time
- Change in respiratory status from Baseline to Week 72 as measured by St. George's Hospital Respiratory Questionnaire (SGRQ)
- Change in resting alveolar-arterial gradient (A-a gradient) from Baseline to Week 72
- Absolute change in percent predicted total lung capacity (TLC) from Baseline to Week 72
- Time from randomization to first requirement for prescribed outpatient use of supplemental oxygen for patients not on supplemental oxygen at Baseline
- Change in quality of life from Baseline to Week 72 as measured by the World Health Organisation Quality-of-Life (WHO QOL) Questionnaire
- Change in biomarkers from Baseline to Week 24 (this analysis has not been conducted and is not part of this clinical study report [CSR])
- Change in Borg scale difference before and after 6MWT from Baseline to Week 72
- Number of days alive without a respiratory hospitalization through Week 72

The Applicant has used the EMA/SAWP endorsed primary endpoint of FVC. An extensive list of secondary and exploratory endpoints has been presented to further explore and substantiate the potential benefits of pirfenidone.

Sample size

The original sample size was 260 patients to be randomised 1:1 to receive pirfenidone 2403 mg/day or placebo.

During the study enrolment period, based on emerging data, the sponsor decided to increase the sample size and extend the duration of treatment to provide appropriate powering for evaluating primary and secondary efficacy outcome measures. These changes increased the power of the study to demonstrate statistically significant effects on the primary and secondary endpoint analyses.

A total of 60 patients were added to the previously planned 260 patients and the treatment duration was increased by 12 weeks, from 60 to 72 weeks. The primary efficacy endpoint remained the change

in forced vital capacity (FVC) but assessed at Week 72. The increased sample size and treatment duration provided approximately 97% power to detect a 50% reduction in the rate of FVC progression after 72 weeks of treatment with pirfenidone compared to placebo and also increased the power on the various secondary endpoints.

Randomisation

Patients were randomised 1:1 to receive pirfenidone 2403 mg/day or placebo.

Blinding (masking)

The blinding methods of Study PIPF-006 were the same as in Study PIPF-004.

Statistical methods

In trial PIPF-006 patients were randomised in a 1:1 ratio to pirfenidone 2403 mg/day or placebo. The randomisation was stratified by region (US or ROW). The intent-to-treat (ITT) population was defined to include all randomised patients who received any amount of study treatment. This was the primary population for efficacy analysis.

The primary efficacy endpoint was the absolute change from baseline to week 72 in percent predicted forced vital capacity (FVC).

FVC was assessed at screening, day 1 (before randomisation), week 12 and every 12 weeks thereafter until the end of the study. Patients were scheduled to remain on blinded study treatment from randomisation until approximately 72 weeks after the last patient had been randomised into the study.

At each visit at least three acceptable FVC measures were to be recorded. Baseline percent predicted FVC was defined as the mean of the maximum acceptable measurements obtained at screening and Day 1. The week 72 percent predicted FVC was defined as the mean of the maximum acceptable measurements obtained at each of the week 72A and 72B visits (two separate days on the week 72 visit).

Differences between the treatment groups and placebo were analysed using rank analysis of covariance (the Mantel-Haenszel mean score chi-square test) stratified by geographic region (US or ROW). Rank baseline percent predicted FVC value was included as a covariate. Data for patients who died (imputed as percent predicted FVC = 0%) were ranked according to time to death, with the shortest time receiving the worst rank.

To be included in the studies patients had to have a 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).

Results

Participant flow

Figure 6 Participant flow

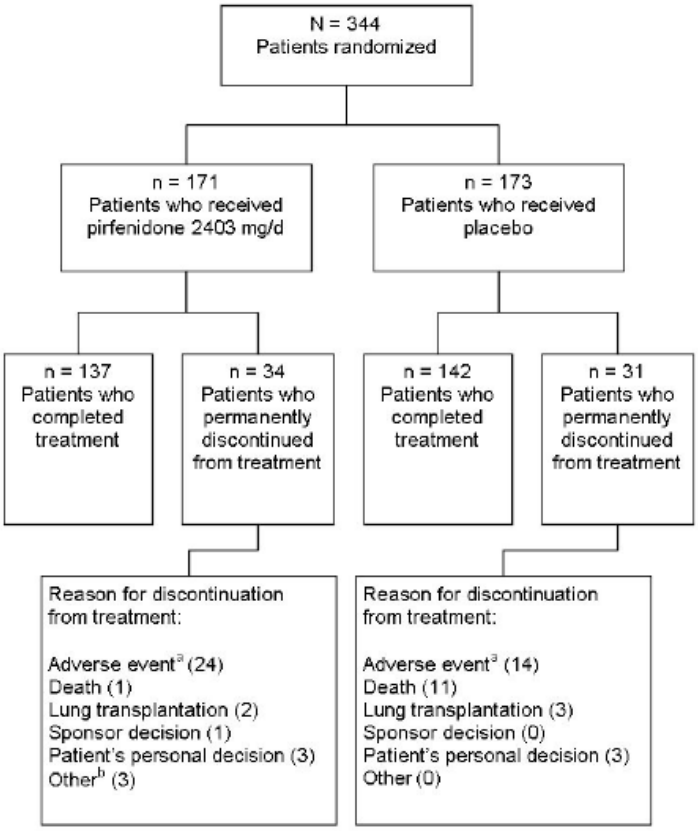


Figure 10-1 Disposition of Patients by Study Treatment

Source: Table 14.1-2; Listing 16.2.1-1

[a] Because of differences in the approach to data collection on the Discontinuation from Treatment CRF and the AE CRF, there are inconsistencies in the number of patients who discontinued from treatment because of an AE between Listing 16.2.1-1 and Listing 16.2.7-6 (see Table 12-12).

[b] Other reasons for discontinuation from study treatment included 1 patient placed on a lung transplantation schedule and 1 patient with an unknown reason. In addition, Patient 15046023 discontinued treatment during the study due to a prolonged QTc interval that was subsequently recognized as being present at Baseline; thus, the QTc prolongation was not reported as an AE.

Recruitment

Date of First Patient Visit: 27 April 2006; date Last Patient Completed Study: 31 October 2008.

Conduct of the study

The most important protocol amendment concerned the increase of the sample size and the extension of the duration of the study to 72 weeks to increase the power and broaden the clinical experience.

Baseline data

Table 8 Patient demographics (all randomised patients)

Table 11-1 Patient Demographics (All Randomized Patients)

Demographic Parameter	Pirfenidone 2403 mg/d (N = 171)	Placebo (N = 173)
Geographic Region, n (%)		
USA	148 (86.5%)	150 (86.7%)
ROW	23 (13.5%)	23 (13.3%)
Age (years)		
n	171	173
Mean ± SD	66.8 ± 7.90	67.0 ± 7.80
Median	67.0	68.0
Range (Min, Max)	45, 80	42, 80
Age Distribution (years), n (%)		
<55	11 (6.4%)	10 (5.8%)
55–64	59 (34.5%)	51 (29.5%)
65–74	64 (37.4%)	83 (48.0%)
≥75	37 (21.6%)	29 (16.8%)
Sex, n (%)		
Male	123 (71.9%)	124 (71.7%)
Female	48 (28.1%)	49 (28.3%)
Primary Race, n (%)		
White	169 (98.8%)	171 (98.8%)
Black or African American	1 (0.6%)	2 (1.2%)
Asian	1 (0.6%)	0
American Indian or Alaska Native	0	0
Ethnicity, n (%)		
Hispanic or Latino	3 (1.8%)	3 (1.7%)
Not Hispanic or Latino	168 (98.2%)	170 (98.3%)

Table 11-1 Patient Demographics (All Randomized Patients), continued

Demographic Parameter	Pirfenidone 2403 mg/d (N = 171)	Placebo (N = 173)
Weight (kg)		
Male		
n	123	124
Mean ± SD	95.4 ± 17.36	93.2 ± 15.09
Median	92.1	90.9
Range (Min, Max)	68, 168	66, 139
Female		
n	48	49
Mean ± SD	76.6 ± 14.02	77.5 ± 14.81
Median	73.5	74.4
Range (Min, Max)	56, 120	40, 109
BMI (kg/m^2)		
Male		
n	123	124
Mean ± SD	31.1 ± 4.67	30.4 ± 4.15
Median	30.1	29.9
Range (Min, Max)	24, 44	23, 46
Female		
n	48	49
Mean ± SD	29.9 ± 5.33	30.2 ± 5.26
Median	29.5	29.7
Range (Min, Max)	22, 47	15, 41

Source: Table 14.1-1 and Table 14.1-5
BMI = body mass index; SD = standard deviation; ROW = rest of the world; Max = maximum; Min = minimum

Table 9 Other baseline characteristics (all randomised patients)

Table 11-2 Other Baseline Characteristics (All Randomized Patients)

Baseline Characteristic	Pirfenidone 2403 mg/d (N = 171)	Placebo (N = 173)
FVC (% predicted)[a]		
n	171	173
Mean ± SD	74.9 ± 13.15	73.1 ± 14.21
Median	74.5	70.3
Range (Min, Max)	50, 108	52, 128
DL_{CO} (% predicted)[b]		
n	171	173
Mean ± SD	47.8 ± 9.82	47.4 ± 9.15
Median	45.6	46.2
Range (Min, Max)	31, 81	33, 78
UCSD SOBQ (total score)		
n	168	171
Mean ± SD	35.6 ± 20.24	36.6 ± 21.95
Median	33.0	32.0
Range (Min, Max)	1, 100	1, 105
6MWT Distance (m)		
n	169	168
Mean ± SD	378.0 ± 82.24	399.1 ± 89.74
Median	381.0	395.5
Range (Min, Max)	112, 616	171, 660
Worst SpO_2, 6MWT (% saturation)		
n	168	168
Mean ± SD	88.4 ± 3.79	88.6 ± 5.86
Median	88.0	89.0
Range (Min, Max)	77, 99	32, 97
Supplemental Oxygen Use, n (%)		
Yes	48 (28.1%)	49 (28.3%)
No	123 (71.9%)	124 (71.7%)
Time Since IPF Diagnosis to Randomization (years)		
n	171	172
Mean ± SD	1.2 ± 1.09	1.1 ± 0.99
Median	0.7	0.7
Range (Min, Max)	>0, 4	>0, 4
IPF Diagnosis by HRCT, n (%)		
Definite IPF	149 (87.6%)	158 (91.3%)
Probable IPF	20 (11.8%)	15 (8.7%)
Uncertain IPF	1 (0.6%)	0

Table 11-2 Other Baseline Characteristics (All Randomized Patients), continued

Baseline Characteristic	Pirfenidone 2403 mg/d (N = 171)	Placebo (N = 173)
Surgical Lung Biopsy/Diagnosis of UIP, n (%)		
Number of Patients with Lung Biopsy	94 (55.0%)	94 (54.3%)
Definite UIP	90	87
Probable UIP	3	6
Uncertain UIP	1	1
IPF Diagnostics Performed, n (%)		
Surgical lung biopsy	76 (44.4%)	86 (49.7%)
BAL	40 (23.4%)	33 (19.1%)
Transbronchial biopsy	8 (4.7%)	11 (6.4%)
Surgical lung biopsy and BAL	4 (2.3%)	1 (0.6%)
Surgical lung biopsy and transbronchial biopsy	3 (1.8%)	5 (2.9%)
BAL and transbronchial biopsy	29 (17.0%)	35 (20.2%)
Surgical lung biopsy, BAL, and transbronchial biopsy	11 (6.4%)	2 (1.2%)
Smoking Status at Screening, n (%)		
Never smoked (<100 cigarettes in life)	59 (34.5%)	64 (37.0%)
Previously smoked (≥100 cigarettes in life)	112 (65.5%)	101 (58.4%)
Currently smokes cigarettes	0	8 (4.6%)

Source: Table 14.1-6
Note: Patients with missing data are not included in Table 11-2 but are summarized in Table 14.1-5.
FVC = forced vital capacity; SD = standard deviation; DL_{CO} = carbon monoxide diffusing capacity;
UCSD SOBQ = University of San Diego Shortness of Breath Questionnaire; Min = minimum
Max = maximum; 6MWT = 6-Minute Walk Test; SpO_2 = oxygen saturation by pulse oximetry;
HRCT = high-resolution computed tomography; IPF = idiopathic pulmonary fibrosis;
UIP = usual interstitial pneumonia; BAL = bronchoalveolar lavage
[a] Baseline FVC is the mean of the two maximum acceptable FVC measurements obtained during the screening and Day 1 visits.
[b] Baseline DL_{CO} is the mean of the two closest acceptable values obtained at screening.

Baseline demographics indicate that the patients recruited in both groups were sufficiently similar to satisfy the protocol requirements.

Numbers analysed

Table 10 Patient disposition –study PIPF-006

	2403 mg/day	Placebo
Randomised	171	173
Treated	171	173
ITT population	171 (100%)	173 (100%)
Completed study	139 (81%)	146 (84%)
Discontinued because of death	15 (9%)	14 (8%)
Withdrew for reason other than death	17 (10%)	13 (8%)
Adverse Event	5	4
Lung transplantation	4	4
Sponsor decision	1	0
Patient's personal decision	6	5
Other*	1	0

*placed on lung transplantation schedule

Outcomes and estimation

Table 11 Change from baseline to week 72 in FVC (% predicted) – PIPF-006

	2403 mg/day		Placebo	
Baseline				
Mean (sd)	74.9 (13.15)		73.1 (14.21)	
Median	74.5		70.3	
Week 72				
N observed	148		149	
N imputed due to death	13		15	
N imputed, other	10		9	
	Value	Change	Value	Change
Mean	65.9	-9.0	63.6	-9.6
SD	23.53	19.58	25.06	19.12
25th percentile	59.0	-8.8	54.7	-9.7
Median	68.2	-4.2	65.5	-5.3
75th percentile	80.4	0.0	78.7	-1.0
p-value*		p=0.5013		

In this trial no statistically significant result was seen at week 72, though the trend favours the active treatment group, with a median of -4.2 for pirfenidone compared to -5.3 for placebo.

Table 12 Change from baseline in FVC (% predicted) – PIPF-006

	2403 mg/day	Placebo
Week 12		
Mean (sd)	-1.5 (10.67)	-1.1 (4.51)
Median	0.0	-1.2
p-value	p=0.0212	
Week 24		
Mean (sd)	-1.7 (11.20)	-4.5 (12.70)
Median	-0.3	-2.7
p-value	p=0.0001	
Week 36		
Mean (sd)	-2.5 (13.39)	-4.9 (15.02)
Median	-0.2	-2.6
p-value	p=0.0107	
Week 48		
Mean (sd)	-5.0 (15.61)	-6.9 (15.45)
Median	-1.7	-4.1
p-value	p=0.0048	
Week 60		
Mean (sd)	-7.4 (18.15)	-8.0 (17.17)
Median	-3.4	-4.2
p-value	p=0.1722	

Looking at the pattern over time, statistical significance was achieved at the first assessment (week 12) and was maintained until week 48. At all time-points the trend in terms of the median and both the lower and upper quartiles favoured active treatment.

Therefore, while this trial was negative in the sense that it failed on the primary endpoint (the week 72 assessment) it does provide some supportive evidence of efficacy. There is no clear explanation for why efficacy is apparently diminishing at the final time-points in this trial, though the decline in both active and placebo groups is smaller in this trial than in PIPF-004, maybe giving less room for showing a slowing in decline.

Figure 7 Median change from baseline over time – PIPF-006

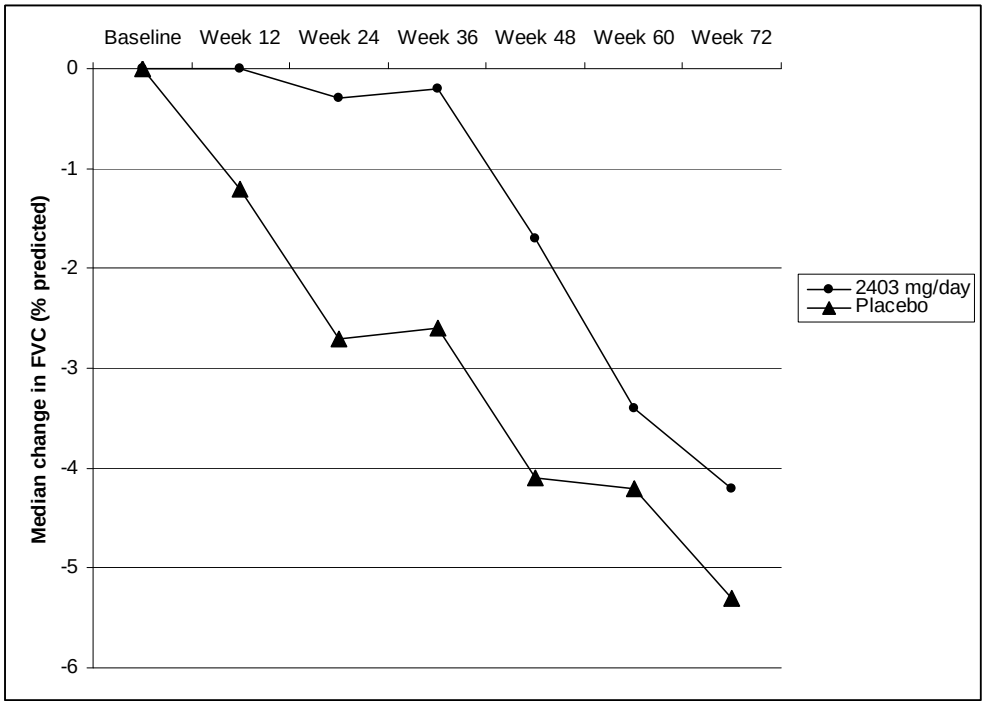
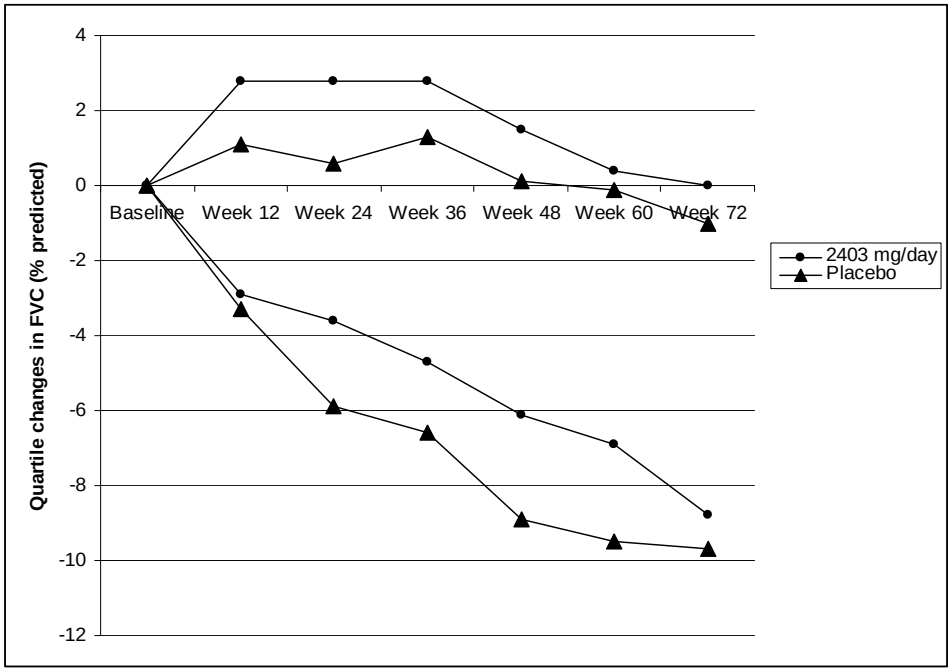


Figure 8 Lower and upper quartile changes from baseline over time – PIPF-006



In PIPF 006, the difference between the pirfenidone and placebo group is a bit smaller than in PIPF-004 and is statistically significant until week 48 after which it becomes non-significant.

Ancillary analyses

All parameters studied did not show any statistical significance with the exception of the 6MWT which is presented here below.

6MWT distance

Table 13 Change from baseline to week 72 in 6MWT Distance (all randomised patients)

Table 11-11 Change from Baseline to Week 72 in 6MWT Distance (All Randomized Patients)

Week	Mean[b] ± SD Change (m)		Absolute Difference (m)	Relative Difference	p-value[a]
	Pirfenidone 2403 mg/d (N = 171)	Placebo (N = 173)			
12	-8.3 ± 77.75	-9.0 ± 66.79	0.7	8.1%	0.975
24	-7.7 ± 94.86	-27.7 ± 94.40	20.1	72.3%	0.038
36	-16.4 ± 102.53	-37.4 ± 107.40	21.0	56.2%	0.044
48	-23.5 ± 114.70	-44.9 ± 105.74	21.5	47.8%	0.023
60	-31.9 ± 130.98	-56.0 ± 118.20	24.1	43.1%	0.014
72	-45.1 ± 139.81	-76.9 ± 127.5	31.8	41.3%	<0.001

Source: Table 14.2.2-13
SD = Standard deviation
[a] 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.
[b] For missing values, if the patient was alive on the protocol-specified visit, the imputation was by the SSD method. If the patient died on or before the protocol-specified date, 0 meters 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.

At Baseline, the 6MWT distance was 378.0 meters in the pirfenidone 2403-mg/day group and 399.1 meters in the placebo group. At Week 72, there was strong evidence of a treatment effect in the mean decline in 6MWT distance in patients treated with pirfenidone 2403 mg/day compared with patients treated with placebo (-45.1 vs.-76.9 meters, respectively; difference of 31.8 meters; p <0.001).

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 14 Summary of Efficacy for trial PIPF-004

Title: A Randomised, Double-Blind, Placebo-Controlled, Phase 3, Three-Arm Study of the Safety and Efficacy of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis				
Study identifier	Protocol number: PIPF-004 EudraCT number: 2006-000252-41			
Design	Randomised, double-blind, placebo-controlled, 3-arm study in patients with IPF. Patients were randomised 2:2:1 to receive pirfenidone 2403 mg/day, placebo, or pirfenidone 1197 mg/day, respectively. Dose was escalated over a period of 15 days as follows: Days 1-7: one capsule TID Days 8-14: two capsules TID Day 15 and continuing: three capsules TID (maintenance dose) Multi-centre, 64 sites in: USA, Canada, Mexico, UK, France, Italy, Poland and Australia.			
	Duration of main phase:	72 weeks		
	Duration of Washout period:	At least 28 days		
	Duration of Run-in phase:	Up to 42 days		
	Duration of Extension phase:	3-4 weeks		
Hypothesis	Assess safety and efficacy of treatment with pirfenidone 2403 mg/day compared with placebo and treatment with pirfenidone 1197 mg/day in patients with IPF.			
Treatments groups (2:2:1)	Pirfenidone 2403mg/day		Treatment: Pirfenidone 2403 mg/day Duration: 70.7 weeks Number randomised: 174 patients	
	Placebo		Treatment: Placebo Duration: 71.4 weeks Number randomised: 174 patients	
	Pirfenidone 1197 mg/day		Treatment: Pirfenidone 1197 mg/day Duration: 73.0 weeks Number randomised: 87 patients	
Endpoints and definitions	Primary endpoint:	Change in FVC Week 72	Absolute change in percent predicted FVC from baseline to week 72	
	Secondary endpoint:	6MWT Week 72	Change in distance walked in the 6 Minute Walk Test from Baseline to Week 72	
Database lock	Once the study was complete (Study period 14/07/2006-07/11/2008)			

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	The modified Intent to treat (MITT) population, which consisted of all randomised patients who received any amount of study drug. 72 weeks			
Descriptive statistics and estimate variability	Treatment group	Pirfenidone 2403 mg/day	Placebo	Pirfenidone 1197 mg/day
	Number of subjects	174	174	87
	Change in FVC			
	Week 12			
	Mean	-1.2	-2.7	-1.2
	Median	-0.6	-1.3	-0.7
	Week 24			
	Mean	-1.4	-3.9	-2.5

	Median	-0.7	-2.1	-1.3
	Week 36			
	Mean	-2.6	-7.2	-3.8
	Median	-1.6	-3.8	-2.5
	Week 48			
	Mean	-4.4	-9.2	-6.4
	Median	-3.0	-4.6	-2.6
	Week 60			
	Mean	-6.6	-10.7	-8.6
	Median	-3.7	-5.9	-4.4
	Week 72			
	Mean	-8.0	-12.4	-10.0
	SD	16.47	18.45	16.68
	25th percentile	-9.4	-12.5	-10.2
	Median	-5.8	-6.9	-5.6
	75th percentile	-0.2	-3.2	-2.9
	6MWT (Week 72)			
	Mean	-60.4	-76.8	-75.5
	SD	120.61	135.40	132.2

Effect estimate per comparison	Primary endpoint: Change in FVC (Week 72)	Comparison groups	Pirfenidone 2403 mg/day versus Placebo
		P-value (ANCOVA)	0.001
	Secondary endpoint: 6MWT (Week 72)	Comparison groups	Pirfenidone 2403 mg/day versus Placebo
		P-value (absolute difference of 16.4 m)	0.171
Notes	The primary efficacy comparison in this study is between the pirfenidone 2403-mg/day and placebo groups; the pirfenidone 1197-mg/day group was included for exploring a dose response relationship of pirfenidone in the treatment of patients with IPF. At Week 72, a treatment effect with pirfenidone 2403 mg/day compared with placebo was shown in the categorical assessment of percent predicted FVC and progression-free survival analysis. There was also a favourable trend for $Sp0_2$. None of the other secondary efficacy analyses (worsening of IPF, changes from Baseline in dyspnoea and percent predicted Hgb-corrected DLco) suggested a treatment effect with pirfenidone 2403 mg/day compared with placebo at Week 72.		

Table 15 Summary of Efficacy for trial PIPF-006

Title: A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Study of the Safety and Efficacy of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis			
Study identifier	Protocol number: PIPF-006 EudraCT number: 2006-000136-11		
Design	Randomised, double-blind, placebo-controlled study in patients with IPF. Patients were randomised 1:1 to receive pirfenidone 2403 mg/day or placebo. Dose was escalated over a period of 15 days as follows: Days 1-7: one capsule TID Days 8-14: two capsules TID Day 15 and continuing: three capsules TID (maintenance dose) Multi-centre, 46 sites in: USA, Australia, Belgium, Germany, Ireland, Spain, Switzerland.		
	Duration of main phase:		72 weeks
	Duration of Washout period:		At least 28 days
	Duration of Run-in phase:		Up to 42 days
	Duration of Extension phase:		3-4 weeks
Hypothesis	Assess safety and efficacy of treatment with pirfenidone 2403 mg/day compared with placebo and treatment with pirfenidone 1197 mg/day in patients with IPF.		
Treatments groups (1:1)	Pirfenidone 2403mg/day		Treatment: Pirfenidone 2403 mg/day Duration: 75.4 weeks Number randomised: 171 patients
	Placebo		Treatment: Placebo Duration: 74.9 weeks Number randomised: 173 patients
Endpoints and definitions	Primary endpoint:	Change in FVC Week 72	Absolute change in percent predicted FVC from baseline to week 72
	Secondary endpoint:	6MWT Week 72	Change in distance walked in the 6 Minute Walk Test from Baseline to Week 72
Database lock	Once the study was complete (Study period 27/04/2006-31/10/2008)		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	The modified Intent to treat (MITT) population, which consisted of all randomised patients who received any amount of study drug. 72 weeks		
Descriptive statistics and estimate variability	Treatment group	Pirfenidone 2403 mg/day	Placebo
	Number of subjects	171	173
	Change in FVC		
	Week 12		
	Mean	-1.5	-1.1
	Median	0.0	-1.2
	Week 24		
	Mean	-1.7	-4.5

	Median	-0.3	-2.7
	Week 36		
	Mean	-2.5	-4.9
	Median	-0.2	-2.6
	Week 48		
	Mean	-5.0	-6.9
	Median	-1.7	-4.1
	Week 60		
	Mean	-7.4	-8.0
	Median	-3.4	-4.2
	Week 72		
	Mean	-9.0	-9.6
	SD	19.58	19.12
	25^{th} percentile	-8.8	-9.7
	Median	-4.2	-5.3
	75^{th} percentile	0.0	-1.0
	6MWT (Week 72)		
	Mean	-45.1	-76.9
	SD	139.81	127.5
Effect estimate per comparison	Primary endpoint: Change in FVC (Week 72)	Comparison groups	Pirfenidone 2403mg/day versus Placebo
		P-value (ANCOVA)	0.501
	Secondary endpoint: 6MWT (Week 72)	Comparison groups	Pirfenidone 2403mg/day versus Placebo >
		P-value (ANCOVA absolute difference of 31.8 m)	<0.001
Notes	None of the other secondary efficacy analyses (categorical change in FVC from baseline to week 72, progression-free survival, worsening of IPF, change from baseline in the worst SpO2, changes from Baseline in dyspnoea, percent predicted Hgb-corrected DLco and change from baseline in HRCT assessment) suggested a treatment effect with pirfenidone 2403 mg/day compared with placebo at Week 72.		

Analysis performed across trials (pooled analyses and meta-analysis)

A combined analysis of the studies PIPF-004 and PIPF-006 was provided. The primary endpoint was analysed using the same method as used in the individual trials, except that trial was added into the model as an additional term.

Table 16 Change from baseline in FVC (% predicted) – Combined studies

	2403 mg/day (n=345)	Placebo (n=347)
Week 12		
Mean (sd)	-1.3 (8.91)	-1.9 (7.48)
Median	-0.2	-1.2
p-value	p=0.0031	
Week 24		
Mean (sd)	-1.5 (9.51)	-4.2 (12.39)
Median	-0.5	-2.3
p-value	p<0.0001	
Week 36		
Mean (sd)	-2.6 (11.41)	-6.1 (15.32)
Median	-1.0	-3.1
p-value	p<0.0001	
Week 48		
Mean (sd)	-4.7 (13.92)	-8.0 (16.36)
Median	-2.0	-4.4
p-value	p<0.0001	
Week 60		
Mean (sd)	-7.0 (16.84)	-9.4 (17.40)
Median	-3.6	-5.4
p-value	p=0.0003	
Week 72		
Mean (sd)	-8.5 (18.06)	-11.0 (18.81)
Median	-5.0	-6.2
p-value	p=0.0052	

When the results from the two trials are combined the results achieve the extreme levels of statistical significance that would be hoped for from a meta-analysis. This level of evidence is achieved at all time-points.

Though the second trial failed to achieve statistical significance for the primary endpoint, the trends were all favourable and statistical significance was achieved on the majority of the early time-points. From the table below we can see that the addition of PIPF-006 to the already positive PIPF-004 generally increases the evidence of efficacy, though it is slightly weakened for the final two time-points.

Table 17 Change from baseline in FVC (% predicted)

	Study 004	Study 006	Combined
Week 12	p=0.0610	p=0.0212	p=0.0031
Week 24	p=0.0139	p=0.0001	p<0.0001
Week 36	p=0.0001	p=0.0107	p<0.0001
Week 48	p=0.0009	p=0.0048	p<0.0001
Week 60	p=0.0002	p=0.1722	p=0.0003
Week 72	p=0.0010	p=0.5013	p=0.0052

As before the median values are probably a better representation of the size of the treatment effect. The two graphs below plot the median and the upper and lower quartiles over time for the combined

analysis. It can be seen that pirfenidone did better than placebo at all time-points for all three measures.

Figure 9 Median change from baseline over time – Combined studies

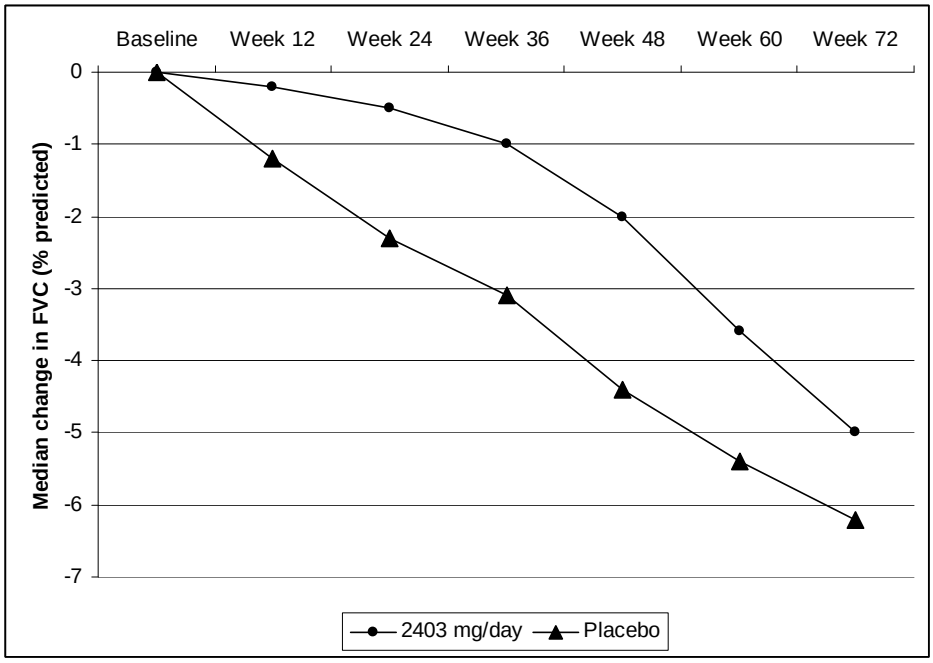
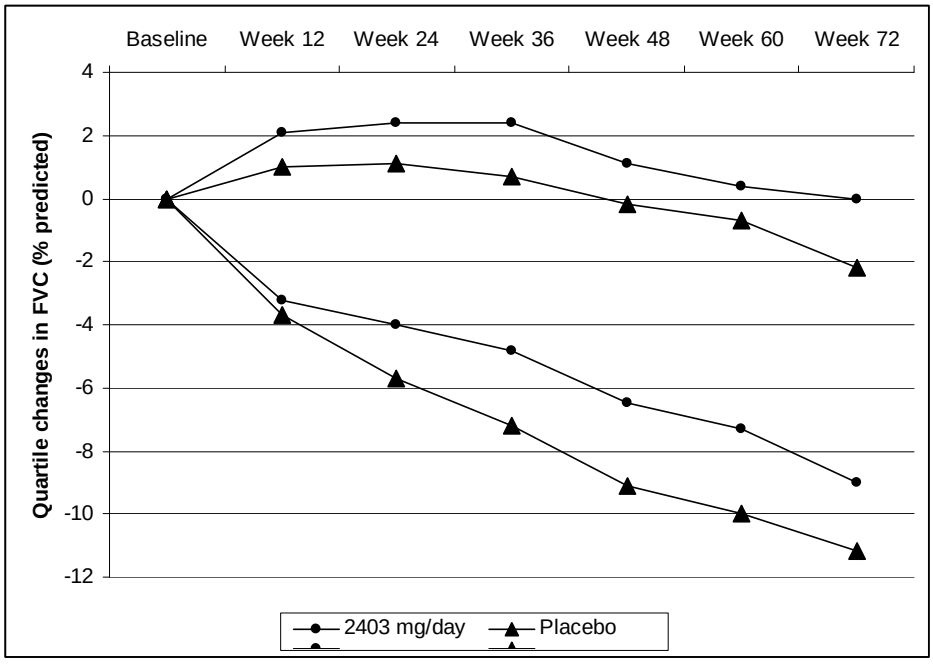


Figure 10 Lower and upper quartile changes from baseline over time – Combined studies



Secondary endpoints

The main secondary endpoints were time to death or disease progression and the 6 minute walk test. In concordance with the primary analysis the result in PIPF-004 reached statistical significance while only a trend was seen in PIPF-006. The combined analysis also achieved statistical significance.

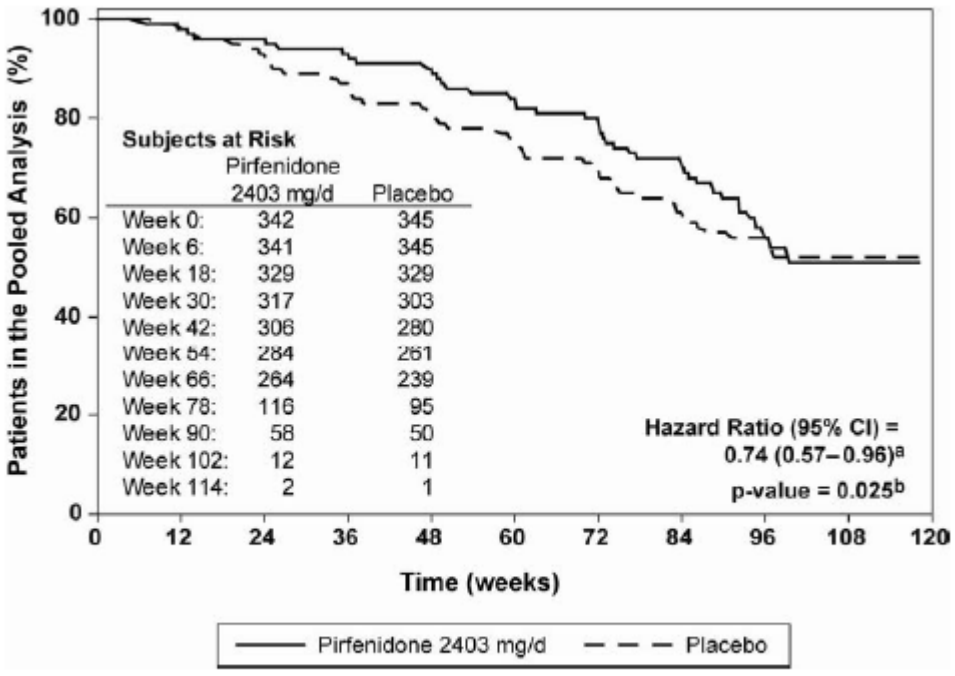
This is essentially a duplication of the primary analysis as the dominating event was disease progression in the form of a ≥10% decline from baseline in % predicted FVC. The other definition of progression was a ≥15% decline in DLco. As such the result should not be emphasised in the SPC, especially is it may give the erroneous impression that some mortality benefit was shown.

Table 18 Progression –free survival in the pooled analysis (all randomised patients)

Table 7-22 Progression-Free Survival in the Pooled Analysis (All Randomized Patients)

	Study PIPF-004/Study PIPF-006	
	Number of Patients, n (%)	
	Pirfenidone 2403 mg/d (N = 345)[a]	Placebo (N = 347)[a]
Death or Disease Progression[b]	99 (28.9%)	122 (35.4%)
Disease Progression		
Decline in FVC	59 (17.3%)	80 (23.2%)
Decline in DL_{CO}	19 (5.6%)	18 (5.2%)
Death Before Disease Progression[c]	21 (6.1%)	24 (7.0%)
Patients censored	243 (71.1%)	223 (64.6%)
Hazard ratio[d] (95% CI)	0.74 (0.57–0.96)	
p-value[e]	0.025	

Figure 11 Progression –free survival in the pooled analysis, Kaplan-Meier estimates (all randomised patients)



5 Progression-Free Survival in the Pooled Analysis, Kaplan-Meier Estimates (All Randomized Patients)

For the six minute walk test the analysis method was the same as for the primary endpoint. A distance of 0 m was used for patients who died. As for the primary endpoint the median would be the better statistic to summarise the differences, though the company has focused on means.

Table 19 Results of change from baseline in 6MWT at week 72 (meters)

Median change (LQ, UQ)

	2403 mg/day	Placebo	p-value
-004	-27.5 (-91, 15)	-37.5 (-126, 5)	p=0.1709
-006	-1 (-96, 36)	-41.5 (-117, 2)	p=0.0009
Combined	-13 (-95, 23)	-41 (-121, 3)	p=0.0009

Baseline median

-004: 421 on pirfenidone, 415.5 on placebo

-006: 381 on pirfenidone, 395.5 on placebo

Combined: 393 on pirfenidone, 404.5 on placebo

In the pooled analysis of survival in PIPF-004 and PIPF-006 the mortality rate with Esbriet 2403 mg/day group was 7.8% compared with 9.8% with placebo (HR 0.77 [95% CI, 0.47–1.28]).

Clinical studies in special populations

Clinical studies in special populations were not conducted, which was considered acceptable.

Supportive study(ies)

Three studies have been considered as supportive data. These were two Japanese studies SP2 and SP3 as well as PIPF 002.

SP3 Phase 3 Clinical Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis Double-Blind, Placebo-Controlled, Parallel-Group Comparative Study

The study was designed as a double-blind, placebo-controlled comparative trial. The treatment groups consisted of a high dose (1800 mg/day), which served as the focus of the study, and a low-dose group (1200 mg/day), which was designed to test the benefits and risks of a reduced dose. For both treatment groups, the dosing regimen was 3 doses per day after every meal. The dosing period consisted of a dose escalation and 48 weeks of treatment for a total of 52 weeks.

Results

Primary efficacy results:

Table 20 Between-group comparison of VC variations (ANOVA) 52-week FAS

Table 11.4-1 Between-group comparison of VC variations (ANCOVA): 52-week (FAS)

Group	No. of cases	Adjusted mean	Standard deviation
H group	104	-0.09	0.02
L group	54	-0.08	0.03
P group	103	-0.16	0.02

Comparison groups	Adjusted mean difference	Standard deviation	90% Confidence interval		Two-sided p value
			Lower limit	Upper limit	
H group - P group	0.07 0.03		0.01	0.13	0.0416
L group - P group	0.09 0.04		0.02	0.16	0.0394
H group - L group	-0.02 0.04		-0.08	0.05	0.7077

Note: Cases discontinued by the fourth week after the start of dosing were excluded from analysis.

The mean value (adjusted value) of the vital capacity (VC) variation was -0.09 in the high dose group and -0.16 in the placebo group and the variation in the high dose group was significantly higher than in the placebo group (p=0.0416) Based on this it was concluded that the higher dose of pirfenidone inhibited the reduction in VC more effectively than placebo. The lower dose of pirfenidone was also significantly more effective than placebo. There was no difference between the high and low dose of pirfenidone used in this study.

SP2 Phase II Study on Pirfenidone in Patients with Idiopathic Interstitial Pneumonia

This study was a parallel group comparison conducted under double-blind conditions as a multicentre study with randomised assignment of placebo controls. The dosage was gradually increased over seven days (gradual increase period), followed by continued administration for 48 weeks (treatment period). The objective was to examine the efficacy and safety of pirfenidone in patients with chronic idiopathic interstitial pneumonia using a placebo as the control drug.

Results

Primary efficacy results: Analysis of covariance of the SpO_2 area, which is the principal analysis indicator, based on data following six-month administration to Full Analysis Set (FAS) subjects suggested a tendency to superiority by the pirfenidone group compared to the placebo group (p=0.0880, final analysis results; p=0.0892).

Secondary efficacy results: Analysis of the secondary evaluation variables on FAS subjects revealed a tendency for the pirfenidone group to be superior to the placebo group in terms of variations in VC after six months of administration compared to the preadministration values (p=0.0995). A significant difference was found at the nine-month point (p=0.0366). The pirfenidone group was significantly superior to the placebo group in terms of VC and TLC in comparisons of the distribution in assessment of the degree of improvement of secondary evaluation variables based on data at the six-month point (p values of 0.0341 and 0.0302, respectively). Similar results were obtained at the nine-month point (p values of 0.0028 and 0.0155, respectively). The onset of acute exacerbation at the intermediate analysis point (after six months of administration) revealed absolutely no occurrences in the pirfenidone group (72 patients) but 5/35 cases in the placebo group. A significant difference was found in the incidence rates of the two groups (p=0.0031). Subsequently, by completion of the treatment period (including nine months of administration or more), acute exacerbation occurred in one member of the pirfenidone group and in five members of the placebo group. The pirfenidone group exhibited a tendency to superiority over the placebo group in assessment of the degree of improvement of high-resolution CT images at the six-month point by medical specialists based on image assessment (final analysis results: p=0.0921).

PIPF 002 An Open-Label, Phase 2 Study of the Safety and Efficacy of Oral Pirfenidone in Patients with Pulmonary Fibrosis/Idiopathic Pulmonary Fibrosis

Methods: the patients were enrolled in three groups: Group 1 patients were receiving oral pirfenidone or had received pirfenidone within 4 weeks before enrolment; Group 2 patients were initiating therapy with pirfenidone or reinitiating therapy after a lapse of greater than 4 weeks, and Group 3 patients who had not previously received pirfenidone enrolled via the EAP. After Amendment 2, Group 2 patients also enrolled via the EAP. [Note: these were enrolment groups only; data were not analysed by group.]

Objectives: The objectives of this study of pirfenidone in patients with pulmonary fibrosis/idiopathic pulmonary fibrosis (PF/IPF) were:

– To assess the safety of treatment with pirfenidone (up to 3600 mg/day) in patients with PF/IPF

– To assess the efficacy of treatment with pirfenidone (up to 3600 mg/day) in patients with PF/IPF

- To provide PF/IPF patients with early access to pirfenidone

Results: A total of 83 patients were enrolled across 27 sites and are included in the analyses for this interim clinical study report. The study group consisted primarily of white males. Median age was 70 years (range 47 to 88); most patients (97.6%) had a diagnosis of IPF and most had not previously received pirfenidone (88%).

Most patients (70) were enrolled through the EAP implemented with Amendment 2 (Group 3). A total of 13 patients "rolled over" from other pirfenidone trials in Groups 1 and 2. Of these, 10 patients in Groups 1 and 2 had received pirfenidone in their original study; the other 3 patients had received an active control.

As of the interim database cut-off of 30 April 2009, 50 patients (60.2%) had prematurely withdrawn from the study. The most frequent reasons for early withdrawal were adverse events (17 patients, 20.5%) and death (15 patients, 18.1%).

Median percent predicted FVC was 65.6% at Baseline (N = 79), 66.8% at Week 48 (N = 57), 68.7% at Week 96 (N = 47), 65.2% at Week 144 (N = 35), and 70.9% at Week 192 (N = 11). Median Hgb-corrected percent predicted DLco was 36.5% at Baseline (N = 73), 35.2% at Week 48 (N = 55), and 38.3% at Week 96 (N = 44), 37.9% at Week 144 (N = 34), and 41.1% at Week 192 (N = 11). Median resting oxygen saturation by pulse oximetry on room air was 95.0% at Baseline (N = 71), Week 48 (N = 47), Week 96 (N = 36), and Week 144 (N = 30) and 96.5% at Week 192 (N = 8). Of the 41 patients who were not receiving supplemental oxygen at start of study, 19 (46.3%) started supplemental oxygen during the study. The Kaplan-Meier estimate of median time to first supplemental oxygen use was 151.7 weeks.

As of the 30 April 2009 data cut-off, most patients had not experienced a protocol-defined IPF exacerbation while enrolled in the study (63/83, 75.9%); 20 patients (24.1%) had an IPF exacerbation while on study. Of these 20 patients, 5 died due to IPF, 3 discontinued study drug due to AEs, 4 discontinued due to non-AE-related reasons, and 8 remained on treatment as of 30 April 2009. A total of 15 patients died during the study (18.1%); 14 deaths (16.9%) were treatment emergent; and 12 deaths (14.5%) were IPF related.

2.5.3. Discussion on clinical efficacy

IPF is a heterogeneous collection of idiopathic disease conditions which manifest themselves as pulmonary fibrosis. Once a patient is diagnosed with this condition it should be noted that death is the final outcome within 2 to 5 years.

The ATS/ ERS Joint Statement published in 2000 offers some guidance regarding the measurement of therapeutic effect. In this Joint Statement there is a Section dedicated to "Length of Treatment" and evaluation of therapeutic impact. The Guidance states:

A discernible objective response to therapy may not be evident until the patient has received > 3 months of therapy. Evaluation should be conducted at 6 months and 12 months to determine if therapy has a favourable, stabilising or a failure to respond to therapy.

More than 18 months after onset of therapy. At this point, therapy should be individualised on the basis of the clinical response and tolerance of the patient to the therapy. The committee recommends that the therapy be continued indefinitely only in individuals with objective evidence of continued improvement or stabilisation.

The ATS/ERS Joint Statement also gives Guidance regarding how to measure therapeutic impact:

A favourable (or improved) response to therapy is defined by two or more of the following, documented on two consecutive visits over a 3- to 6-month period:

- A decrease in symptoms, specifically an increase in the level of exertion required before the patient must stop because of breathlessness or a decline in the frequency or severity of cough
- Reduction of parenchymal abnormalities on chest radiograph or HRCT scan
- Physiologic improvement defined by two or more of the following:
    - ≥10% increase in TLC or VC (or at least ≥200-ml change)
    - ≥15% increase in single-breath DLco (or at least ≥3 ml/min/mm Hg)
    - An improvement or normalization of O_2 saturation (≥4 percentage point increase in the measured saturation) or PaO_2 (≥4-mm Hg increase from the previous measurement) achieved during a formal cardiopulmonary exercise test

A stable (and presumed favourable) response to therapy is defined by two or more of the following, documented on two consecutive visits over a 3- to 6-mo period:

- 10% change in TLC or VC, or <200-ml change
- <15% change in DLCO, or <3 ml/min/mm Hg
- No change in O_2 saturation (<4% increase) or PaO_2 (<4 mm Hg increase) achieved during a formal cardiopulmonary exercise test

A failure to respond to therapy (e.g., after 6 mo of treatment) is defined as:

- An increase in symptoms, especially dyspnoea or cough
- An increase in opacities on chest radiograph or HRCT scan, especially the development of honeycombing or signs of pulmonary hypertension
- Evidence of deterioration in lung function in two or more of the following:
    - ≥10% decrease in TLC or VC (or ≥200-ml change)

- ≥15% decrease in single-breath DLco (or at least ≥3-ml/min/mm Hg change)
- Worsening (greater fall) of O_2 saturation (≥4 percentage point decrease in the measured saturation) or rise in the $AaPO_2$ at rest or during a formal cardiopulmonary exercise test (≥4 mm Hg increase from the previous measurement)

Percentage change in predicted FVC is a well recognised measure of disease progression or prognosis in IPF. The literature describes this measure as being more sensitive than many of the others that have been proposed such as DLco, SpO_2 and AaGradient changes. HCRT is useful regarding identifying current status of pulmonary fibrosis but has not been shown to be sensitive enough to indicate disease progression. The 6MWT is the other parameter which has been recognised as sensitive in determining prognosis.

Four double blind placebo controlled studies of the safety and efficacy of pirfenidone in the treatment of IPF support the marketing authorisation application (MAA). In chronological order they are SP2 (2000 to 2002) SP3 (2004 to 2006) both conducted in Japan; PIPF-004 and PIPF–006 (2006 to 2008) both conducted internationally.

SP2 is the smallest and weakest of the studies. It used a non-validated primary endpoint, oxygen desaturation during a treadmill exercise test and failed to distinguish active from placebo treatment. However, there was a statistically significant difference in the rate of decline of FVC and there was an important difference in the acute exacerbation rate at six months (which is not stated). By nine months 14% of placebo patients and none of the pirfenidone group had experienced an acute exacerbation. Data presentation in the CSR included in the MAA is very poor, in many sections it is so bad as to be uninterpretable. This is compounded by a poor translation; the linguistics may be correct but the translator has a poor grasp of the technical elements of the study. For these reasons the published version (Azuma 2005) has also been used in this assessment report.

SP3 is a considerably improved study compared to SP2 but still has significant shortcomings, the most significant of which is the change in the primary endpoint during the study. As with SP2 the initial primary endpoint was oxygen desaturation during exercise. However, during the study the DSMB recommended that it be altered to a pulmonary function endpoint change in VC. This recommendation appears to have been made with knowledge of the accruing comparative data. Overall, the study shows a statistically significant advantage for pirfenidone treatment in terms of rate of decline of VC and in exacerbation free survival.

PIPF-004 used lung function (FVC) as the primary variable and demonstrates a statistically significant, and clinically meaningful advantage in reduction of the rate of loss of lung volume and also in terms of a composite endpoint of death or disease progression.

PIPF-006 was conducted to a similar design as PIPF-004 other than only one dose of pirfenidone was studied. The advantage for pirfenidone in terms of rate of loss of lung which was seen in the 'central' part of the study (weeks 24 to 48) had lost statistical significance and clinical relevance by study end. For the composite endpoint of death or disease progression there isn't even a suggestion of a trend.

Pirfenidone has been shown to have a modest but measurable effect on reducing the rate of decline in the percentage predicted FVC which has been used as the primary efficacy endpoint in studies PIPF-004 and the pooled analysis of PIPF-004 and PIPF-006 at 72 weeks. PIPF-006 did not show any effect at 72 weeks In addition the PIPF-006 and the pooled analysis of PIPF-004 and PIPF-006 showed a significant increase in the walking distance in the 6MWT at 72 weeks. The mixed results obtained for the primary endpoint and the 6MWT which was a secondary endpoint remain unexplained by the Applicant. Perhaps the change in both protocols from a 60 week treatment period to a 72 week period

may explain in part what occurred. The pooled analysis of PIPF-004 and PIPF-006 however is acceptable from a statistical analysis point of view. This pooled analysis clearly showed that pirfenidone at a dose of 2403 mg/day was effective on the primary endpoint at 72 weeks and a highly relevant secondary end-point the 6MWT.

If the ATS/ERS joint statement is considered regarding the evaluation of clinical effectiveness of pirfenidone at 6 and 12 months it could be deduced that this product has a stabilising (presumed favourable effect) since the results comply with the parameters set in this document.

The Japanese study SP3 supports these findings with a small but significant effect on VC at 52 weeks with a 1800 mg/day dose of pirfenidone. The exploratory Japanese SP2 study showed a significant effect on VC which was a secondary parameter.

Other parameters measured did not show any significant effect at either dose tested of pirfenidone. This lack of effect of efficacy on these other parameters is disappointing and supports the assumption that the effect is modest. The implications for morbidity can only be assumed to be modest and the effects on mortality hypothesised if one bases the conclusions on the survival parameters defined in the exploratory analysis.

IPF is a disease characterised by its remorseless progression and refractoriness to treatment; so much so that, on an individual level, if a patient responds to treatment the diagnosis warrants careful re-evaluation. In these circumstances it is remarkable to have four studies showing a beneficial effect on the rate of decline of pulmonary function. The heterogeneity of the results, the methodological imperfections, the statistical shortcomings, are all acknowledged, but all the data point in the same direction namely that pirfenidone has a beneficial effect on slowing the rate of loss of functional lung volume in IPF.

A consideration in evaluating the benefit of pirfenidone is that it is not curative; patients still suffer from a fatal disease; therefore their quality of life during the extension offered by treatment is of major importance. Studies SP2 and SP3 utilised patient-reported outcome instruments to assess symptoms (principally dyspnoea): the Chronic Respiratory Questionnaire and the Hugh-Jones Classification. However, neither study incorporated other instruments to measure classical quality of life.

2.5.4. Conclusions on the clinical efficacy

Pirfenidone has a modest but measurable effect on FVC and the 6MWT. It can be assumed that pirfenidone at a dose of 2403 mg/day reduces the decline in FVC normally seen in patients with this condition. This would be the first time that a treatment would have shown some effect in reducing the rate of loss in pulmonary function in IPF as has been measured through parameters which are recognised as sensitive in determining the prognosis of these patients.

There is persuasive evidence that pirfenidone has a retarding effect on the rate of fibrosis in idiopathic pulmonary fibrosis.

2.6. Clinical safety

The safety database for pirfenidone contained in this application is derived from nine controlled and uncontrolled studies in patients with IPF plus the six clinical pharmacology studies.

Patient exposure

The Randomised Patient Subset contains only patients from the two Phase 3 studies, PIPF-004 and PIPF-006. Patients treated with pirfenidone in these two studies are included, together with the 83 pirfenidone-treated patients from PIPF-002, in the Pirfenidone Patient Subset (N = 515).

The Expanded Pirfenidone Patient Subset contains pooled data from 789 unique patients treated with pirfenidone in the two Phase 3 studies, the ongoing uncontrolled Phase 2 study (PIPF-002) and the ongoing uncontrolled Phase 3 extension study (PIPF-012).

In total, across all studies the total of pirfenidone-treated patients is 1103. An additional 242 subjects (healthy subjects or with hepatic or renal impairment) were exposed to pirfenidone in Phase 1 studies. The grand total of patients and subjects exposed to pirfenidone is 1345.

Adverse events

Results in this analysis of AEs concentrate on TEAEs in the Randomised Patient Subset and the Pirfenidone Patient Subsets in the pooled safety analyses. In these studies, TEAEs were defined as AEs that occurred after the first dose and within 28 days after the last dose of study treatment. Patients who discontinued study treatment but remained on study were followed for AEs until they withdrew from study; patients who withdrew prematurely from study were followed for AEs for 28 days after last dose of study treatment.

Common adverse events

Common TEAEs are presented in the table below.

Table 21 Common TEAEs in the randomised patient subset

Table 2.7.4-18 Common TEAEs in the Randomized Patient Subset

Common TEAEs	Number of Patients, n (%)		
System Organ Class Preferred Term	Pirfenidone 1197 mg/day (N = 87)	Pirfenidone 2403 mg/day (N = 345)	Placebo (N = 347)
Patients with Any Common TEAE	**85 (97.7%)**	**336 (97.4%)**	**326 (93.9%)**
Cardiac Disorders	**12 (13.8%)**	**20 (5.8%)**	**18 (5.2%)**
Angina Pectoris	6 (6.9%)	13 (3.8%)	16 (4.6%)
Atrial Fibrillation	6 (6.9%)	7 (2.0%)	4 (1.2%)
Ear and Labyrinth Disorders	**5 (5.7%)**	**10 (2.9%)**	**8 (2.3%)**
Vertigo	5 (5.7%)	10 (2.9%)	8 (2.3%)
Eye Disorders	**5 (5.7%)**	**7 (2.0%)**	**11 (3.2%)**
Cataract	5 (5.7%)	7 (2.0%)	11 (3.2%)
Gastrointestinal Disorders	**53 (60.9%)**	**254 (73.6%)**	**173 (49.9%)**
Nausea	22 (25.3%)	125 (36.2%)	60 (17.3%)
Diarrhoea	22 (25.3%)	99 (28.7%)	67 (19.3%)
Dyspepsia	12 (13.8%)	66 (19.1%)	26 (7.5%)
Vomiting	11 (12.6%)	47 (13.6%)	15 (4.3%)
Gastrooesophageal Reflux Disease	11 (12.6%)	36 (10.4%)	26 (7.5%)
Constipation	9 (10.3%)	34 (9.9%)	33 (9.5%)
Abdominal Distension	3 (3.4%)	33 (9.6%)	20 (5.8%)
Stomach Discomfort	4 (4.6%)	29 (8.4%)	6 (1.7%)
Abdominal Pain	6 (6.9%)	26 (7.5%)	12 (3.5%)
Abdominal Pain Upper	9 (10.3%)	25 (7.2%)	22 (6.3%)
Flatulence	8 (9.2%)	22 (6.4%)	19 (5.5%)
General Disorders and Administration Site Conditions	**39 (44.8%)**	**147 (42.6%)**	**112 (32.3%)**
Fatigue	25 (28.7%)	104 (30.1%)	71 (20.5%)
Asthenia	10 (11.5%)	24 (7.0%)	13 (3.7%)
Oedema Peripheral	7 (8.0%)	21 (6.1%)	32 (9.2%)
Non-Cardiac Chest Pain	7 (8.0%)	19 (5.5%)	15 (4.3%)
Pyrexia	6 (6.9%)	19 (5.5%)	20 (5.8%)

Table 2.7.4-18 Common TEAEs in the Randomized Patient Subset, continued

Common TEAEs	Number of Patients, n (%)		
System Organ Class Preferred Term	Pirfenidone 1197 mg/day (N = 87)	Pirfenidone 2403 mg/day (N = 345)	Placebo (N = 347)
Infections and Infestations	**59 (67.8%)**	**232 (67.2%)**	**231 (66.6%)**
Upper Respiratory Tract Infection	19 (21.8%)	106 (30.7%)	102 (29.4%)
Nasopharyngitis	20 (23.0%)	71 (20.6%)	82 (23.6%)
Bronchitis	13 (14.9%)	49 (14.2%)	60 (17.3%)
Sinusitis	7 (8.0%)	48 (13.9%)	40 (11.5%)
Urinary Tract Infection	6 (6.9%)	35 (10.1%)	29 (8.4%)
Influenza	3 (3.4%)	27 (7.8%)	25 (7.2%)
Gastroenteritis Viral	4 (4.6%)	19 (5.5%)	13 (3.7%)
Pneumonia	3 (3.4%)	16 (4.6%)	19 (5.5%)
Lower Respiratory Tract Infection	10 (11.5%)	11 (3.2%)	17 (4.9%)
Investigations	**12 (13.8%)**	**43 (12.5%)**	**20 (5.8%)**
Weight Decreased	8 (9.2%)	28 (8.1%)	12 (3.5%)
GGT Increased	5 (5.7%)	17 (4.9%)	8 (2.3%)
Metabolism and Nutrition Disorders	**12 (13.8%)**	**65 (18.8%)**	**22 (6.3%)**
Anorexia	9 (10.3%)	37 (10.7%)	13 (3.7%)
Decreased Appetite	3 (3.4%)	30 (8.7%)	10 (2.9%)
Musculoskeletal and Connective Tissue Disorders	**33 (37.9%)**	**92 (26.7%)**	**84 (24.2%)**
Arthralgia	9 (10.3%)	36 (10.4%)	24 (6.9%)
Back Pain	15 (17.2%)	35 (10.1%)	28 (8.1%)
Pain In Extremity	7 (8.0%)	29 (8.4%)	31 (8.9%)
Myalgia	6 (6.9%)	19 (5.5%)	16 (4.6%)
Nervous System Disorders	**23 (26.4%)**	**107 (31.0%)**	**79 (22.8%)**
Headache	14 (16.1%)	65 (18.8%)	56 (16.1%)
Dizziness	14 (16.1%)	63 (18.3%)	35 (10.1%)
Psychiatric Disorders	**21 (24.1%)**	**64 (18.6%)**	**52 (15.0%)**
Insomnia	13 (14.9%)	34 (9.9%)	23 (6.6%)
Depression	9 (10.3%)	21 (6.1%)	20 (5.8%)
Anxiety	6 (6.9%)	14 (4.1%)	17 (4.9%)
Respiratory, Thoracic and Mediastinal Disorders	**55 (63.2%)**	**196 (56.8%)**	**207 (59.7%)**
Cough	32 (36.8%)	103 (29.9%)	100 (28.8%)
Dyspnoea	22 (25.3%)	64 (18.6%)	77 (22.2%)
Idiopathic Pulmonary Fibrosis	9 (10.3%)	55 (15.9%)	74 (21.3%)
Productive Cough	8 (9.2%)	24 (7.0%)	21 (6.1%)
Pharyngolaryngeal Pain	2 (2.3%)	24 (7.0%)	16 (4.6%)
Nasal Congestion	5 (5.7%)	22 (6.4%)	26 (7.5%)
Postnasal Drip	3 (3.4%)	12 (3.5%)	20 (5.8%)
Wheezing	6 (6.9%)	9 (2.6%)	5 (1.4%)
Haemoptysis	5 (5.7%)	7 (2.0%)	6 (1.7%)

Table 2.7.4-18 Common TEAEs in the Randomized Patient Subset, continued

Common TEAEs	Number of Patients, n (%)		
System Organ Class Preferred Term	Pirfenidone 1197 mg/day (N = 87)	Pirfenidone 2403 mg/day (N = 345)	Placebo (N = 347)
Skin and Subcutaneous Tissue Disorders	**28 (32.2%)**	**152 (44.1%)**	**62 (17.9%)**
Rash	15 (17.2%)	111 (32.2%)	40 (11.5%)
Photosensitivity Reaction	6 (6.9%)	42 (12.2%)	6 (1.7%)
Pruritus	5 (5.7%)	22 (6.4%)	14 (4.0%)
Erythema	6 (6.9%)	13 (3.8%)	12 (3.5%)
Vascular Disorders	**9 (10.3%)**	**30 (8.7%)**	**19 (5.5%)**
Hot Flush	3 (3.4%)	18 (5.2%)	4 (1.2%)
Hypertension	6 (6.9%)	14 (4.1%)	15 (4.3%)

Source: ISS Table 3.2-1
Common TEAEs are those occurring in ≥5% of patients in any treatment group.

Anorexia

Anorexia was reported by 37 (10.7%) patients treated with pirfenidone 2403 mg/day, compared with 13 (3.7%) patients treated with placebo and 9 (10.3%) patients treated with pirfenidone 1197 mg/day. Across all three treatment groups, most patients had a single event, and for most affected patients, the investigator considered anorexia to be related to study treatment.

One patient treated with pirfenidone 2403 mg/day experienced Grade 3 anorexia. No patients experienced Grade 4 anorexia. Just four patients in the pirfenidone 2403 mg/day group required medical treatment for anorexia. The dose of study treatment was modified in one patient each in the pirfenidone 2403 mg/day and 1197 mg/day groups and in no patients in the placebo group.

Pirfenidone 1800 mg/day and placebo rates of anorexia were 32.9% and 5.6%, respectively, in SP2, and 16.5% and 2.8%, respectively, in study SP3.

Decreased appetite

Decreased appetite was reported by 30 (8.7%) patients treated with pirfenidone 2403 mg/day, 10 (2.9%) patients treated with placebo, and 3 (3.4%) patients treated with pirfenidone 1197 mg/day. In the pirfenidone 2403 mg/day group, older patients were slightly more likely than younger patients to report decreased appetite. In the three treatment groups, decreased appetite was mild or moderate, most patients had a single event, and for most patients, the investigator considered decreased appetite to be related to study treatment. No patients discontinued study treatment for this event. The median duration of decreased appetite was longer in the pirfenidone 2403 mg/day group compared with the placebo group.

Most patients treated with pirfenidone 2403 mg/day who first reported decreased appetite did so within the first 18 weeks of treatment.

In study SP3, decreased appetite was recorded for 9.2% in the pirfenidone 1800 mg/day group and 2.8% in the placebo group

Photosensitivity Reactions

A photosensitivity reaction was reported by 42 (12.2%) patients treated with pirfenidone 2403 mg/day, compared with 6 (1.7%) patients treated with placebo and 6 (6.9%) patients treated with pirfenidone 1197 mg/day. The majority of patients had a single event, most events resolved, and

for all affected patients, the investigator considered the photosensitivity reaction to be related to study treatment. The median duration of the photosensitivity reaction was longer in the pirfenidone 2403 mg/day group than in the placebo group. Nearly half of the patients in the pirfenidone 2403 mg/day group who reported photosensitivity reaction first did so between Weeks 0 and 18.

Three patients treated with pirfenidone 2403 mg/day and one patient treated with placebo experienced a Grade 3 photosensitivity reaction. No patients experienced a Grade 4 photosensitivity reaction. No patients were hospitalized for a photosensitivity reaction.

More patients in the pirfenidone 2403 mg/day group than in the placebo group required medical treatment for the photosensitivity reaction. Approximately half of the patients who developed a photosensitivity reaction were treated with a corticosteroid, which was more often a topical than a systemic product. The dose of study treatment was modified for a photosensitivity reaction in more patients treated with pirfenidone 2403 mg/day than with placebo.

Slightly more male than female patients treated with pirfenidone 2403 mg/day reported a photosensitivity reaction.

Figure 12 Kaplan Meier estimates of time to photosensitivity reaction or rash in the randomised patient subset

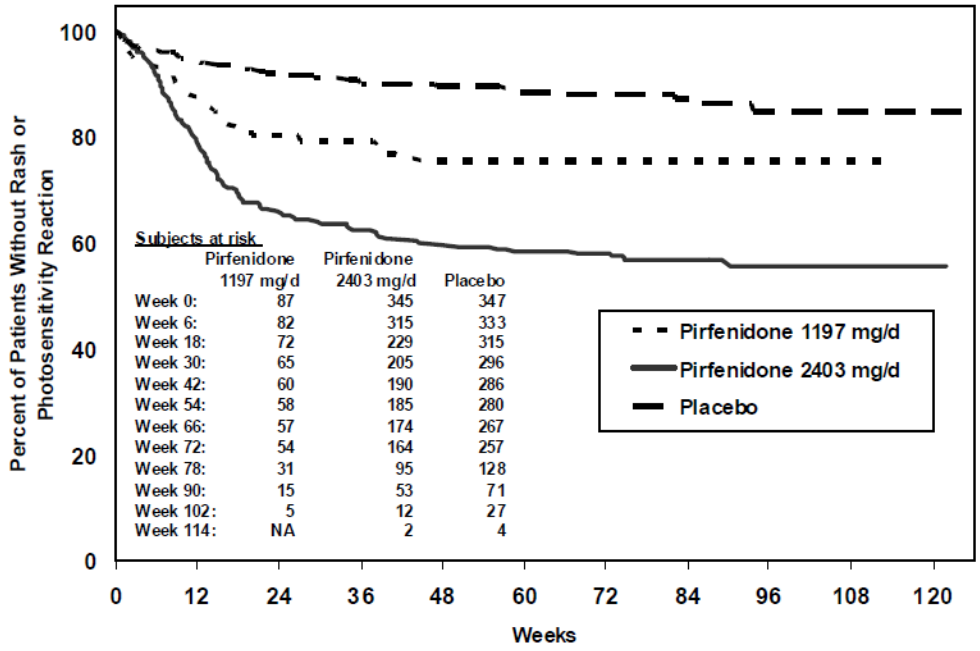


Figure 2.7.4-2 Kaplan-Meier Estimates of Time to Photosensitivity Reaction or Rash in the Randomized Patient Subset

Source: ISS Figure 11

Note: Time to event is defined as onset of rash or photosensitivity date minus study treatment start date plus one. Includes AEs whose PTs are "Rash" or "Photosensitivity Reaction" using MedDRA version 11.0.

Figure 13 Rate of photosensitivity reaction or rash by month of occurrence in patients in the randomised patient subset

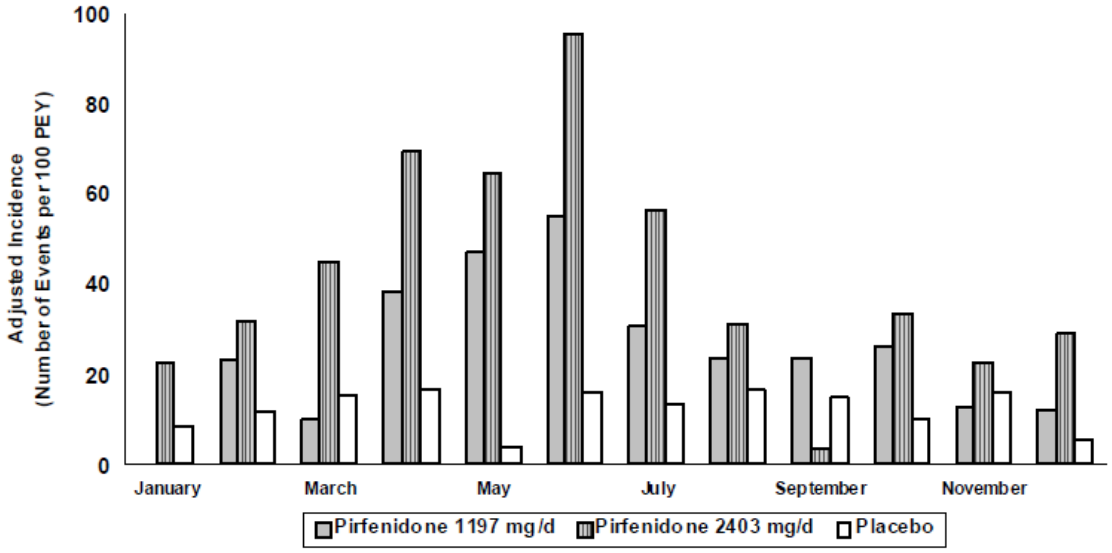


Figure 2.7.4-3 Rate of Photosensitivity Reaction or Rash by Month of Occurrence in Patients in the Randomized Patient Subset

The intermediate frequency of these events in patients receiving pirfenidone 1197 mg/day compared with pirfenidone 2403 mg/day further supports an association with pirfenidone.

The following terms related to skin cancer were identified within the SOC of Neoplasms Benign, Malignant and Unspecified (including Cysts and Polyps) and the SOC of Skin and Subcutaneous Tissue Disorders, respectively: basal cell carcinoma, keratocanthoma, malignant melanoma, melanocytic nevus, metastatic squamous cell carcinoma, skin cancer, squamous cell carcinoma, and squamous cell carcinoma of skin; actinic keratosis, precancerous skin lesion, skin ulcer, and subcutaneous nodule. The percentages of patients in the pirfenidone and placebo groups who developed these TEAEs are similar.

Photosensitivity reactions and rashes represent a readily manageable tolerability issue that is not associated with significant clinical sequelae. No cases of Stevens-Johnson syndrome, erythema multiforme, pemphigus, or toxic epidermal necrolysis have been reported in patients receiving pirfenidone in the studies.

Serious adverse event/deaths/other significant events

The incidence of death from any cause was 7.6%, the adjusted mortality incidence was 5.1, and the majority of deaths (28/39) were related to IPF in the Pirfenidone Patient Subset. The most common causes of death were IPF (n = 13) and respiratory failure (n = 11).

Figure 14 Incidence and IPF-relatedness of treatment-emergent deaths

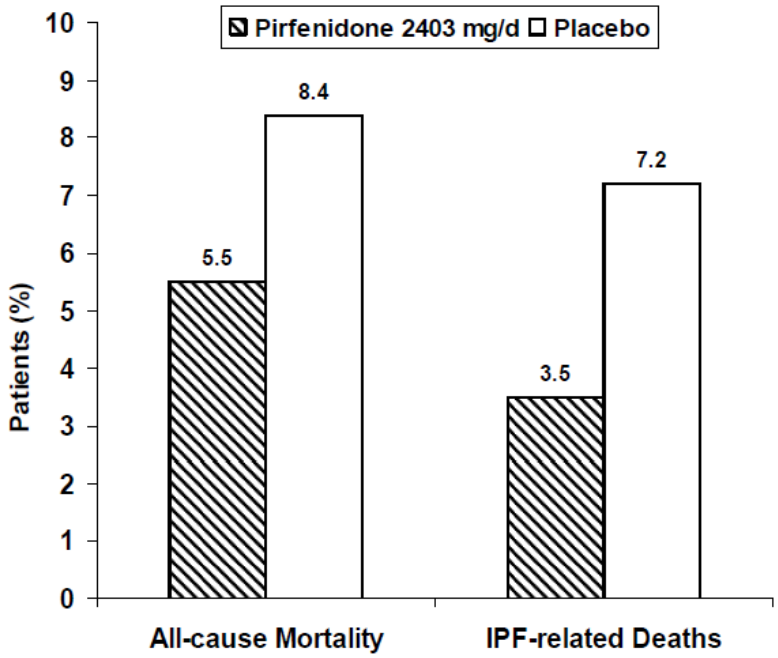


Figure 2.7.4-1 Incidence and IPF-Relatedness of Treatment-Emergent Deaths

Source: ISS Table 3.3-3

Serious Adverse Events

Overall, the proportions of patients who experienced SAEs were comparable across all treatment groups and patient subsets (range 32.3% to 35.7%). The numbers of patients experiencing individual TE SAEs were small; however, no striking imbalances were noted.

Table 22 Treatment-emergent SAEs that occurred in ≥2 patients and at a greater incidence in either pirfenidone group than in the placebo group in the randomised patient subset

Table 2.7.4-26 Treatment-Emergent SAEs that Occurred in ≥2 Patients and at a Greater Incidence in Either Pirfenidone Group than in the Placebo Group in the Randomized Patient Subset

Treatment-Emergent SAEs	Number of Patients, n (%)		
System Organ Class Preferred Term	Pirfenidone 1197 mg/day (N = 87)	Pirfenidone 2403 mg/day (N = 345)	Placebo (N = 347)
Patients with Any TE SAE	28 (32.2%)	113 (32.8%)	109 (31.4%)
Cardiac Disorders	11 (12.6%)	21 (6.1%)	17 (4.9%)
Coronary Artery Disease	3 (3.4%)	6 (1.7%)	2 (0.6%)
Atrial Fibrillation	3 (3.4%)	3 (0.9%)	2 (0.6%)
Angina Pectoris	2 (2.3%)	3 (0.9%)	2 (0.6%)
Cardiac Failure Congestive	0	2 (0.6%)	1 (0.3%)
Sick Sinus Syndrome	0	2 (0.6%)	0
Gastrointestinal Disorders	**3 (3.4%)**	**8 (2.3%)**	**13 (3.7%)**
Colitis	0	2 (0.6%)	1 (0.3%)
Gastrooesophageal Reflux Disease	0	2 (0.6%)	0
General Disorders and Administration Site Conditions	**3 (3.4%)**	**8 (2.3%)**	**5 (1.4%)**
Chest Pain	0	4 (1.2%)	0
Infections and Infestations	**10 (11.5%)**	**27 (7.8%)**	**32 (9.2%)**
Respiratory Tract Infection	0	2 (0.6%)	0
Injury, Poisoning and Procedural Complications	**1 (1.1%)**	**10 (2.9%)**	**2 (0.6%)**
Fall	0	3 (0.9%)	1 (0.3%)
Hip Fracture	0	2 (0.6%)	0
Investigations	**1 (1.1%)**	**2 (0.6%)**	**3 (0.9%)**
Liver Function Test Abnormal	1 (1.1%)	2 (0.6%)	0
Musculoskeletal and Connective Tissue Disorders	**3 (3.4%)**	**7 (2.0%)**	**4 (1.2%)**
Intervertebral Disc Protrusion	0	2 (0.6%)	0

Table 2.7.4-26 Treatment-Emergent SAEs that Occurred in ≥2 Patients and at a Greater Incidence in Either Pirfenidone Group than in the Placebo Group in the Randomized Patient Subset, continued

Treatment-Emergent SAEs	Number of Patients, n (%)		
System Organ Class Preferred Term	Pirfenidone 1197 mg/day (N = 87)	Pirfenidone 2403 mg/day (N = 345)	Placebo (N = 347)
Neoplasms Benign, Malignant and Unspecified (including cysts and polyps)	**5 (5.7%)**	**12 (3.5%)**	**17 (4.9%)**
Bladder Cancer	0	3 (0.9%)	1 (0.3%)
Small Cell Lung Cancer Stage Unspecified	0	2 (0.6%)	1 (0.3%)
Rectal Cancer	2 (2.3%)	0	0
Nervous System Disorders	**3 (3.4%)**	**8 (2.3%)**	**10 (2.9%)**
Syncope	1 (1.1%)	3 (0.9%)	1 (0.3%)
Cerebrovascular Accident	0	2 (0.6%)	1 (0.3%)
Psychiatric Disorders	**0**	**2 (0.6%)**	**2 (0.6%)**
Suicidal Ideation	0	2 (0.6%)	0
Renal and Urinary Disorders	**2 (2.3%)**	**8 (2.3%)**	**5 (1.4%)**
Renal Failure Acute	2 (2.3%)	3 (0.9%)	2 (0.6%)
Nephrolithiasis	0	2 (0.6%)	0
Respiratory, Thoracic and Mediastinal Disorders	**11 (12.6%)**	**40 (11.6%)**	**46 (13.3%)**
Pneumothorax	2 (2.3%)	4 (1.2%)	1 (0.3%)
Pleural Effusion	1 (1.1%)	2 (0.6%)	0
Pulmonary Embolism	3 (3.4%)	1 (0.3%)	1 (0.3%)
Vascular Disorders	**3 (3.4%)**	**6 (1.7%)**	**3 (0.9%)**
Aortic Aneurysm	1 (1.1%)	2 (0.6%)	1 (0.3%)
Hypotension	0	2 (0.6%)	1 (0.3%)

Source: ISS Table 3.4-5

Laboratory findings

Haematology

Overall, the mean changes from Baseline to Week 72 in haematology parameters were similar across treatment groups.

Serum Chemistry

Overall, the mean changes from Baseline to Week 72 in serum chemistry parameters were similar across treatment groups with the exception of GGT and creatinine. The mean increase in GGT level for patients in the pirfenidone 2403 mg/day group was 7.6 U/L compared with 0.0 U/L for patients in the placebo group. The mean change for patients in the pirfenidone 1197 mg/day group was slightly less at 5.1 U/L. In patients treated with pirfenidone 2403 mg/day, the mean creatinine level decreased -5.6 µmol/L compared with -1.1 µmol/L in patients treated with placebo. The mean creatinine decrease in patients in the pirfenidone 1197 mg/day group was -4.5 µmol/L. Minimal mean changes were observed in the three treatment groups in all other clinical chemistry parameters.

Safety in special populations

Study PIPF-011 was performed to study possible pharmacokinetic and safety issues in patients with moderate hepatic insufficiency. It showed a 60% increase in exposure to pirfenidone. This is reflected in the SPC recommendation for close monitoring of such patients.

Study PIPF-009 was performed to study possible pharmacokinetic and safety issues in patients with mild to moderate renal insufficiency. No relationship between renal insufficiency and pirfenidone levels was found. However, increased exposure to the metabolite 5-carboxy-pirfenidone was seen with decreasing creatinine clearance. It should be noted that this metabolite does not seem to have any significant biological action.

Safety related to drug-drug interactions and other interactions

Effect of Antacid Co-administration

The results of Study PIPF-005 indicated that co-administration of Mylanta Maximum Strength Liquid did not appear to substantially affect the PK of pirfenidone in either fed or fasted subjects.

Concomitant CYP1A2 Inhibitors and Inducers

Results of nonclinical, in vitro experiments indicate that pirfenidone is primarily metabolized by CYP enzymes. Of the portion converted, CYP1A2, 2C9, and 2C19 accounted for 65% of the metabolism; combining these three isozymes with CYP2D6 and 2E1 accounted for 85% of the low-level oxidative metabolism (PCLN-PIRF-111). In a separate study (PCLN-PIRF-112), antibodies against CYP1A2 caused an approximate 40% inhibition of conversion to the 5-hydroxy and 5-carboxy metabolites. Smaller extents of inhibition (<15%) were observed with antibodies against other CYPs. Therefore a multitude of CYP isozymes appear to play a role in pirfenidone metabolism, although the results shown and the modelling performed indicate that CYP1A2 is the most important.

PIPF-010 was designed to assess the effect of CYP1A2 inhibition and/or induction on the pharmacokinetics of pirfenidone in subjects. The co-administration of fluvoxamine resulted in a significant drug interaction such that exposure ($AUC_{0-\infty}$) to pirfenidone was, on average, nearly 6 times higher after 10 days of dosing with fluvoxamine. Subjects also experienced, on average, a 2-fold increase in C_{max} after administration of fluvoxamine. The $AUC_{0-\infty}$ of 5-carboxy pirfenidone was not significantly different before and after fluvoxamine administration. This is most likely due to the fact that the 5-carboxy metabolite is cleared predominantly through renal mechanisms. The results of PIPF-010 also indicated that smoking has the potential to induce pirfenidone metabolism as $AUC_{0-\infty}$ estimates were significantly lower in smokers as compared to non-smokers. Smoking did not have an effect on 5-carboxy pirfenidone clearance.

Drugs that are moderate-strong inhibitors of both CYP1A2 and other CYP isozymes (CYP2C9, 2C19, and 2D6) should not be used in combination with pirfenidone. Despite the lack of apparent drug interactions with co-administration of specific CYP1A2 inhibitors in the Phase 3 clinical trial, and no evidence of a clinical pattern of AEs with pirfenidone 2403 mg/day being associated with concomitant use of CYP1A2 inhibitors, results of nonclinical studies suggest that strong CYP1A2 inhibitors should be used with caution in patients receiving pirfenidone due to the potential for reduced pirfenidone clearance.

Concomitant strong CYP1A2 inducers should also be avoided based on the established relationship between cigarette smoking, which causes CYP1A2 induction, and reduced pirfenidone PK exposure.

There was no evidence of a clinical pattern of TEAEs with pirfenidone and the concomitant use of commonly used medications or prohibited IPF medications.

Discontinuation due to adverse events

Relatively few patients overall discontinued treatment early due to AEs, particularly when considering the length of these studies and the progressive IPF disease state. Only 6.2% more patients in the pirfenidone 2403 mg/day group than in the placebo group discontinued treatment due to an AE (14.8% versus 8.6%, respectively).

A smaller percentage of patients in the pirfenidone 1197 mg/day group discontinued treatment early (10.3%) compared with the pirfenidone 2403 mg/day patients. Too few patients discontinued study treatment to draw meaningful conclusions about a pattern as to when patients were discontinuing due to the AE.

IPF was the most common AE leading to discontinuation in all three treatment groups (range, 2.3% to 2.9%). AEs leading to discontinuation by ≥2 patients in the pirfenidone 2403 mg/day group and at a higher rate than the placebo or pirfenidone 1197 mg/day groups included nausea (1.4%), rash (1.4%), bladder cancer (0.9%), respiratory failure (0.9%), photosensitivity reaction (0.9%), and weight decreased (0.6%).

2.6.1. Discussion on clinical safety

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

Pirfenidone does not appear to be associated with unexpected serious adverse events which could be considered to be life threatening. The death rate in the combined Phase III data sets indicates that the death rate for the 2403 mg dose of pirfenidone was lower than the placebo rate at 72 weeks. This would correlate with the effects on FVC that have been presented in the pooled analysis. There were no notable effects on cardiac QTc or other cardiac associated adverse events.

Pirfenidone is however associated with a dose response effect regarding gastro-intestinal side-effects notably nausea, vomiting, diarrhoea, dyspepsia. There was an increase in anorexia and poor appetite but this was not consistently dose related. There was a dose ranging effect regarding phototoxicity which presents itself as a rash primarily which is transient. It should however be noted that the reporting incidence is closely associated with increased exposure to sunlight. The phototoxic potential of pirfenidone does not seem to associated with life threatening skin side-effects.

Asthenia has been also reported more frequently in the pirfenidone group but this is not dose related.

Pirfenidone has the potential for drug interactions hepatically. In renally impaired patients its metabolite 5-carboxy-pirfenidone is excreted at a lower rate leading to an increase in plasma concentrations. In addition it should be noted that hepatic metabolism produces two other metabolites. These aspects are adequately addressed in the SmPC and the Risk Management Plan.

2.6.2. Conclusions on the clinical safety

Pirfenidone is associated with a dose effect regarding gastro-intestinal and phototoxicity adverse events. There are no serious unexpected adverse events which report at a higher rate than those seen in placebo. The death rate is lower than that seen in placebo and this seems to be driven by an effect on IPF.

The phototoxicity was transient (up to 18months following initiation of therapy) and presented itself often as a rash. The incidence of reporting increases in the summer months indicating that there is a relationship with increased exposure to solar light.

There was a slight increase in adverse events associated with connective tissue disorders (2% 2403 mg pirfenidone vs 1.2% placebo). This is a very small difference but maybe be due to the proposed antifibrotic mode of action of this product.

Discontinuation of therapy due to adverse events was higher and dose related when compared with placebo. This was primarily driven by an increase in adverse events associated with respiratory, gastro-intestinal and skin system reporting areas.

Pirfenidone has the ability to interact hepatically with other drugs and its plasma levels increase in patients with hepatic insufficiency. In renally impaired patients the plasma concentrations of its minimally active metabolite 5-carboxy pirfenidone increase.

The SmPC adequately describes the safety profile of pirfenidone based on the available data. Additional aspects are covered by the Risk Management Plan. This includes the conduct of a prospective observational registry to evaluate the long-term safety of pirfenidone for the treatment of IPF in a real-world setting.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important Identified risks		
1.Photosensitivity reaction and rash	- Monitor and follow-up spontaneous reports - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - Prepare a case definition for photosensitivity reaction and the related rash - A PASS Registry will be used to collect additional data regarding this risk	- Recommendation for dose modification in section 4.2 of the SmPC - Warning in section 4.4 of the SmPC that cautions against direct exposure to sunlight - Listed under section 4.8 of the SmPC as a very common undesirable effect - A Safety Checklist on monitoring and management of photosensitivity reaction and rash
2.Abnormal liver function tests, increased ALT and AST levels	- Monitor and follow-up spontaneous reports - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - Prepare a case definition	- Recommendation for dose modification in section 4.2 of the SmPC - Contraindicated in section 4.3 in patients with severe hepatic impairment or end stage liver disease - Warning in section 4.4 of the SmPC with respect to liver function test monitoring

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	for hepatic ADRs - Standard MedDRA Queries (SMQs) will be used to identify safety signals - A PASS Registry will be used to collect additional data regarding this risk	- Listed under section 4.8 of the SmPC as common undesirable effects - A Safety Checklist on monitoring and management of hepatic related events
3.Dizziness	- Monitor and follow-up as spontaneous adverse reactions. - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this risk	- Recommendation in section 5.2 of the SmPC regarding method of administration that Esbriet is to be taken orally with food to reduce the possibility of nausea and dizziness - Warning in section 4.4 of the SmPC that patients should know how they react to this medicinal product before they engage in activities requiring mental alertness or coordination - Caution in section 4.7 of the SmPC that Esbriet may cause dizziness and fatigue, which could influence the ability to drive or use machines - Listed under section 4.8 of the SmPC as a common undesirable effect
4.Weight loss	- Monitor and follow-up as spontaneous adverse reactions of special interest - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this risk	- Warning in section 4.4 of the SmPC that patient's weight should be monitored by the Physician - Listed under section 4.8 of the SmPC as a common undesirable effect
5.GI symptoms (Diarrhoea, dyspepsia, nausea, vomiting, GERD and stomach discomfort)	- Monitor and follow-up as spontaneous adverse reactions - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this risk	- Advice in section 4.2 of the SmPC regarding method of administration that Esbriet is to be taken orally with food in patients who experience intolerance due to GI side effects - Listed under section 4.8 of the SmPC as very common and common undesirable effects
6.Fatigue	- Monitor and follow-up as spontaneous adverse reactions - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this risk	- Warning in section 4.4 of the SmPC that patients should know how they react to the drug before engaging in activities requiring mental alertness and coordination - Caution in section 4.7 of the SmPC that Esbriet may cause dizziness and fatigue, which could influence the ability to drive or use machines - Listed under section 4.8 of the SmPC as a very common undesirable effect

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Important Potential risks		
1. Falls	- Monitor and follow-up as spontaneous adverse reactions of special interest - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this risk	- Warning in section 4.4 of the SmPC that patients should know how they react to this medicinal product before they engage in activities requiring mental alertness or coordination
2. Specific cardiac events (supraventricular tachyarrhythmia, atrioventricular block/sick sinus syndrome, ventricular arrhythmia, bundle branch block, aortic or pulmonic valvular incompetence)	- Monitor and follow-up as spontaneous adverse reactions of special interest - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this risk	None
3. Increased platelet count	- Monitor and follow-up as spontaneous adverse reactions of special interest - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this risk	None
4. Off-label use	- Monitor and follow-up spontaneous reporting after having advised healthcare professional to report all cases of off-label use - A PASS Registry will be used to collect additional data regarding this risk - Quarterly review of all off-label use reports and assess if any action is required to maintain patient safety	None
5. Potential drug interactions (including smoking)	- Monitor and follow-up spontaneous reporting and carefully distinguish suspect from concomitant medicines. - The database will be screened for pairing of pirfenidone with other products and resulting	- Interaction possibility with inhibitors and inducers of CYP1A2 enzyme mentioned in section 4.5 of the SmPC

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	ADRs - A post-approval DDI study will be carried out to determine the impact of a moderate CYP1A2 inhibitor on the PK and safety of pirfenidone in healthy subjects - A PASS Registry will be used to collect additional data regarding this risk	
Important Missing information		
1. Patients being treated concomitantly with immunosuppressants	- Monitor and follow-up spontaneous reporting after having advised healthcare professional to report all clinically significant ADRs in these patients - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this missing information.	None
2. Patients with secondary causes of pulmonary fibrosis	- Monitor and follow-up spontaneous reporting after having advised healthcare professional to report all clinically significant ADRs in these patients - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this missing information.	None
3. Patients with pre-existing risk factors for hepatic dysfunction such as alcohol abuse and diabetes	- Monitor and follow-up spontaneous reporting after having advised healthcare professional to report all clinically significant ADRs in these patients - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this missing	- Recommendation for dose modification in section 4.2 of the SmPC. To be used with caution in patients with pre-existing mild to moderate hepatic impairment - Contraindicated in section 4.3 of the SmPC in patients with severe hepatic impairment or end stage liver disease - Warning in section 4.4 of the SmPC with respect to use in hepatic impairment

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	information.	
4. Patients with pre-existing prolonged QT interval	- Monitor and follow-up spontaneous reporting after having advised healthcare professional to report all clinically significant ADRs in these patients - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this missing information.	None
5. Patients with severe underlying cardiac, hepatic or any other form of pulmonary disease	- Monitor and follow-up spontaneous reporting after having advised healthcare professional to report all clinically significant ADRs in these patients - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this missing information.	- Recommendation for dose modification in section 4.2 of the SmPC. To be used with caution in patients with pre-existing mild to moderate hepatic impairment - Contraindicated in section 4.3 of the SmPC in patients with severe hepatic impairment or end stage liver disease - Warning in section 4.4 of the SmPC with respect to hepatic effects. To be used with caution in patients with pre-existing mild to moderate hepatic impairment, not recommended in patients with severe hepatic impairment
6. Patient treated concomitantly with other IPF treatments	- Monitor and follow-up spontaneous reporting after having advised healthcare professional to report all clinically significant ADRs in these patients - Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this missing information.	None
7. Patients suffering from severe stages of IPF	- Monitor and follow-up spontaneous reporting after having advised healthcare professional to report all clinically significant ADRs in these patients	None

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
	- Quarterly review of all ADR reports and assess if any action is required to maintain patient safety - A PASS Registry will be used to collect additional data regarding this missing information.	
8. Exposure during pregnancy and lactation	- Monitor and follow-up spontaneous reporting after having advised healthcare professional to report all cases of exposure during pregnancy and lactation - A PASS Registry will be used to collect additional data regarding the exposure and outcome during pregnancy and lactation - Quarterly review of all reports of exposure during pregnancy and lactation, and assess if any action is required to maintain patient safety	None

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

A risk minimisation plan has been proposed to address safety concerns with photosensitivity/rash, abnormal liver function tests, dizziness, weight loss, gastrointestinal symptoms, fatigue, falls and potential drug interactions in clinical practice. In addition to routine labelling, this entails educational materials for prescribers (comprising a Direct Healthcare Professional Communication, safety checklist, and educational materials):

Safety concern	**Photosensitivity reaction and rash**	
Routine risk minimisation activities	- Recommendation for dose modification in section 4.2 of the SmPC - Warning in section 4.4 of the SmPC that cautions against direct exposure to sunlight - Listed under section 4.8 of the SmPC as a very common undesirable effect	
Additional risk minimisation activity	Proposed actions:	A Safety Checklist about monitoring and management of photosensitivity reaction and rash will be made available at the time of launch for all medical staff involved in managing patients. It will recommend reporting to the InterMune of all clinically significant ADRs of photosensitivity reaction and rash where an association is suspected.
	Objective and rationale:	Intensify communication and education around photosensitivity reaction and rash with measures to avoid exposure to sun and other UV sources and risk of photosensitivity reactions.
	Criteria to be used to verify success of proposed risk minimisation activity:	Monitor spontaneous reports and ADRs received through the PASS Registry assess if comparable to that expected in clinical trial programme. Anticipate low reporting frequency of clinically significant ADRs.
	Proposed review period:	At a minimum every 3 months
Safety concern	**Abnormal liver function tests, increased ALT and AST levels**	
Routine risk minimisation activities	- Recommendation for dose modification in section 4.2 of the SmPC - Contraindicated in section 4.3 in patients with severe hepatic impairment or end stage liver disease - Warning in section 4.4 of the SmPC with respect to liver function test monitoring - Listed under section 4.8 of the SmPC as common undesirable effects	
Additional risk minimisation activity	Proposed actions:	A Safety Checklist about monitoring and management of hepatic related events including asymptomatic abnormal levels of ALT /AST will be made available at the time of launch for all medical staff involved in managing patients. It will recommend reporting to the InterMune of all clinically significant ADRs of liver related abnormalities.
	Objective and rationale:	Additional communication and educational materials will help to minimise the risk of hepatotoxicity.
	Criteria to be used to verify success of proposed risk minimisation activity:	Monitor spontaneous reports and ADRs received through the PASS Registry and assess if comparable to that expected in clinical trial programme. Anticipate low reporting frequency of clinically significant ADRs.
	Proposed review period:	At a minimum every 3 months.

Other safety concerns are addressed through routine risk minimisation measures (labelling).

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the Applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8. Benefit-Risk Balance

Benefits

Pirfenidone has been shown to have some modest effect on idiopathic pulmonary fibrosis following 72 weeks therapy. This would appear to affect patient outcome by reducing mortality rates which are primarily linked to idiopathic pulmonary fibrosis. Indeed there was a reduction in the reported death rate in the pirfenidone treated patients when compared to the control group in the integrated safety summary.

- Beneficial effects

The Applicant has presented data which has shown potential benefits on absolute change to percent predicted FVC and the 6MWT after 72 weeks in patients diagnosed with mild to moderate idiopathic pulmonary fibrosis in a pooled analysis of two Phase III studies PIPF-004 and PIPF-006.These findings were supported by two Japanese studies SP2 (Phase II) and SP3 (Pivotal Phase III). Measurable effects were seen with 1800 mg and 2403 mg/day of pirfenidone. The data would support the concept of a dose effect with the maximal effect being obtained with a dose of 2403 mg/day. There was a noted decrease in the reporting rate for mortality at 72 week in both Phase III studies when compared to the control group for the higher dose of pirfenidone. The Applicant indicates that this is associated with deaths driven by causes associated with idiopathic pulmonary fibrosis.

- Uncertainty in the knowledge about the beneficial effects

The primary problem with this submission and the beneficial effects presented is that the PIPF-006 did not show a significant effect at 72 weeks for the absolute change in percent predicted FVC. This trial showed a positive effect until week 48 between the treated and active groups. This was lost at week 60. Inversely the 6MWT showed a favourable trend in PIPF-004 in favour of the 2403 mg dose of pirfenidone at week 72, whereas in PIPF-006 this parameter was highly significantly in favour of the 2403 mg/day treated pirfenidone group. The higher reduction in the mortality reporting rate is based on observational data and is derived from small numbers. To substantiate this claim a proper outcome study over a period of several years would be necessary.

Risks

Pirfenidone has not been associated with serious life threatening adverse events, however two organ systems the gastro-intestinal system and skin system are primarily affected by undesirable adverse events associated with pirfenidone. There is an increase in the reporting rates for loss of appetite and loss of weight which are not dose related. Pirfendone has a potential for hepatic drug interactions. Its plasma concentration increases in patients with hepatic insufficiency. In patients with renal insufficiency the plasma concentrations of its metabolite 5-carboxy pirfenidone increase, however, the metabolite does not seem to be significantly active or affect adverse event rates.

Pirfenidone has been shown to have phototoxicity and rash where the reporting rate has also been shown to be dose related. These events affecting the skin progressively disappear after 18 weeks therapy. In man pirfendione is metabolised into three different metabolites. While the Applicant has discussed some of the characteristics of 5-carboxy pirfenidone, little is known regarding the othertwo, although they do not seem to be produced in any detectable amounts in humans. Pirfenidone has been described as an antifibrotic agent, which would suggest that it could affect the connective repairing systems in other parts of the body.

- Unfavourable effects

The gastro-intestinal side-effects are associated with increases in nausea, vomiting, dyspepsia and diarrhoea. These adverse events increase in rate with an increase in the dose of pirfenidone. Anorexia and loss of weight have also been noted. Skin phototoxicity and rash have also been reported in patients and the reporting rate increases with dose. Hepatic drug interactions have been demonstrated with pirfenidone and its plasma concentrations increase in patients with hepatic insufficiency. The plasma concentrations of 5-carboxy pirfenidone increase in patients with renal insufficiency, however, the metabolite does not seem to be significantly active or affect adverse event rates.

- Uncertainty in the knowledge about the unfavourable effects

Dosing effects have been noted for two organ system adverse events, the gastro-intestinal and skin systems. The mechanisms by which pirfenidone is affecting both systems are unknown and could be different. The use of pirfenidone has been only shown with fluvoxamine and in patients who smoke. It is not clear if there are other mechanisms by which pirfenidone is metabolised.

Benefit-risk balance

A modest but measureable therapeutic effect on FVC has been demonstrated in patients with idiopathic pulmonary fibrosis when high dose pirfenidone is used for 72 weeks. This was also seen for the 6MWT. No serious unexpected life threatening adverse events have been reported in the safety data set which is extensive and has measured the use of pirfenidone up to 144 weeks. A dose effect in the reporting rate of gastro-intestinal and skin associated adverse events has been recorded. Pirfenidone is associated with hepatic drug interactions and increased plasma levels in patients with hepatic impairment. Increased plasma levels of 5-carboxy pirfenidone are associated with renal impairment.

- Importance of favourable and unfavourable effects

An improvement seen in FVC over 72 weeks with the use of 2403 mg pirfenidone has been submitted. A similar effect was seen with the 6MWT. A decrease in the mortality reporting rate was also noted in those treated with pirfenidone. To date it has been noted that no current therapeutic algorithm for idiopathic pulmonary fibrosis would appear to produce a similar improvement. Gastro-intestinal and skin phototoxicity adverse events have not been shown to be life threatening nor have has the potential for drug interactions or higher doses of pirfenidone. Plasma concentrations of pirfenidone increase in hepatic insufficiency but have not been associated with life threatening adverse events. Plasma concentrations of 5-carboxy pirfenidone increase in renally impaired patients but are not associated with life threatening adverse events.

- Benefit-risk balance

The benefit risk balance would appear to be favourable since the risks while present do not appear to put patients at serious risk and the benefits offer the potential for modest benefits in a condition which has to date responded poorly or not at all to current therapeutic algorithms.

2.8.1. Discussion on the benefit-risk balance

The benefit risk balance would appear to be favourable since the risks while present do not appear to put patients at serious risk and the benefits offer the potential for modest benefits in a condition which has to date responded poorly or not at all to current therapeutic algorithms.

A measureable improvement in the absolute percent predicted change in FVC presented by the Applicant in PIPF-004 and PIPF-006 and the pooled analysis is modest but meaningful. While studies SP2 and SP3 may have methodological concerns a modest signal was noted for parameters measure VC. This would support the findings in the pivotal Phase III studies. It should not be forgotten that idiopathic pulmonary fibrosis has a heterogeneous etiopathology making it a very difficult condition to study. In addition the 6MWT showed a favourable trend in PIPF-004 at 72 weeks and was highly significant in PIPF-006. The pooled analysis showed an overall significant effect. Death reporting rates were lower in the pirfenidone treated groups when compared to placebo. While it is very disappointing that other secondary and exploratory parameters did not show trends or favourable changes which could be considered as a consistent signal in both studies, there was no worsening when compared with placebo.

The dose ranging adverse events associated with the gastro-intestinal system are a concern as are those associated with skin rash and phototoxicity. Gastro-intestinal adverse events will affect compliance and the underlying cause should be explored further, however to date they do not appear to be life threatening. Similarly the skin rashes and phototoxicity are of concern in particular the increase in their reporting rate regarding exposure to sunlight and the association with dose. Again they have not to date been shown to life threatening and appear to resolve after 18 weeks of therapy. No unexpected serious adverse events were reported by the Applicant. This strengthens support of the benefits of the product in this condition.

The overall B/R of Esbriet is positive. The Applicant will conduct a prospective observational registry to evaluate the long-term safety of pirfenidone for the treatment of IPF in a real-world setting.

2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

Pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

The additional risk minimisation activities required are shown under section 3.7

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Esbriet in the treatment of Idiopathic Pulmonary Fibrosis was favourable and therefore recommended the granting of the marketing authorisation.