23 February 2023
EMA/117564/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Esbriet

International non-proprietary name: pirfenidone

Procedure No. EMEA/H/C/002154/II/0074

Note

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

6MWD- 6-minute walk distance
ADR -adverse drug reaction
AE adverse event
ACM all-cause mortality
ALAT Latin American Thoracic Association
ATS American Thoracic Society
DLco carbon monoxide diffusion capacity of the lung
ERS European Respiratory Society
EU European Union
FVC forced vital capacity
HRCT high-resolution computed tomography
ILD interstitial lung disease
IPF idiopathic pulmonary fibrosis
JRS Japanese Respiratory Society
MAH Marketing Authorization Holder
PH pulmonary hypertension
PRO patient-reported outcome
PT preferred term
PY patient-year
QoL quality of life
SAP statistical analysis plan
SCE Summary of Clinical Efficacy
SCS Summary of Clinical Safety
SE standard error
SOC System Organ Class
TEAE treatment-emergent adverse event
TTE transthoracic echocardiography
UIP usual interstitial pneumonia

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 26 January 2022 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of 'advanced' idiopathic pulmonary fibrosis (IPF) by the deletion of the current qualifier 'mild to moderate', based on the results from Study MA29957; this is a 52-week Phase IIb, multicentre, randomised, double-blind, placebo-controlled clinical trial in IPF patients with advanced lung function impairment (DLco < 40% of predicted) and at high risk of grade 3 pulmonary hypertension, and additional analyses performed on the original pivotal trials for pirfenidone in IPF.
As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. In addition, the MAH took the opportunity to include information in section 4.4 of the SmPC related to the content of sodium per Esbriet capsule and tablet. The Package Leaflet is updated in accordance. Version 12.1 of the RMP has also been submitted.
The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Finbarr Leacy Co-Rapporteur: Johann Lodewijk Hillege

Timetable	Actual dates
Submission date	26 January 2022
Start of procedure:	19 February 2022
CHMP Joint Rapporteur Assessment Report	13 April 2022
PRAC members comments	26 April 2022
CHMP Co-Rapporteur Assessment	28 April 2022
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	5 May 2022
CHMP members comments	n/a
Updated CHMP Rapporteur(s) (Joint) Assessment Report	12 May 2022
Request for supplementary information (RSI)	19 May 2022
CHMP Joint Rapporteur Assessment Report	13 September 2022
PRAC members comments	n/a
Updated PRAC Rapporteur Assessment Report	n/a
PRAC Outcome	29 September 2022
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	6 October 2022
2nd Request for supplementary information (RSI)	13 October 2022
CHMP Rapporteur Assessment Report	8 February 2023
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	15 February 2023
Opinion	23 February 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Idiopathic Pulmonary Fibrosis (IPF) is a devastating disease of unknown aetiology characterized by fibrosis of the lung interstitium, decrease in lung volume, and progressive pulmonary insufficiency typically leading to death (Lynch and Toews 1998).

IPF is recognized by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) as a distinct form of interstitial lung disease (ILD), defined by a constellation of clinical, histopathologic, and radiologic features (Raghu et al. 2018, Raghu et al. 2011, and ATS/ERS 2002) and is also categorized

as the most common histopathologic form of idiopathic interstitial pneumonia (Katzenstein and Myers 1998).

The claimed therapeutic indication is "Esbriet is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF)."

Epidemiology

The incidence and prevalence of IPF varies across studies, depending on the case definition and the population studied. The annual incidence of IPF has been estimated as 6.8 to 17.4 per 100,000 in the United States and 0.22 to 7.4 per 100,000 in the European Union. Prevalence estimates range from 14.0 to 63.0 per 100,000 in the United States and from 1.25 to 23.4 per 100,000 in the European Union (Raghu et al. 2006; Fernández Pérez et al. 2010; Nalysnyk et al. 2012). IPF is most prevalent in middle-aged and elderly patients, and most studies have found a higher frequency in men than in women (Nalysnyk et al. 2012). Symptoms have usually been present for at least 6 months before the diagnosis is made.

Biologic features, aetiology and pathogenesis

IPF is believed to result from a series of microinjuries to the alveolar epithelium, triggering release of profibrotic mediators. The characteristic pathologic finding on biopsy of lung tissue is a pattern of usual interstitial pneumonia (UIP), with subepithelial fibroblastic foci throughout the lung. Inflammation, although it may initially be present, is not typically a prominent histopathologic finding. Rather, an unremitting fibrotic response relocates from the alveolar space to the interstitium, with fibroblast and myofibroblast proliferation, organization into fibroblastic foci, and excessive collagen deposition and accumulation (du Bois et al. 2010). Although the majority of patients have a history of cigarette smoking, the aetiology of IPF remains unknown.

Clinical presentation, diagnosis and stage/prognosis

The initial clinical presentation of IPF is typically that of slowly progressive dyspnea and non-productive cough. Digital clubbing occurs in up to 50% of patients. Lung auscultation reveals fine end inspiratory crackles, initially at the base of the lung and ultimately diffusely (Raghu et al. 2011). In advanced disease, features of right heart failure develop.

Pulmonary function tests demonstrate a restrictive pattern, with a decrease in carbon monoxide diffusing capacity (DLco), and oxygen desaturation on exertion. Chest radiographs show diffuse interstitial opacities with volume loss, and high-resolution computed tomography (HRCT) scans show a characteristic pattern of peripheral (subpleural), bibasilar, reticulonodular abnormalities associated with architectural

distortion, honeycomb changes, and traction bronchiectasis (Raghu et al. 2011).

IPF, untreated, is a rapidly progressive disease with an extremely poor prognosis. The clinical course is challenging to predict. For some patients, the course of disease is rapid, with fatal respiratory failure evolving over a few months (Selman et al. 2007).

Other patients have a gradual progression over years, followed by acute exacerbations associated with abrupt and often fatal hypoxemic respiratory failure (Collard et al. 2007).

Spontaneous remissions do not occur with IPF, and 10-year survival is less than 15% (Lynch and Belperio 2012). Clinically, IPF usually presents insidiously, with the gradual onset of a non-productive

cough and dyspnea. Dyspnea is usually the most prominent and disabling symptom and is progressive in nature (ATS/ERS 2000). Pulmonary hypertension (PH) develops in many patients with IPF (the reported prevalence ranges between 30% and 81%), and presence of PH is associated with increased mortality (Corte et al. 2009).

Formal classification of IPF severity does not currently exist. In 2011, the first evidence based clinical guidelines were established to help clinicians diagnose and manage IPF (Raghu et al. 2011). Despite updates to the therapeutic and diagnostic guidelines for IPF (Raghu et al 2015, Raghu et al. 2018), there continues to be no formal guidance on disease staging. Likely, a major factor in the lack of definitive staging criteria is the fact that IPF progression is not always linear and patients may have long periods of stable disease followed by rapid decline.

Despite this, it is generally accepted that forced vital capacity (FVC) and DLco are significant predictors of mortality in IPF. In contrast, HRCT pattern of UIP (probable vs. definite) is not (Hyldgaard 2020, Raghu et al. 2017, Yamauchi 2016). One proposed staging method, GAP (gender, age, physiology) staging (Ley et al. 2012), incorporates the use of FVC and DLco, in addition to gender and age, into its prediction of mortality risk. GAP stage I reflects the lowest risk of 1 and 3-year mortality whereas Stage III is the highest risk. However, GAP staging fails to predict functional changes over the next year (Ley et al. 2016).

The official classification of disease severity in Japan uses the J system and has been discussed recently and evaluated against a revised J system as well as the GAP system (Kondoh et al. 2017). The revised J system and GAP system have been found to be valuable tools to predict mortality and manage IPF. However, the J system has not been used in any pivotal trials for IPF elsewhere and is only used in clinical practice in Japan.

While there is no standardized definition for mild, moderate, and severe disease, clinical studies have used an FVC threshold of 50%–55% predicted and a DLco threshold of 35%–40% predicted to separate mild-to-moderate patients from those with severe disease (Richeldi et al. 2011, Noble et al. 2011, King et al. 2011, IPFCRN 2012).

Due to its relentlessly progressive nature and poor prognosis, the term "mild-to-moderate" IPF potentially misrepresents the seriousness of IPF, as it only refers to the functional status of a patient at the moment of evaluation (e.g., FVC or DLco values), but any patient with even very limited functional impairment ("mild" IPF) at diagnosis will progress to worse functional impairment and ultimately respiratory failure and death.

Management

Currently, two antifibrotic drugs, pirfenidone and nintedanib, have been shown to slow IPF progression (Oldham & Collard 2017) which led to their regulatory approvals across major geographies for the treatment of IPF. Pirfenidone was approved in the European Union (EU) in 2011, followed by nintedanib four years later in 2015. Both drugs were approved in the United Stated (US) in 2014. In contrast to the US and many other countries, the use of pirfenidone in the EU is limited to treatment of mild to moderate IPF only. With this submission, the Marketing Authorization Holder (MAH) seeks to extend the EU indication for pirfenidone to include patients with advanced IPF.

2.1.2. About the product

The currently approved indication in the EU is: ***Esbriet is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).***

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 of pulmonary fibrosis (bleomycin- and transplant-induced fibrosis). IPF is a chronic fibrotic and inflammatory pulmonary disease affected by the synthesis and release of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β) and pirfenidone has been shown to reduce the accumulation of inflammatory cells in response to various stimuli. Pirfenidone attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as, transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Esbriet is authorised for the treatment of adult patients with mild to moderate idiopathic pulmonary fibrosis (IPF), as follows: "*Esbriet is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).*"

With this variation, the applicant proposes to include treatment of 'advanced' idiopathic pulmonary fibrosis (IPF) by the deletion of the current qualifier 'mild to moderate', based on the results from Study MA29957 as follows:

"*Esbriet is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).*"

Utilising the data from the original pivotal trials investigating Esbriet as a treatment for IPF, as well as from study MA29957, a recently completed Phase 2 study in patients with advanced IPF, the Sponsor has performed retrospective analyses to compare the efficacy and safety profile of Esbriet in patients with mild to moderate IPF versus patients with advanced IPF. Data from the following studies has been used:

- PIPF-004, PIPF-006 and PIPF-012 supported the original Marketing Authorisation (MA) for Esbriet on 28 February 2011 (EU/1/11/667/001-003 - EMEA/H/C/2154). PIPF-016 supported a subsequent variation to the Esbriet MA (EMEA/H/C/2154/II/0021). PIPF-025 was the post-authorisation safety study performed to assess long-term safety of pirfenidone in a real-world setting.
- MA29957, a recently completed phase IIb study of pirfenidone plus sildenafil performed in patients with advanced IPF and at risk of group 3 pulmonary hypertension.

The MAH did not seek Scientific Advice at the CHMP.

2.2. Non-clinical aspects

2.2.1. Ecotoxicity/environmental risk assessment

The pharmacologically active ingredient Pirfenidone (RO0220912-000) was assessed for its potential environmental risk arising from the extended medical use to the entire IPF population, following the 2006 EMA Guideline (corr. 2, 2015) for the Environmental Risk Assessment of Human Non-GMO Pharmaceuticals.

The applicant refined the PECsw to account for the extension of indication, and adjusted their Tier A and B risk ratios accordingly. Risk assessment updates were performed for the surface water, sewage treatment plant (STP), groundwater and sediment compartments.

Compartment	PEC (µg/L)	PNEC (µg/L)	Risk Quotient (PEC/PNEC)	Trigger value
Surfacewater	PEC_{SW} = 0.376	$PNEC_{SW}$ = 1060	0.00036	>1
Groundwater	PEC_{GW}= 0.094	$PNEC_{GW}$= 9400	0.00001	>1
STP	PEC_{SW} = 3.76	$PNEC_{bacteria, STP}$ = 10,000	0.00038	>0.1
Sediment	PEC_{SED}= 0.0044 mg/kg dw	$PNEC_{SED}$= 4.95 mg/kg	0.0009	>1

Risk characterization ratios for these compartments were below their respective triggers and thus it can be concluded that the active substance is unlikely to represent a risk to these compartments.

Updated summary of main study results

Substance (INN/Invented Name): pirfenidone					
CAS-number (if available): 53179-13-8					
PBT screening	**Test protocol**	**Result**			**Conclusion**
Bioaccumulation potential- log K_{ow}	unknown	0.9			Potential PBT (N)
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$, refined (prevalence)	0.376	µg/L			>0.01 threshold (Y)
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	*K*oc = 51.3 L/kg (Warsop-loamy sand) 50.5 L/kg (Evesham 3 Clay loam) 28.2 L/kg (Elmton Sandy clay loam) 24.0 L/kg (Arrow sandy loam) 5.27 L/kg (Sewage sludge)			
Ready Biodegradability Test	OECD 301	not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50, water: 34 days (Silt loam); 46 days (Sand) DT50, whole system: 191 days (silt loam); 116 days (sand) % shifting to sediment = >10%			DT_{50} values at 20°C; Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Pseudokirchneriella subcapitata*	OECD 201	NOEC	18.3	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	94	mg/L	
Fish, Early Life Stage Toxicity Test/*Pimephales promelas*	OECD 210	NOEC	10.6	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	100	mg/L	respiration
Phase IIb Studies					

Sediment dwelling organism/*Chironomus riparius*	OECD 218	NOEC	495	mg/kg	level of o.c. unknown

Pirfenidone is considered not to be PBT, nor vPvB.

A risk to the STP, surface water, groundwater, sediment and terrestrial compartment is not anticipated based on the prescribed use of pirfenidone.

2.2.2. Conclusion on the non-clinical aspects

The updated data submitted in this application do not lead to a significant increase in environmental exposure further to the use of Pirfenidone. Considering the above data, Pirfenidone is not expected to pose a risk to the environment.

No further new non-clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH

The MAH 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.

- Tabular overview of clinical studies

Table 1 Pirfenidone Studies Included in Dossier and Corresponding Previous Regulatory Submissions to EMA

Study	Application	Submission Date	Approval Date
PIPF-004	EMEA/H/C/2154	26 Feb 2010	28 Feb 2011
PIPF-006	EMEA/H/C/2154	26 Feb 2010	28 Feb 2011
PIPF-012	EMEA/H/C/2154	26 Feb 2010 (initial CSR)	28 Feb 2011
	EMEA/H/C/002154/II/0021	3 Jul 2014 (CSR report)	12 Feb 2015
	PSUSA/00002435/201702	28 Apr 2017 (final report summary included with PSUR #7)	28 Sept 2017 (PRAC recommendation)
PIPF-016	EMEA/H/C/002154/II/0021	3 Jul 2014	12 Feb 2015
PIPF-025	EMEA/H/C/002154/PSU/005	22 Oct 2012 (1st interim report included with PSUR #3)	7 Mar 2013 (PRAC recommendation)
	PSUSA/00002435/201702	28 Apr 2017 (8th and final report included with PSUR #7)	28 Sept 2017 (PRAC recommendation)

MA29957 is a new study provided with this application

2.4. Clinical efficacy

For the assessment of efficacy of pirfenidone in patients with advanced IPF, the main analysis population was derived from the pooled Phase III Studies PIPF-004/-006, and PIPF-016. These studies supported the original Marketing Authorization for pirfenidone (EMEA/H/C/2154) and a subsequent type II variation (EMEA/H/C/002154/II/0021), respectively. The post-hoc analyses based on the data form these studies were conducted to stratify patients into those with advanced or non-advanced IPF based on their FVC and/or DLco values at baseline. While there is currently no official definition of advanced disease, the cutoffs of FVC <50% and DLco<35% are generally accepted criteria in current clinical studies of IPF.

Moreover, the results from the open-label extension study, PIPF-012, show that the effectiveness of pirfenidone over long-term use is similar in advanced and non-advanced IPF patients.

More recently, during 2020, the Sponsor completed the primary analysis of Study MA29957. MA29957 is a randomized, blinded, placebo-controlled trial investigating the efficacy, safety, and tolerability of sildenafil added to pirfenidone in patients with advanced IPF and at risk of Group 3 PH. Data from the control arm of the study, pirfenidone added to placebo, is presented in this SCE to support conclusions from the analysis of advanced IPF patients in the aforementioned pooled Phase III studies.

Studies Included in Submission

This submission is based on the following studies:

1. For the analysis of efficacy on FVC and all-cause mortality, the pooled Phase III studies (PIPF-004/006/016) are used to compare the effect of pirfenidone vs placebo in the subgroups of advanced (N=170) and non-advanced patients (N=1077).
2. This is complemented by the analysis of the annual rate of decline in FVC in mL of advanced (N=187) compared to non-advanced (N=409) patients from Study PIPF-012.
3. Finally, an indirect comparison is made with the annual rate of decline observed in Study MA29957.

The all-cause mortality rate in PIPF-012 is also reported in both subgroups, as well as for MA29957. However, as there was no placebo control group in either Study PIPF-012 or Study MA29957, no statistical testing has been applied.

2.4.1. Dose response studies

No dose response studies were provided. The dose for patients with advanced lung function impairment is the same as for patients with less advanced disease.

2.4.2. Main studies

Pooled Phase III studies (PIPF-004/006/016)

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.

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.

Study PIPF-0016- A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of the Efficacy and Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis.

Methods

Study PIPF-004

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 2403mg/d, placebo, or pirfenidone 1197mg/d, 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. A Data Monitoring Committee (DMC) was chartered to review unblended safety and efficacy data at regular intervals during the trial and to evaluate the conduct and integrity of the study.

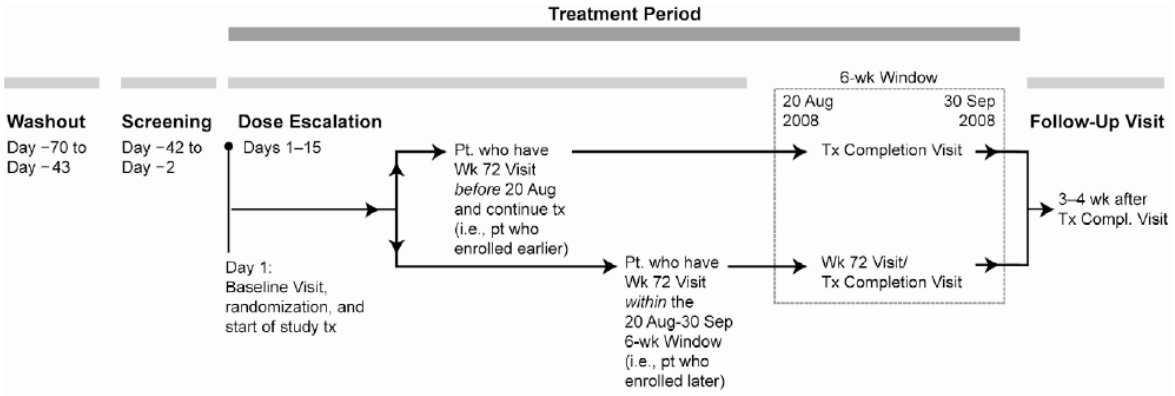


Figure 9-1 Study Flow Diagram

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.

PIPF-006

This study was a randomized, double-blind, placebo-controlled study in patients with IPF. Patients were randomized 1:1 to receive pirfenidone 2403 mg/d or placebo and were to remain on blinded study treatment from randomization until approximately 72 weeks after the last patient had been randomized 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. A Data Monitoring Committee (DMC) was chartered to review unblinded safety and efficacy data at regular intervals during the study and to evaluate the conduct and integrity of the study.

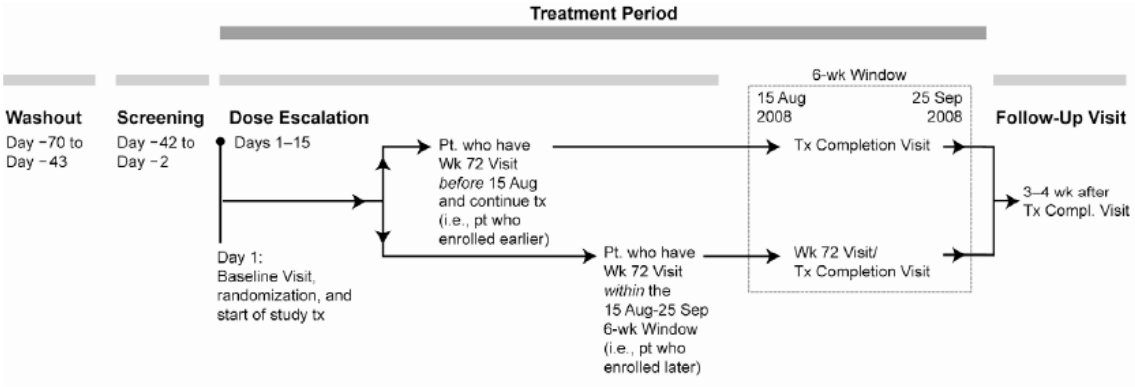


Figure 9-1 Study Flow Diagram

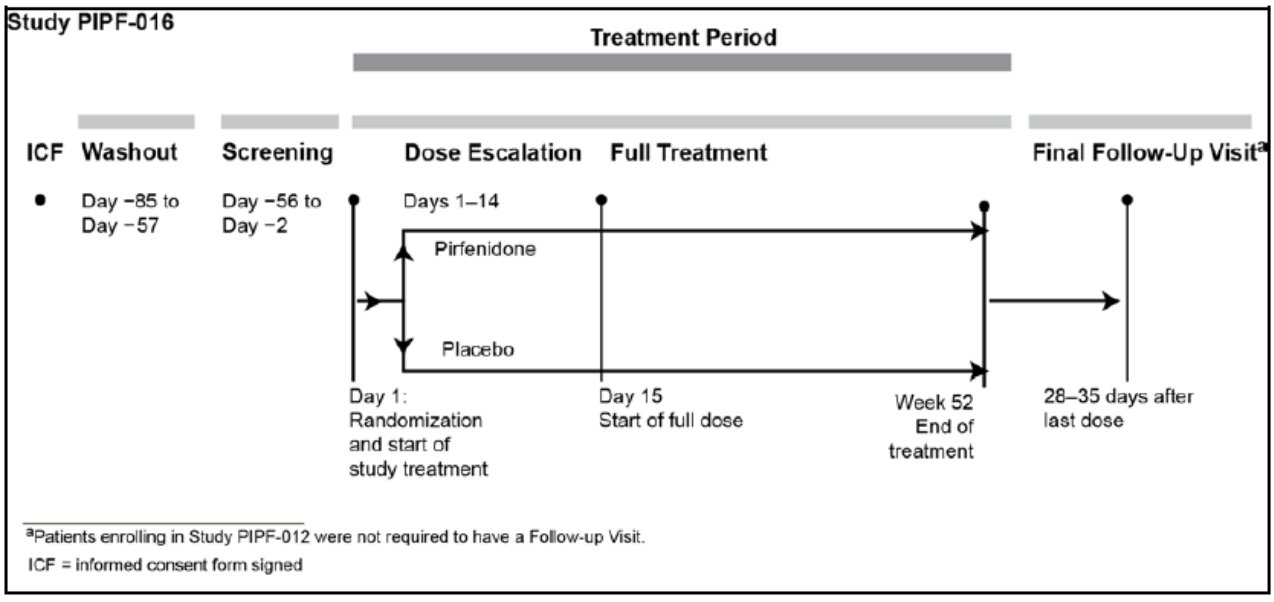
Compl. = Completion; pt = patient(s); tx = treatment; wk = week(s)
Note: Actual Visit windows varied from planned windows as follows: 1st Treatment Completion Visit occurred 12 August 2008; last Treatment Completion Visit occurred 3 October 2008; 1st Final Follow-Up Visit occurred 2 September 2008; last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

PIPF-0016

Study PIPF-016 was a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of pirfenidone in patients with IPF. Approximately 500 patients were to be randomized with equal probability to pirfenidone or placebo, and patients were treated for 52 weeks. The primary efficacy endpoint was the change from Baseline to Week 52 in percent predicted FVC.

There were four study periods: a Washout Period (required only if patients were on a prohibited medication), a Screening Period, a Study Treatment Period, and a Post-treatment Follow-up Visit.

Eligible patients were randomized on Day 1 to pirfenidone 2403 mg or matching placebo. Over the first 14 days, the dose was escalated from 1 capsule (267 mg) three times daily (TID) to the full maintenance dose of 3 capsules TID, as tolerated.



Study participants

Study PIPF-004

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 dyspnoeas 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 VATS lung biopsy that showed definite or probably UIP.
    - Transbronchial biopsy that showed no featuresn 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 FVOC between screening and Day 1 must have been <10% relative difference.
    - Haemoglobin (Hgb)-corrected carbon monoxide diffusing capacity/carbon monoxide transfer (DJco)>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 >150meters with O2 saturation >83% on <6L/minute of O2 during the 6-minute Walking Test (6MWT) oxygen titration procedure performed at screening.

Study PIPF-006

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 dyspnea on exertion of ≥3 months duration Diagnosis of IPF, defined as the first instance a patient was informed of having IPF, within 48 months of randomization
- Age 40 through 80 years, inclusive
- High-resolution computed tomography (HRCT) scan showing a pattern of disease consistent with a confident (definite) radiographic diagnosis of usual interstitial pneumonia (UIP)/IPF. For patients with surgical lung biopsy showing definite or probable UIP, the HRCT criterion of probable (UIP)/IPFIPF 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 randomization. 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 randomization). The change in FVC between screening and Day 1 must have been <10% relative difference.
  - Hemoglobin (Hgb)-corrected carbon monoxide diffusing capacity/carbon monoxide transfer capacity (DLCO) >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 >150m (with O2 saturation >83% on <6-Minute Walk test (6MWT) oxygen titration procedure performed at screening.

Study PIPF-0016

Study Participants

Eligible patients had a confident diagnosis of IPF based on clinical and radiologic data (and histopathologic data, if available), without evidence or suspicion of an alternative diagnosis. In addition, patients had to fulfill all of the following criteria to be eligible for enrollment into the study:

Diagnosis of IPF:

- Clinical symptoms consistent with IPF of ≥12 months duration
- Diagnosis of IPF, defined as the first instance in which a patient was informed of having IPF, at least 6 months and no more than 48 months before randomization
- Age 40 through 80 years, inclusive, at randomization
- Diagnosis of UIP or IPF by HRCT and/or surgical lung biopsy, as outlined in the below table.

  (Note: HRCT scan performed within 1 month of the start of Screening may be used if it meets image acquisition guidelines):

	Surgical Lung Biopsy Not Available	Pathology Assessment: Definite UIP	Pathology Assessment: Probable UIP	Pathology Assessment: Possible UIP	Pathology Assessment: Inconsistent with UIP or Not Classifiable
Radiology Panel: Definite UIP	Eligible	Eligible	Eligible	Eligible	NOT Eligible
Radiology Panel: Possible UIP	NOT Eligible	Eligible	Eligible	NOT Eligible	NOT Eligible
Radiology Panel: Inconsistent with IPF	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible	NOT Eligible

Extent of fibrotic changes (honeycombing, reticular changes) greater than the extent of emphysema on HRCT scan, as determined by central review

- No features supporting an alternative diagnosis on transbronchial biopsy, bronchoalveolar lavage (BAL), or surgical lung biopsy, if already performed

IPF Disease Severity and Progression:

- Percent predicted FVC ≥50% and ≤90% at Screening, confirmed by central review
- Change in pre- and post-bronchodilator FVC (measured in liters) between Screening and Day 1 must be a <10% relative difference, calculated as shown below:
- Percent predicted DLCO ≥30% and ≤90% at Screening, confirmed by central review
- In the investigator's opinion, no evidence of improvement in measures of IPF disease
- severity over the preceding year
- Able to walk ≥150 m during the 6MWT at Screening

Post-Hoc Statistical Analysis of Efficacy in Advanced and Non-Advanced IPF from Pooled Pivotal Studies

Patient Selection

In this post-hoc analysis of the pooled data from studies PIPF-004, PIPF-006, and PIPF-016, the intent was to compare patients who had advanced IPF (defined as FVC [percent predicted] <50% and/or DLco <35%) at baseline to patients with non-advanced IPF (defined as defined as FVC ≥50% and DLco ≥35%) at baseline. These criteria are different from those used to screen patients at the time the

Phase III studies were conducted (PIPF-016 [FVC ≥50% and DLco ≥30% at screening; King et al. 2014] and

PIPF-004 and -006 [FVC ≥50% at screening and Day 1 and DLco ≥35% at screening; Noble et al. 2011). Although the original inclusion criteria would suggest that patients with more advanced lung function impairment were not eligible for inclusion in these studies, this was not the case for several reasons:

- There were differences in eligibility criteria between the studies, and some inclusion criteria were assessed only at screening.
- There were differences between the definition of baseline used to determine eligibility and that used for statistical analysis purposes.

The application of the post-hoc analysis selection criteria led to the identification of some patients who had changes in FVC or DLco values between screening (used for enrollment eligibility) and randomization (≥8 weeks following screening) with an increase in their lung function impairment by the start of dosing.

Specifically, for PIPF-016, patients could be included in this analysis if they had DLco ≥30% and <35% at screening, or if they experienced a decline in FVC to <50% between screening and baseline (while FVC was assessed again at baseline, these values were not used to determine eligibility).

IPF Disease Severity criteria in PIPF-004/006/016 studies

Table 2 Lung Function Entry Criteria for PIPF-016 Compared with PIPF-004 and PIPF-006

Study PIPF-016	Studies PIPF-004/006
Inclusion Criteria	
Percent predicted FVC ≤90% and Percent predicted DL_{CO} ≤90%	Percent predicted FVC ≤90% or Percent predicted DL_{CO} ≤90%
Percent predicted FVC ≥50% and Percent predicted DL_{CO} ≥30%	Percent predicted FVC ≥50% and Percent predicted DL_{CO} ≥35%
Exclusion Criteria	
FEV_1/FVC <0.8; no bronchodilator response	FEV_1/FVC <0.7; no bronchodilator response

Source: CSR PIPF-016, CSR PIPF-004, and CSR PIPF-006

Treatments

The maintenance daily dose of Esbriet was three 267 mg capsules three times a day with food for a total of 2403 mg/day. In study PIPF-004 an additional dose was tested (1197 mg/day) but this dose was not included in the post-hoc analysis.

Objectives

Efficacy assessments conducted during each of the pivotal studies PIPF-004, PIPF-006, PIPF-016 have been previously described in the original Marketing Application (EMEA/H/C/2154) and subsequent Type II variation (EMEA/H/C/2154/II/0021) and are summarized in **Table 3** below.

Outcomes/endpoints

The analysis presented in this SCE focuses on change in FVC volume from baseline to Week 52 of treatment as well as the difference in the risk of all-cause death at 52 weeks.

The assessment at 52 weeks was chosen as it was the duration of treatment in Study PIPF-016 for which data were available to be pooled with studies PIPF-004 and PIPF-006. While the pivotal studies included several additional endpoints, change in FVC volume was chosen for evaluation here because the annual rate of decline of FVC has become the most widely accepted endpoint in studies on IPF and other interstitial

lung diseases (ILDs) and also facilitates descriptive comparisons with other studies. Moreover, it was the measure with the most data available for pooling across the three studies.

Table 3 Efficacy Outcome Variables (Studies PIPF-004, PIPF-006, and PIPF-016)

PIPF-004 and PIPF-006	PIPF-016
Primary Efficacy Outcome Variable	
• Percent predicted FVC analyzed as the absolute change from Baseline to Week 72	• Percent predicted FVC analyzed as the absolute change from Baseline to Week 52
Secondary Efficacy Outcome Variables	
• PFS[c], defined as the first occurrence of any of the following events: o 10% absolute decline in percent predicted FVC or o 15% absolute decline in percent predicted Hgb-corrected DLco or o All-cause mortality	• PFS[a,c] defined as the time to the first occurrence of any of the following: o Death or o Confirmed ≥10% absolute decline from Baseline in percent predicted FVC or o Confirmed ≥50 meter decline from Baseline in 6MWT distance
• Change from Baseline to Week 72 in 6MWT distance	• Change from Baseline to Week 52 in 6MWT distance[a]
• Change in dyspnea as measured by UCSD SOBQ from Baseline to Week 72	• Change in dyspnea as measured by UCSD SOBQ from Baseline to Week 52
• Time to worsening of IPF, defined as the first to occur of one of the following events: o Acute IPF Exacerbation o IPF-related death (excluding deaths that were not the reason for treatment or study discontinuation and more than 28 days after the last study treatment and more than 98 days after the last study visit for patients who did not complete the study). o Lung transplantation o Respiratory hospitalization	• All-cause mortality[d,e] • Treatment-emergent IPF-related mortality[d,e]
• Change in percent predicted Hgb-corrected DLco from Baseline to Week 72	
• Change in the worst oxygen SpO_2 measurement observed during the 6MWT from Baseline to Week 72	
• Change in the HRCT assessment of lung fibrosis from Baseline to Week 72 (evaluated only in Study PIPF-006)	
• Categorical assessment of the absolute change in percent predicted FVC[b] from Baseline to Week 72	

Sample size

This is a post-Hoc Statistical Analysis of Efficacy in Advanced and Non-Advanced IPF from Pooled Pivotal Studies. The sample sizes of Studies PIPF-004, PIPF-006 and PIPF-0016 are described in the EPAR on the initial MA and variation EMEA/H/C/2154/II/0021.

Randomisation

Studies PIPF-004, PIPF-006 and PIPF-0016 were randomized, double-blind, placebo-controlled, Phase 3 Studies. PIPF-004, PIPF-006 supported the original Marketing Authorisation (MA) for Esbriet on 28 February. PIPF-016 supported a subsequent variation to the Esbriet MA (EMEA/H/C/2154/II/0021).

Blinding (masking)

See above

Statistical methods

FVC volume data up to 52 weeks of treatment for patients in the pirfenidone 2403 mg/day and placebo cohorts from the three Phase III studies were pooled. Linear slope analysis of change from baseline to Week 52 in FVC volume was performed using a mixed model. Slopes were calculated based on observed data only and used actual observation times.

Time-to-event outcomes were compared between pirfenidone and placebo using the log-rank test. A proportional hazards model, with treatment as a fixed effect, was used to estimate the hazard ratio (HR) and 95% CI. Kaplan-Meier curves were used to display event times and the numbers of patients at risk. Patients without an event were censored at or prior to 52 weeks, as appropriate for each outcome and 52-week completion status.

Results

Participant flow

The three pivotal Phase III studies (PIPF-004, PIPF-006, and PIPF-016) recruited 1334 patients, of whom 623 were treated with pirfenidone 2403 mg/day and 624 received placebo; all 1247 patients were included in the analysis of efficacy in advanced/non-advanced IPF patients. The remaining 87 patients received pirfenidone at a dose of 1197 mg/day in PIPF-004 and were not included in the pooled analysis of pirfenidone in advanced/non-advanced patients. Among the 1247 patients analyzed, 1077 patients were categorized as having non-advanced IPF (FVC ≥50% and DLco ≥35%) and 170 patients had advanced IPF (FVC <50% or DLco <35%).

Table 4 Frequency of Patients by Study and Treatment Group Considered for Filing in Clinical Trials (ITT Population)

	Pirfenidone N=623		Placebo N=624	
	Non-Advanced[a] n (%)	Advanced[b] n (%)	Non-Advanced[a] n (%)	Advanced[b] n (%)
Study PIPF-004	159 (25.5)	15 (2.4)	161 (25.8)	13 (2.1)
Study PIPF-006	165 (26.5)	6 (1.0)	164 (26.3)	9 (1.4)
Study PIPF-016	209 (33.5)	69 (11.1)	219 (35.1)	58 (9.3)

Only patients treated with Pirfenidone 2403 mg/day are counted.

[a] Non-advanced patients are defined as patients with %FVC ≥50 and %DLco ≥35; %FVC ≥50 or %DLco ≥35, if other lung function data were missing, at baseline in PIPF-004, PIPF-006, PIPF-016.

[b] Advanced patients are defined as patients with %FVC<50 and/or %DLco<35% at baseline in PIPF-004, PIPF-006, PIPF-016.

Recruitment

PRIC-006:Date of First Patient Visit: 27 April 2006; date Last Patient Completed Study: 31 October 2008.

PIPF-004: Date of First Patient Visit: 14 July 2006; date Last Patient Completed Study: 07 November 2008

PIPF-016: Date first patient enrolled: 13 June 2011; date last patient completed: 6 February 2014

Conduct of the study

This is a post-Hoc Statistical Analysis of Efficacy in Advanced and Non-Advanced IPF from Pooled Pivotal Studies. The conduct of these studies had been assessed in above mentioned procedures.

Baseline data

Demography and Baseline Disease Characteristics

Patient demographics in the non-advanced and advanced IPF groups were consistent across the respective subgroups for pirfenidone versus placebo treatment.

Within the different disease severity groups, baseline FVC or DLco values were fairly well balanced between the pirfenidone and placebo subgroups. The differences in baseline demographics between the severity groups are consistent with the selection criteria and natural history of IPF. It should be noted that the main driver of classifying patients as advanced was a DLco value <35% rather than an FVC value below 50% which is reflected in the median FVC values of pirfenidone (59.2%) and placebo (64.2%).

Table 5 Demographics and Baseline Characteristics for Pooled Studies PIPF-004, PIPF-006 and PIPF-016 by Advanced /Non-Advanced Patients

	Non-advanced (1) (N=1077)		Advanced (2) (N=170)	
	Pirfenidone n = 533 n (%)	Placebo n = 544 n (%)	Pirfenidone n = 90 n (%)	Placebo n = 80 n (%)
Age (years)				
n observed	533	544	90	80
Mean (std)	66.9 (7.47)	67.0 (7.40)	68.9 (7.82)	68.5 (8.27)
Median	68.0	68.0	70.0	69.0
Q1 - Q3	61.0 - 72.0	62.0 - 73.0	63.0 - 76.0	63.0 - 75.5
Min - Max	45 - 80	41 - 80	46 - 80	40 - 80
Age categories [n (%)]				
<65 years	191 (35.8)	198 (36.4)	27 (30.0)	24 (30.0)
>=65 years	342 (64.2)	346 (63.6)	63 (70.0)	56 (70.0)
Gender [n (%)]				
Male	389 (73.0)	406 (74.6)	74 (82.2)	59 (73.8)
Female	144 (27.0)	138 (25.4)	16 (17.8)	21 (26.3)
FVC (% Predicted) at baseline				
n observed	533	544	90	80
Mean (std)	73.2 (12.71)	72.8 (13.48)	61.9 (11.73)	66.6 (13.42)
Median	72.9	71.1	59.2	64.2
Q1 - Q3	63.9 - 80.5	62.4 - 81.7	53.8 - 67.9	56.4 - 75.8
Min - Max	50 - 120	50 - 136	48 - 124	48 - 121
DLCO (% Predicted) at baseline				
n observed	533	542	90	80
Mean (std)	47.7 (9.35)	47.5 (10.56)	32.9 (3.28)	32.3 (2.41)
Median	45.9	45.8	32.5	32.1
Q1 - Q3	40.5 - 53.4	40.1 - 52.3	30.8 - 34.5	30.9 - 33.8
Min - Max	35 - 81	35 - 170	27 - 49	27 - 46
Missing	0	2	0	0
Duration of treatment (months)				

Numbers analysed

Among the 1247 patients analyzed, 1077 patients were categorized as having non-advanced IPF (FVC ≥50% and DLco ≥35%) and 170 patients had advanced IPF (FVC <50% or DLco <35%).

Outcomes and estimation

Change in Forced Vital Capacity Volume at 52 Weeks

In the pooled Phase III studies, the absolute and relative treatment differences between pirfenidone and placebo are not different in a clinically meaningful way between advanced and non-advanced patients, the absolute treatment difference being significant in both cases.

In the linear slope analysis between pirfenidone and placebo subgroups among advanced patients, annual FVC decline was significantly lower with pirfenidone versus placebo (150.9 mL vs 277.6 mL;

p=0.0035). Among patients with non-advanced IPF, annual FVC decline was also significantly lower with pirfenidone versus placebo (128.7 mL vs. 216.7 mL; p=0.0001).

Table 6 FVC Volume (mL) Change with Linear Slope Through Month 12 of Study Treatment (Pooled Studies PIPF-004/-006/-016)

	Non-Advanced IPF N=1077		Advanced IPF N=170	
	Pirfenidone 2403 mg/day N=533	Placebo N=544	Pirfenidone 2403 mg/day N=90	Placebo N=80
Slope change [a] (1 Year) [SE]	-128.7 [13.58]	-216.7 [13.44]	-150.9 [30.24]	-277.6 [33.53]
Difference in Mean [b]	88.02 [17.76]		126.71 [43.09]	
Relative difference in mean	40.6%		45.6%	
P-value [c]	<0.0001		0.0035	

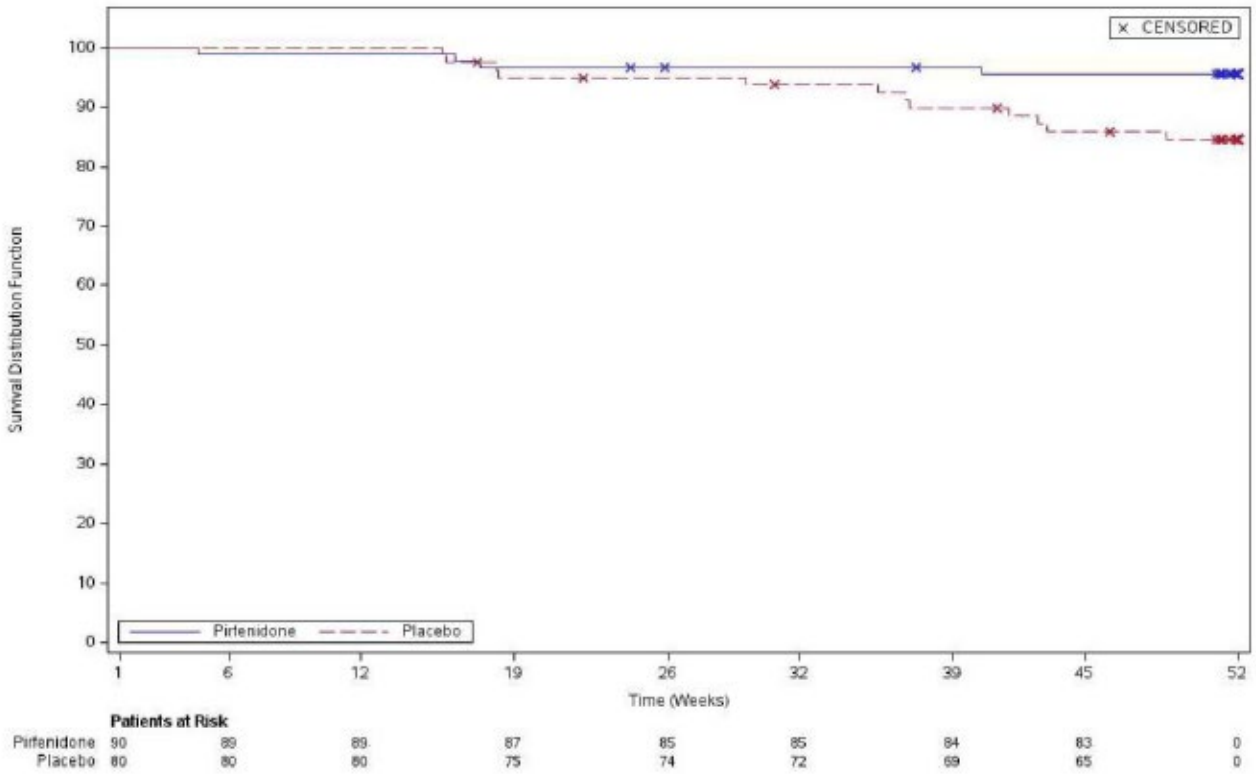
All-Cause Mortality

The all-cause mortality rate is lower among patients treated with pirfenidone versus placebo both in patients with advanced and non-advanced IPF. Consistent with the natural history of IPF, the mortality rate in advanced patients is higher than in nonadvanced patients.

From the analysis of patients from the pooled Phase III studies, the percentage of patients with advanced IPF who died from any cause was 4.4% (4/90) in the pirfenidone subgroup compared with 15.0% (12/80) with placebo over 52 weeks of treatment. In time-to-event analyses, advanced IPF patients treated with pirfenidone had a significantly lower risk of all-cause mortality over 52 weeks versus placebo (HR: 0.28; 95% CI 0.09–0.88; p = 0.0194).

The percentage of patients with non-advanced IPF who died from any cause was 3.4% (18/533) in the pirfenidone subgroup compared with 5.5% (30/544) with placebo over 52 weeks of treatment . In time-to-event analyses, non-advanced patients treated with pirfenidone did not have a significantly lower risk of all-cause mortality over 52 weeks versus placebo (HR: 0.61; 95% CI: 0.34–1.09; p=0.090)

Figure 1 Overall Survival Until Week 52 in Advanced IPF Patients (Pooled Studies PIPF-004, PIPF-006, PIPF-016)



[1] Kaplan-Meier estimates: Median [95% CI] and Q1 - Q3. Minimum and maximum are including censored observations.
[2] Hazard ratio and corresponding 95% CI are calculated by applying Cox-proportional hazard model.
[3] Log-rank test is based on the time to the first event to compare the two treatment arms.
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Ancillary analyses

N/A

Summary of main study(ies)

No new pivotal studies were provided with this application.

The following **Table 7** 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 7 Summary of post-hoc efficacy analyses for trials PIPF-004, PIPF-006 and PIPF-016 (pooled)

PIPF-004 Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3, Three-Arm Study of the Safety and Efficacy of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis
PIPF-006 Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of the Safety and Efficacy of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis
PIPF-016 Title: A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of the Efficacy and Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis

Study identifiers	PIPF-004; NCT00287716 PIPF-006: NCT00287729 PIPF-016: NCT01366209		
PIPF-004 Design	This study was a randomized, double-blind, placebo-controlled, 3-arm study in patients with IPF. Patients were randomized 2:2:1 to receive pirfenidone 2403 mg/d, placebo, or pirfenidone 1197 mg/d, respectively, and were to remain on blinded study treatment from randomization until approximately 72 weeks after the last patient had been randomized in the study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		72 weeks + 4 weeks for final follow-up <not applicable> Patients could roll-over to open-label extension study PIPF-012
PIPF-006 Design	This study was a randomized, double-blind, placebo-controlled study in patients with IPF. Patients were randomized 1:1 to receive pirfenidone 2403 mg/d or placebo, and were to remain on blinded study treatment from randomization until approximately 72 weeks after the last patient had been randomized in the study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		72 weeks + 4 weeks for final follow-up <not applicable> Patients could roll-over to open-label extension study PIPF-012
PIPF-016 Design	Study PIPF-016 was a Phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of pirfenidone in patients with IPF. Approximately 500 patients were to be randomized with equal probability to pirfenidone or placebo, and patients were treated for 52 weeks.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		52 weeks + 4 weeks for final follow-up <not applicable> Patients could roll-over to open-label extension study PIPF-012
Hypothesis	The original hypothesis for each trial was superiority		
PIPF-004/006/0016 Treatments groups	Advanced IPF pirfenidone (aIPF/PFN)		n=90
	Advanced IPF placebo (aIPF/PLO)		n=80
	Non-advanced IPF pirfenidone (naIPF/PFN)		n=533
	Non-advanced IPF placebo (naIPF/PLO)		n=544
PIPF-004/006/0016 Endpoints and definitions for post-hoc analyses	Primary	FVC	Rate of FVC decline
	Secondary	ACM	All-cause mortality
Database locks	PIPF-004: 7 November 2008 PIPF-006: 31 October 2008 PIPF-016: 6 February 2014		
Results and Analysis			

Analysis description	**Primary Analysis – FVC (post-hoc)**		
Analysis population and time point description	Advanced IPF (aIPF), 6 February 2014; for the post-hoc analyses advanced IPF is defined as FVC <50% and/or DLco <35%) at baseline		
Descriptive statistics and estimate variability	Treatment group	aIPF/PFN	aIPF/PLO
	Number of subject	n=90	n=80
	FVC decline (annual)	-150.9 mL	-277.6 mL
	Standard error	30.24	33.53
Effect estimate per comparison	FVC decline, annual	Comparison groups	aIPF/PFN v aIPF/PLO
		Absolute difference	126.71
		Relative difference	45.6%
		P-value (t-test)	0.0035
Notes	The p-value is only descriptive as per SAP, as analysis is post-hoc.		
Analysis population and time point description	Non-advanced IPF, 6 February 2014; for the post-hoc analyses non-advanced IPF is defined as FVC ≥50% and DLco ≥35%) at baseline		
Descriptive statistics and estimate variability	Treatment group	naIPF/PFN	naIPF/PLO
	Number of subject	n=533	n=544
	FVC decline (annual)	-128.7 mL	-216.7 mL
	Standard error	13.58	13.44
Effect estimate per comparison	FVC decline, annual	Comparison groups	naIPF/PFN v naIPF/PLO
		Absolute difference	88.02
		Relative difference	40.6%
		P-value (t-test)	<0.0001
Notes	The p-value is only descriptive as per SAP, as analysis is post-hoc.		
Analysis description	**Secondary analysis – ACM (post hoc)**		
Analysis population and time point description	Advanced IPF, 6 February 2014; for the post-hoc analyses advanced IPF is defined as FVC <50% and/or DLco <35%) at baseline		
Descriptive statistics and estimate variability	Treatment group	aIPF/PFN	aIPF/PLO
	Number of subject	n=90	n=80
	ACM	4 (4.4%	12 (15.0%)
	Weeks	52	52
Effect estimate per comparison	ACM	Comparison groups	aIPF/PFN v aIPF/PLO
		Hazard ratio	0.28
		95% confidence interval	0.09, 0.88

		P-value (Log-rank test)	0.0194
Notes	The p-value is only descriptive as per SAP, as analysis is post-hoc.		
Analysis population and time point description	Non-advanced IPF, 6 February 2014; for the post-hoc analyses non-advanced IPF is defined as FVC ≥50% and DLco ≥35%) at baseline		
Descriptive statistics and estimate variability	Treatment group	naIPF/PFN	naIPF/PLO
	Number of subject	n=533	n=544
	ACM	18 (3.4%)	30 (5.5%)
	Weeks	52	52
Effect estimate per comparison	ACM	Comparison groups	naIPF/PFN v naIPF/PLO
		Hazard ratio	0.61
		95% confidence interval	0.34, 1.09
		P-value (Log-rank test)	0.090
Notes	The p-value is only descriptive as per SAP, as analysis is post-hoc.		

aIPF= advanced idiopathic pulmonary fibrosis, naIPF= non-advanced idiopathic pulmonary fibrosis, PRF= pirfenidone, PLO= placebo

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

Comparison of efficacy results of all studies

Across studies, patients with advanced IPF consistently have a higher rate of death than patients with non-advanced IPF, which is in line with the natural history of this disease.

Table 8 Efficacy Endpoints Across Studies

	Pooled Phase III Studies				PIPF-012		MA29957
	Non-Advanced		Advanced		Non-Advanced	Advanced	Advanced
	Pirfenidone N=533	Placebo N=544	Pirfenidone N=90	Placebo N=80	Pirfenidone N=409	Pirfenidone N=187	Pirfenidone+Placebo N=89
Annual rate of change in FVC volume (mL) (SE)	-128.7 [a] (13.58)	-216.7 [a] (13.44)	-150.9 [a] (30.24)	-277.6 [a] (33.53)	-153.4 [b] (7.61)	-141.5 [b] (11.66)	-93.0 [a] (46.4)
All-Cause mortality rate	18/533 [c] (3.4%)	30/544 [c] (5.5%)	4/90 [c] (4.4%)	12/80 [c] (15.0%)	49/409 [d] (12.0%)	52/187 [d] (27.8%)	18/89 [c] (20.2%)

FVC = forced vital capacity; SE = standard error

Clinical studies in special populations

No clinical studies in special populations had been submitted this was considered acceptable by the CHMP.

Supportive study(ies)

Study PIPF-012

An Open-Label Extension Study of the Long Term Safety of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis (IPF)

Methods

Study PIPF-012 was Phase IIIb, multicenter, long-term, open-label, safety study in patients with IPF who completed one of the previous Phase III studies (PIPF-004, PIPF-006, or PIPF-016). In addition, lung function was assessed for approximately the first 3 years (FVC and DLco). There was no criterion on IPF severity for enrolment into the study. Patients from Studies PIPF-004/ and PIPF-006 were enrolled under either the original protocol (all patients except those in the United Kingdom [UK]) or UK Amendment 1, while patients from Study PIPF-016 were enrolled later under Global Amendment 2 which expanded the studies from which patients could enroll into PIPF-012. Global Amendment 2 was implemented after approximately 3 years of pulmonary function data had been collected in the study and further efficacy assessments were considered of limited utility. Thus, pulmonary function testing was eliminated with this amendment.

All patients in PIPF-012 received open-label pirfenidone with the target maintenance dose being 2403 mg/day. Patients discontinued blinded treatment at the end of Studies PIPF-004/006 □3 weeks prior to starting treatment in PIPF-012, while patients from Study PIPF-016 started treatment in PIPF-012 immediately upon discontinuing blinded treatment in PIPF-016. To maximize tolerability, the dose of pirfenidone in Study PIPF-012 was escalated over 15 days to the target maintenance dose of

2403 mg/day (801 mg, three times daily [TID]), as tolerated. A patient on a lower maintenance dose at the end of Studies PIPF-004/PIPF-006 was limited to a lower dose in Study PIPF-012 until his or her treatment assignment in PIPF-004/-006 was unblinded; thereafter, at the discretion of the investigator and with the medical monitor's concurrence, the patient's dose could be escalated to 2403 mg/day, as tolerated.

Treatments

The target maintenance dose in this study was 2403 mg/day – the same as used in pivotal studies.

Objectives and Outcomes/endpoints

The primary objective (With Global Amendment 2) was to obtain additional safety data for pirfenidone 2403 mg/day in patients with IPF who complete a qualifying trial of pirfenidone.

Post-Hoc Statistical Analysis of Efficacy in Patients with Advanced or non-Advanced IPF

Patient Selection

All patients with baseline FVC and/or DLco values at the time of enrollment into PIPF-012 were included in the analysis. Patients enrolling from PIPF-016 were excluded from the analysis due to the fact that no pulmonary function data were collected from these patients at the time of enrolling into PIPF-012 due to Global Amendment 2.

Patients with missing FVC and missing DLco were excluded from analysis as those patients could not be categorized as having advanced or non-advanced IPF.

Efficacy Assessments

Efficacy endpoints evaluated in Study PIPF-012 (up to the point of Global Amendment 2) were:

- Percent predicted FVC
- Percent predicted DLco (hemoglobin corrected)
- Kaplan-Meier estimate of survival time, relative to first dose in Study PIPF-012
- Kaplan-Meier estimate of lung-transplant−free survival time, relative to first dose in Study PIPF-012

Endpoints Analysed and Methodology

Efficacy of pirfenidone by IPF severity was assessed in this post-hoc analysis by decline in FVC volume over 180 weeks, as measured using change from baseline and linear slope analysis of annual rate of decline. A yearly decline was estimated using a single arm repeated measures model for each subgroup of advanced and non-advanced patients.

Results

Patient Disposition

A total of 609 patients were enrolled into study PIPF-012, of which 596 treated patients (187 patients with advanced IPF and 409 patients with non-advanced IPF) had FVC or DLco data available at baseline for inclusion in the post-hoc analysis of efficacy by IPF severity (non-advanced vs. advanced) (**Table 9** below) Patients from the PIPF-016 study were not included in the analysis due to a lack of available FVC follow-up data due to implementation of Global Amendment 2.

Table 9 Patients Included in Post-Hoc Analysis of Study PIPF-012

	Non-Advanced IPF (N=409)	Advanced IPF (N=187)
Patients[a] from PIPF-004 (previous pirfenidone/ placebo)	238	93
Patients[a] from PIPF-006 (previous pirfenidone / placebo)	171	94
Patients[a] from PIPF-016[b] (previous pirfenidone / placebo)	0	0

Demography and Baseline Disease Characteristics

Demographics were similar between non-advanced and advanced IPF patients in enrolled into PIPF-012. The majority of patients in both groups were ≥65 years (67.5% and 67.4%, in non-advanced and advanced patients, respectively) with the median age in both groups being 69 years. Patients were mostly male, irrespective of having non-advanced (70.7%) or advanced IPF (74.9%) and the median time from IPF diagnosis to start of treatment in PIPF-012 was similar in non-advanced and advanced patients (2.5 and 2.7 years, respectively).

At baseline, the mean (SD) percent predicted FVC was 76.1% (15.25) in the non-advanced group and 59.8% (14.05) in the advanced IPF group. Mean percent predicted DLco was 47.0% (10.34) and 29.2% (6.05), respectively.

Table 10 Demographics and Baseline Characteristics for PIPF-012 by Advanced /Non-Advanced Patients

	Non-advanced (1) n = 409 n (%)	Advanced (2) n = 187 n (%)
FVC (% Predicted) at baseline		
n observed	400	184
Mean (std)	76.1 (15.25)	59.8 (14.05)
Median	74.0	56.7
Q1 - Q3	64.2 - 85.9	49.3 - 69.4
Min - Max	50 - 122	22 - 125
Missing	9	3
DLCO (% Predicted) at baseline		
n observed	364	178
Mean (std)	47.0 (10.34)	29.2 (6.05)
Median	45.7	30.7
Q1 - Q3	40.0 - 51.7	25.2 - 33.5
Min - Max	35 - 152	13 - 46
Missing	45	9

	Non-advanced (1) n = 409 n (%)	Advanced (2) n = 187 n (%)
Duration of treatment (months)		
n observed	409	187
Mean (std)	42.9 (24.55)	28.3 (22.55)
Median	41.4	21.8
Q1 - Q3	21.8 - 66.0	9.1 - 40.7
Min - Max	0 - 80	0 - 79

Numbers analysed

596 patients (187 patients with advanced IPF and 409 patients with non-advanced IPF) had FVC or DLco data available at baseline and therefore they were included in the post-hoc analysis of efficacy by IPF severity.

Outcomes and estimation

Change in Forced Vital Capacity Volume from Baseline

The annual rate of FVC decline was similar with longer-term pirfenidone treatment in patients with advanced and non-advanced IPF.

Among advanced patients treated with pirfenidone during follow-up, the annual rate of FVC decline (slope) was -141.5 mL/year and that for non-advanced patients was -153.5 mL/year.

Table 11 FVC Decline During Follow-up Treatment in PIPF-012

	Non-Advanced IPF N=409	Advanced IPF N=187
Annual Slope (SE)	-153.5 (7.61)	-141.5 (11.66)

SE=standard error

Linear slope is calculated using change from Baseline FVC (mL) values. Study (PIPF-004, PIPF-006), sex by height, sex by age, and assessment time as fixed effects and subject and subject by assessment time as random effects with variance components covariance structure. PIPF-012 patients with prior treatments placebo, pirfenidone 1197 mg/day and pirfenidone 2403 mg/day in PIPF-006 and PIPF-004 are included.

All-Cause Mortality

Among patients treated in Study PIPF-012, the all-cause mortality rate over 180 weeks was lower among patients with non-advanced IPF (49/409; 12.0%) compared to patients with advanced IPF (52/187; 27.8%) which is consistent with the natural history of IPF.

Study MA29957

The trial title:

Phase IIb, Multicenter, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy, Safety, and Tolerability of Sildenafil Added to Pirfenidone in Patients with Advanced

Idiopathic Pulmonary Fibrosis and Risk of Group 3 Pulmonary Hypertension.

Methods

MA29957 was a Phase IIb, multicenter, randomized, double-blind, placebo-controlled, international study of the efficacy, safety, and tolerability of combination treatment of **pirfenidone with added sildenafil** in patients with advanced IPF and at risk of Group 3 PH who had been on pirfenidone treatment in a dose range of 1602-2403 mg/day for ≥12 weeks with demonstrated tolerability. Eligible patients were randomly assigned in a 1:1 ratio to receive 1 year (52 weeks) of treatment with either oral sildenafil (20 mg) or matching placebo TID while they continued to take pirfenidone.

Treatment with sildenafil was initiated and monitored by a physician experienced in the treatment of PAH. The randomized patients were stratified according to availability of a previous right heart

catheterization (RHC) for inclusion (yes or no) and degree of pulmonary function, which was measured with the forced expiratory volume in 1 second (FEV1)/FVC ratio being below or above 0.8.

The patients were provided pirfenidone for the study by the Sponsor and were instructed on proper use. Patients were instructed to stop taking their commercial pirfenidone and start taking the study-provided pirfenidone.

The study consisted of 5 phases:

- Run-in period of 12 weeks (if needed)
- Screening period
- 28-day washout period (if needed);
- Double-blind treatment period (52 weeks)

- Follow-up period (4 weeks)

Additionally, there was the possibility for patients to continue to receive pirfenidone within the study protocol after the follow-up visit at Week 56 during a safety follow up period.

After patients completed a washout period, patients entered a screening period, which lasted for up to 28 days; during screening, patients were evaluated for eligibility based on the inclusion and exclusion criteria. A run-in period was provided for countries where patients were not able to take pirfenidone for 12 weeks due to reimbursement issues.

At the start of screening, patients were on oral pirfenidone taken TID for at least 12 weeks, and the dose was in the range of 1602-2403 mg/day for ≥4 weeks prior to the first screening visit. It was expected that the dose would remain within the range of 1602-2403 mg/day throughout the study and in accordance with the product label.

In addition, in the 4 weeks before the first screening visit, patients should have not experienced either a new or ongoing adverse event (AE) of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 that was Grade 2 or higher and considered by the investigator to be related to pirfenidone, or had an interruption of pirfenidone treatment f,or >7 days for any reason. During screening, patients could return for the baseline visit (Day 1) as soon as eligibility was confirmed.

Patients who experienced an event that was part of the composite primary endpoint (other than all-cause mortality) continued treatment and were encouraged to complete the study.

The primary analysis for the study was conducted when all patients completed the 52-week treatment phase and the mandatory 4-week follow-up visit.

Study participants

- Main inclusion criteria
- Were 40–80 years (inclusive) of age at screening
- Had been diagnosed with IPF for ≥3 months prior to screening
- Had confirmed diagnosis of IPF by the investigator, in accordance with the 2011 international consensus guidelines (Raghu et al. 2011), at screening
- For the purposes of this study, presented with:

  Advanced IPF, defined as a measurable DLco ≤40% of predicted value at screening;

  - Risk of Group 3 PH, defined as: o mPAP ≥20 mmHg together with pulmonary artery wedge pressure ≤15 mmHg on a previous RHC of acceptable quality
  - In the absence of a previous RHC, echocardiography (ECHO) results that showed intermediate or high probability of Group 3 PH at screening, as defined by the 2015 European Society of Cardiology (ESC)/European Respiratory Society (ERS) (peak tricuspid regurgitation velocity [TRV] ≥2.9 m/s), assuming that the patients met all other eligibility criteria (Galiè et al. 2015)
  - Prior to the start of screening, had received pirfenidone for ≥12 weeks at a dose in the range of 1602–2403 mg/day for ≥4 weeks prior to the first screening visit.
- During this 4-week period, patients had not experienced either a new or ongoing AE of NCI CTCAE (version 4.03) of Grade 2 or higher and considered by the investigator to be related to

pirfenidone, or an interruption in pirfenidone treatment for >7 days for any reason. It was expected that the dose of pirfenidone would be in the range of 1602–2403 mg/day throughout the study (in countries where patients were not able to take pirfenidone for 12 weeks due to reimbursement issues, this 12-week run-in supply was provided by the Sponsor)

- Had World Health Organization (WHO) Functional Class II or III disease (Rubin 2004) at screening
- Had 6MWD of 100–450 m at screening

Treatments

At the start of screening, patients were on oral pirfenidone taken TID for at least 12 weeks, and the dose was in the range of 1602–2403 mg/day for ≥4 weeks prior to the first screening visit. It was expected that the dose would remain within the range of 1602–2403 mg/day throughout the study and in accordance with the product label.

Objectives and Outcomes/endpoints

The primary efficacy objective was evaluated using a composite endpoint based on a comparison of the proportion of patients who showed disease progression over 52 weeks of treatment, as evidenced by reaching the combined endpoint of relevant decline in 6MWD of ≥15% from baseline, respiratory-related non-elective hospitalization, or all-cause mortality.

The secondary objective was evaluated as the individual components of the primary endpoint as well as other assessments.

Table 12 Overview of Efficacy Objectives and Endpoints

Objective	Corresponding Endpoint
Primary Efficacy Objective • To evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone treatment	Relevant decline in 6MWD of at least 15% from baseline, respiratory-related non-elective hospitalization, or all-cause mortality Relevant decline in 6MWD from baseline was defined as: • Any decline >25% from baseline or • A decline between 15%–25% from baseline, if accompanied by at least one of the following: ○ Worsening of SpO_2 desaturation during the 6MWT compared to baseline ○ Worsening of the maximum Borg scale during the 6MWT compared to baseline ○ Increased O_2 requirements during the 6MWT compared to baseline.

Objective	Corresponding Endpoint
Secondary Efficacy Objective	
• To evaluate the efficacy of adding sildenafil compared with placebo to pirfenidone treatment	• PFS, defined as time to first occurrence of decline in 6MWD of ≥15% from baseline as defined above, or respiratory-related non-elective hospitalization, or death from any cause • Proportion of patients with relevant decline in 6MWD of ≥15% from baseline as defined above • Time to respiratory-related non-elective hospitalization • Time to death from any cause • Lung transplant • Time to all-cause, non-elective hospitalization • Time to respiratory-related death • Change from baseline in transthoracic ECHO parameters • Change from baseline in PFTs • Change from baseline in SpO_2 at rest and during the 6MWT • WHO functional class • Dyspnea (assessed with the UCSD-SOBQ) • HRQoL (assessed with the SGRQ) NT-proBNP level

6MWD=6-minute walk distance; 6MWT=6-minute walk test; ECG=electrocardiogram; ECHO=echocardiography; HRQoL=health-related quality of life; NT-proBNP=N-terminal pro-brain natriuretic peptide; PFS=progression-free survival; PFT=pulmonary function test; SGRQ=St. George's Respiratory Questionnaire; SpO_2=oxyhemoglobin saturation; UCSD-SOBQ=University of California, San Diego–Shortness of Breath Questionnaire; TEAE=treatment emergent adverse event; WHO=World Health Organization.

Statistical methods

Analysis Methods

The statistical hypothesis for the treatment comparison was based on the proportion of patients who experienced a decline of ≥15% from baseline in 6MWD, were hospitalized for cardiac or respiratory non-elective reasons, or who died.

Statistical Analysis of Primary and Secondary Endpoints

The primary and secondary efficacy analyses included all randomized patients, with patients grouped according to their assigned treatment.

Table 13 Statistical Analysis of Primary and Secondary Efficacy Endpoints

Variable	Test	Stratification Variable/Cofactors	Handling of Missing Data (Imputation Methods)
Primary Endpoint: Relevant decline in 6MWD of ≥15% from baseline, respiratory-related non-elective hospitalization, or all-cause mortality	Chi-square test Logistic regression model Cochran-Mantel Haenszel test	Availability of RHC FEV1/FVC ratio	Patients who discontinued treatment prematurely were analyzed based on the available data. No imputation method was applied.
Secondary Endpoints: PFS, defined as time to decline in 6MWD of ≥15% compared with baseline as defined above, respiratory-related non-elective hospitalization, or death from any cause	Kaplan-Meier techniques Log-rank test Cox-proportional hazard mode	—	Patients who did not experience the combined endpoint during the double-blind treatment period were censored at the time of double-blind treatment completion/ discontinuation
Proportion of patients with at least one decline in 6MWD of ≥15% from baseline	Chi-square test	—	—
Change in 6MWD (m) from baseline to 52 weeks	Rank ANCOVA model with the change from baseline as the outcome variable and standardized rank baseline 6MWD as a covariate	—	Patients who discontinued treatment prematurely were analyzed based on the available data. No imputation method was applied.
Respiratory-related, non-elective hospitalization, all-cause mortality, all-cause non-elective hospitalization, and respiratory-related mortality	Kaplan-Meier techniques Log-rank test Cox-proportional hazard model	—	Patients who did not experience the parameter of interest by the time of completion or discontinuation from the double-blind treatment period were censored.

Variable	Test	Stratification Variable/Cofactors	Handling of Missing Data (Imputation Methods)
Change from baseline in transthoracic ECHO parameters	Rank ANCOVA with change from baseline as the outcome variable and standardized rank baseline value as covariate	—	—
Lung transplant	—	—	—
Change from baseline in PFTs	Rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate	—	—
Change from baseline in SpO_2 at rest and during the 6MWT	—	—	—
WHO functional class	—	—	—
Dyspnea (assessed with the UCSD-SOBQ)	Rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate	—	—
NT-proBNP level	—	—	—

6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; ANCOVA = analysis of covariance; ECHO = echocardiography; FEV1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HRQoL = health-related quality of life; NT-proBNP = N-terminal pro-brain natriuretic peptide; PFS = progression-free survival; PFT = pulmonary function test; SGRQ = St. George's Respiratory Questionnaire; SpO2 = oxyhemoglobin saturation; UCSD-SOBQ = University of California, San Diego-Shortness of Breath Questionnaire.

Results

Patient Disposition

A total of 271 patients were enrolled in the study (signed informed consent), of which 173 patients were screened without run-in period and 98 patients were included in run-in period. Of 98 patients, 24 patients were run-in failures; thus, 74 patients were screened after the run-in period.

Of 247 screened patients, 70 patients were screen failures. The reasons for screen failures included inclusion/exclusion criteria (59 patients [62.8%]) and other (11 patients [11.7%]). A total of 88 patients in the pirfenidone with added sildenafil group and A total of 271 patients were enrolled in the study (signed informed consent), of which 173 patients were screened without run-in period and 98 patients were included in run-in period. Of 98 patients, 24 patients were run-in failures; thus, 74 patients were screened after the run-in period.

Of 247 screened patients, 70 patients were screen failures. The reasons for screen failures included inclusion/exclusion criteria (59 patients [62.8%]) and other (11 patients [11.7%]). A total of 88 patients in the pirfenidone with added sildenafil group and 89 patients in the pirfenidone with added placebo group were randomly assigned to receive study treatment during double-blind period. All patients received study treatment in both groups. Therefore, the safety population included all 177 randomized patients.

During the study, one patient in the pirfenidone with added sildenafil group was unblinded after completing 52 weeks of double-blind treatment. The unblinding occurred during the additional safety follow-up period and, thus, the patient was not excluded from the analysis.

A total of 51 patients (58.0%) in the pirfenidone with added sildenafil group and 37 patients (41.6%) in the pirfenidone with added placebo group completed the double blind treatment period of the study.

Baseline data

Demography and Baseline Disease Characteristics

Demographic and baseline characteristics for the study population are representative of the advanced IPF population and were generally well balanced between the pirfenidone with added sildenafil and pirfenidone with added placebo groups, with few exceptions.

The median age of patients was similar between the two groups (pirfenidone with added sildenafil was 70.0 years and pirfenidone with added placebo was 69.0 years). The majority of patients was male, White, and not Hispanic or Latino.

The median body-mass index (BMI) value and NT-proBNP level at baseline were 27.1 kg/m2 and 125.5 pg/mL in the pirfenidone with added sildenafil group and 27.2 kg/m2 and 161.0 pg/mL in the pirfenidone with added placebo group, respectively. Most of the females were postmenopausal.

Table 14 Demographics and Baseline Characteristics (MA29957; ITT Population)

	Pirfenadone + Sildenafil N=88	Pirfenadone + Placebo N=89
Age (years) at screening		
n observed	88	89
Mean (std)	68.2 (7.66)	68.9 (7.07)
Median	70.0	69.0
Q1 - Q3	63.5 - 74.0	65.0 - 74.0
Min - Max	48 - 80	48 - 80
Age categories [n (%)]		
<45 years	0	0
≥45 - <65 years	27 (30.7)	22 (24.7)
≥65 - <85 years	61 (69.3)	67 (75.3)
≥85 years	0	0
<65 years	27 (30.7)	22 (24.7)
≥65 years	61 (69.3)	67 (75.3)
Gender [n (%)]		
Male	69 (78.4)	65 (73.0)
Female	19 (21.6)	24 (27.0)
Race [n (%)]		
American Indian or Alaskan Native	0	0
Asian	1 (1.1)	0
Black or African American	0	1 (1.1)
Native Hawaiian or Other Pacific Islander	1 (1.1)	0
White	85 (96.6)	88 (98.9)
Mixed	0	0
Unknown	(1.1)	0
Ethnicity [n (%)]		
Hispanic or Latino	(2.3)	3 (3.4)
Not Hispanic or Latino	78 (88.6)	79 (88.8)
Not reported	0	0
Unknown	8 (9.1)	7 (7.9)
Weight (kg) at baseline		
n observed	88	89
Mean (std)	77.6 (14.85)	75.6 (15.41)
Median	75	74
Q1-Q3	67.5-87.3	65.0-84.5
Min-Max	50-129	39-115

The baseline values were also well balanced between treatment groups. There were 88 patients in the pirfenidone with added sildenafil group and 89 patients in the pirfenidone with added placebo group who had data available for DLco (% predicted), and the baseline mean (SD)/median values were as follows: 26.833 (9.4558)/26.165 in the pirfenidone with added sildenafil group and 25.390 (9.2052)/25.000 in the

pirfenidone with added placebo group.

Numbers analysed

A total of 177 patients (88 patients in the pirfenidone+sildenafil group and 89 patients in the pirfenidone+placebo group) were randomly assigned to receive treatment.

Outcomes and estimation

Primary endpoint

This study has shown that adding sildenafil to pirfenidone was not associated with any meaningful reduction of the risk to experience a composite primary endpoint event nor on any of its components (relevant decline in 6MWD of ≥15% from baseline, respiratory related non-elective hospitalization, or all-cause mortality). The result of the primary endpoint was similar across pre-specified patient subgroups.

The primary analysis of the primary endpoint showed that the risk difference for pirfenidone+sildenafil vs. pirfenidone+placebo was 3.06% (95% CI: -11.30, 17.97; p = 0.6527), demonstrating that addition of sildenafil to pirfenidone was not associated with a meaningful reduction of the risk to experience a disease progression event.

For PFS, the median time to event occurrence was similar between treatment groups (26.00 weeks vs. 25.43 weeks), with an HR (95% CI) of 0.95 (0.67, 1.34; p = 0.7568).

The median time to occurrence of multiple events was 7 weeks longer in the pirfenidone+sildenafil group (20.57 weeks) than in the pirfenidone+placebo group (13.29 weeks), and the HR (95% CI) to experience multiple disease progression events was 0.89 (0.68, 1.15; p = 0.3760).

The proportion of patients with relevant 6MWT declines ≥15% from baseline was similar between treatment groups (53.4% in the pirfenidone+sildenafil group and 50.6% in the pirfenidone+placebo group) with risk difference (95% CI) of 2.85 (-12.13, 17.84; p = 0.7046).

Median time from randomization to first occurrence of relevant declines ≥15% in 6MWD (m) was similar between treatment groups (39.0 weeks in the pirfenidone+sildenafil group and 38.71 weeks in the pirfenidone+placebo group), with an HR (95% CI) of 0.94 (0.62, 1.41; p = 0.7550).

Table 15 Overall Summary of Efficacy (Primary Analyses) – primary endpoint and selected secondary endpoints

Parameter	Pirfenidone+Sildenafil n=88)	Pirfenidone+Placebo (n=89)	Pirfenidone+Sildenafil vs. Pirfenidone+Placebo[a]
Primary endpoint: patients with disease progression[b]			
n (%)	64 (72.7)	62 (69.7)	
Difference (95% CI), %[c]			3.06 (-11.30, 17.97)
P-value[d]			0.6527
Time to first occurrence of disease progression[b]			
Median (95% CI), weeks	26.00 (20.57, 38.14)	25.43 (13.00, 37.71)	
HR (95% CI)[e]			0.95 (0.67, 1.34)
Log-rank P-value[f]			0.7568
Time to multiple occurrence event (weeks)			
Median (95% CI), weeks	20.57 (13.14, 26.43)	13.29 (12.71, 23.29)	
HR (95% CI)[e]			0.89 (0.68, 1.15)
Log-rank P-value[f]			0.3760
Patients with a relevant ≥15% decline from baseline in 6MWD[g]			
n (%)	47 (53.4)	45 (50.6)	
Difference (95% CI), %[c]			2.85 (-12.13, 17.84)
P-value[d]			0.7046
Time to first occurrence of relevant ≥15% decline from baseline in 6MWD			
Median (95% CI), weeks	39.00 (27.86, 52.14)	38.71 (25.14, 52.57)	
HR (95% CI)[e]			0.94 (0.62, 1.41)
Log-rank P-value[f]			0.7550

Change in FVC Volume at Week 52 (Pirfenidone + Placebo)

The annual rate of FVC decline from baseline to Week 52 among patients in the pirfenidone with added placebo group was -93 mL (SE: 46.4).

All-Cause Mortality (Pirfenidone + Placebo)

During the double-blind treatment period, 18/89 (20.2%) patients in the pirfenidone with added placebo group had died from all causes. The median time to occurrence of event was not calculable (as the median time was not reached).

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Esbriet is authorised for the treatment of adult patients with mild to moderate idiopathic pulmonary fibrosis (IPF), as follows: "*Esbriet is indicated in adults for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF).*"

This variation proposes to add advanced stages of the disease to the indication to allow treatment in all adult patients with IPF. The proposed indication is *Esbriet is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF).*"

No new pivotal data were provided with this application.

Utilising the data from the original pivotal trials investigating Esbriet as a treatment for IPF, as well as from study MA29957, a recently completed Phase 2 study in patients with advanced IPF, the applicant has performed **retrospective post-hoc analyses** to compare the efficacy and safety profile of Esbriet in patients with mild to moderate IPF versus patients with more advanced IPF. Data from the following studies has been used for the assessment of the efficacy in patients with advanced IPF:

- Pooled Phase III studies (PIPF-004/006/016)
- PIPF-012 study
- MA29957 study

Efficacy data and additional analyses

Analysis of pooled phase III studies (PIPF-004/006/016)

Studies PIPF-004 and PIPF-006 were submitted in 2010 with the original MAA. The PIPF-0016 study was submitted in 2014 with the variation application supporting an update to section 5.1.

PIPF-004 and PIPF-006 compared treatment with Esbriet 2403 mg/day to placebo. The studies were nearly identical in design, with few exceptions including an intermediate dose group (1197 mg/day) in PIPF-004. In both studies, treatment was administered three times daily for a minimum of 72 weeks. The primary endpoint in both studies was the change from Baseline to Week 72 in percent predicted Forced Vital Capacity (FVC).

The design of PIPF-0016 study was similar to that of the previous pivotal studies, with the only significant differences being the study length (52 vs 72 weeks) and an update of the inclusion/exclusion criteria to bring them into line with the more recent diagnostic standards.

It is noted that pivotal studies submitted at the stage of the original MAA only enrolled subjects with FVC >50% (% predicted) at screening and a Day 1 and DLCO >35% (% predicted) at screening. In relation to FVC the same criteria for enrolment were used also in study PIPF-0016, i.e. patients had to have FVC >50% (% predicted) at screening. In relation to DLCO, the inclusion criteria were slightly different, i.e. PIPF-0016 study could enrol patients with slightly lower DLCO value, i.e. DLCO>30%.

For the purpose of this submission, advanced IPF was defined by the applicant as patients with an FVC <50% predicted and/or DLCO <35% predicted at baseline, which can be accepted.

It is noted that the majority of patients in the post-hoc analysis of pivotal studies who were included in advanced IPF group come from PIPF-0016 study (74% of patients) and only 25% from PIPF-004/006 studies. This is due to the fact that PIPF-016 study enrolled patients with DLco ≥30% and therefore patients could be included in the advanced IPF group of this post hoc analysis if they had DLco ≥30% and <35% at baseline, or if they experienced a decline in FVC to <50% between screening and randomization.

Although the original lung function entry criteria of PIPF-004/006 studies suggest that patients with more advanced lung function impairment were not eligible, some patients could have changes in DLco values between screening and randomization (≤8 weeks following screening) with an increase in their lung function impairment by the start of dosing.

In the PIPF-004/006/016 studies a number of endpoints were investigated however the post-hoc analysis presented by the applicant focuses on two outcome measures, i.e. change in FVC volume from baseline to Week 52 of treatment as well as the difference in the risk of all-cause death at 52 weeks.

1247 patients were included in the post hoc analysis of PIPF-004/006/016 studies. 1077 patients were categorized as having non-advanced IPF (FVC ≥50% and DLco ≥35%) and 170 patients as having advanced IPF (FVC <50% or DLco <35%). The mean age of the analyzed subjects was 67-68. The majority of patients were male (more than 73 % in any treatment group) and elderly (i.e. ≥65 years of age). It needs to be highlighted that patients included in the post-hoc analysis of PIPF-004/006/016 studies represent only a small subset of patients with advanced IPF; the minimal FVC (% Predicted) of included patients was 48% and minimal DLCO (% Predicted) of included patients was 27%. The applicant was requested to discuss and justify if the subgroup of patients included in this post hoc analysis could be considered as a sufficient representation of patients with advanced IPF and whether the results could be extrapolated to a broader population of patients with advanced IPF.

The applicant clarified that the results of studies PIPF-012 and MA29957 inclusion criteria that allowed for a more severe population and can be considered supportive for the extrapolation to the broader population of advanced IPF. In Study PIPF-012, in the patients with advanced IPF 50% had a DLco at baseline below **30.7%** and 25% a DLco at baseline below **25.2%**, thereby representing a much more IPF-advanced population than the one included in the pooled Phase 3 cohort. In Study MA29957 advanced IPF patients were also at risk of group 3 pulmonary hypertension, representing other patients with advanced IPF. Additionally provided results for quartile 1, median and quartile 3 for FVC form baseline until 52 weeks, did not indicate that the beneficial effect of pirfenidone is less in the more affected population. With all the data provided, it is sufficiently supported that the results of the affected patients with advanced IPF investigated in studies provided by the applicant can be extrapolated to all advanced IPF patients.

Based on the results of the post-hoc analysis of PIPF-004/006/016 studies the applicant concluded that a similar treatment effect of pirfenidone was observed in patients with advanced as compared to patients with non-advanced IPF. The annual FVC decline was lower in the pirfenidone treated patients as compared patients on placebo regardless of the disease status. Among patients with advanced IPF, the annual FVC decline was significantly lower with pirfenidone versus placebo (150.9 mL vs 277.6 mL; nominal p=0.0035). Among patients with non-advanced IPF, annual FVC decline was also significantly lower with pirfenidone versus placebo (128.7 mL vs. 216.7 mL; nominal p=0.0001). The additional provided results of ppFVC support the findings of FVC volume. They show that the decline in ppFVC is somewhat greater in the advanced patient group, but the difference between the non-advanced and advanced patient group is even greater for the placebo. Furthermore, the similar lower rate of FVC decline compared to placebo already suggests similar protection against clinically and prognostically relevant respiratory deterioration. In both the non-advanced and advanced patient group pirfenidone lowered the proportion of patients with a decline of ≥ 10 absolute percentage points or death compared to their respective placebo group.

In relation to all-cause mortality assessment among patients with advanced IPF, less patients died in the pirfenidone group as compared to the placebo group. The percentage of patients with advanced IPF who died from any cause was 4.4% (4/90) in the pirfenidone subgroup compared with 15.0% (12/80) with placebo over 52 weeks of treatment (annual mortality rate).

All-Cause Mortality (ACM)

The Applicant considered the reduction of mortality the ultimate goal of treatment in IPF. A significant reduction in all-cause mortality was found in the pooled Phase III studies of pirfenidone (King et al 2014[1], Nathan et al 2017[2]). Although all-cause mortality may indeed allow for the assessment of

[1] T E King, Jr., W Z Bradford, S Castro-Bernardini, E A Fagan, I Glaspole, M K Glassberg, E Gorina, P M Hopkins, D Kardatzke, L Lancaster, D J Lederer, S D Nathan, C A Pereira, S A Sahn, R Sussman, J J Swigris, P W Noble. A Phase 3 Trial of Pirfenidone in Patients with Idiopathic Pulmonary Fibrosis. N ENGL J MED 370;22 MAY 29, 2014

[2] S D Nathan, C Albera, W Z Bradford, U Costabel, I Glaspole, M K Glassberg, D R Kardatzke, M Daigl, K-U Kirchgaessler, L H Lancaster, D J Lederer, C A Pereira, J J Swigris, D Valeyre, Pl W Noble. Effect of pirfenidone on

benefit in survival, it is a composite endpoint that does not differentiate between death from progression/complications of idiopathic pulmonary fibrosis and eventually death of TEAEs. To understand the meaning of the difference in ACM, additional treatment-emergent all-cause mortality, treatment-emergent IPF-related mortality and IPF-related mortality outcomes would inform about the different aspects. However, the numbers are too low for a further meaningful exploration.

Considering the choice of the endpoint, it cannot fully excluded that the post-hoc decisions for the endpoints were influenced by the results of the analyses of the initial submissions. While the presented endpoints as such could be acceptable endpoints, no other endpoints are analysed, because of issues around missing data in certain data constellations, according to the Applicant. However, missing data might (according to reasons for missing data) indicate that there was no positive effect. Therefore, analysis of these endpoints with imputation based on the reasons for missing data can be informative. Alternatively, if results of these endpoints used in the studies, especially the placebo-controlled main studies, would support the outcome of the primary analyses, the totality of post-hoc data would be strengthened and less prone to selection bias. After imputing the missing outcomes apart from death by an average of the three most similar patients based on previous visits, the results of the 6MWT confirm the observation made for FVC that there is a treatment effect of pirfenidone in both non-advanced and advanced patient compared to respective placebo groups. For 6 UCSD SOBQ score, there was a consistent effect of pirfenidone in reducing the worsening of dyspnoea in both populations compared to the greater deterioration in the placebo group. Therefore, these endpoints support the results of the primary endpoints.

Statistical analysis

The SAP acknowledged that analyses are post-hoc and no confirmatory testing was performed (p-values are descriptive). The analysis presented in this SCE focuses on change in FVC volume from baseline to Week 52 of treatment as well as the difference in the risk of all-cause death at 52 weeks. No order of importance was placed on the endpoints (e.g. primary, secondary).

FVC volume data up to 52 weeks of treatment for patients in the pirfenidone 2403 mg/day and placebo cohorts from the three Phase III studies were pooled. Linear slope analysis of change from baseline to Week 52 in FVC volume was performed using a mixed model. Slopes were calculated based on observed data only and used actual observation times.

Time-to-event outcomes were compared between pirfenidone and placebo using the log-rank test. A proportional hazards model, with treatment as a fixed effect, was used to estimate the hazard ratio (HR) and 95% CI. Kaplan-Meier curves were used to display event times and the numbers of patients at risk. Patients without an event were censored at or prior to 52 weeks, as appropriate for each outcome and 52-week completion status

Post-hoc analyses are by definition not prespecified, hence type I error control is not possible. However, the endpoints accounting for death as a negative outcome (imputation for death in FVC as FVC=0; considering death as failure for the clinical responder; imputing for death in UCSD as UCSD=120) showed all positive effects for pirfenidone in all studies in both advanced (albeit with more variation across studies) and non-advanced population. These endpoints are considered of more clinical importance than those where data are considered missing after the patient died (hypothetical estimand: the effect as if patient would not have died). So the lack of type I error is mitigated by the replication of a positive effect in clinically relevant outcomes, and hence the risk of a chance finding is considered acceptably low.

mortality: pooled analyses and meta-analyses of clinical trials in idiopathic pulmonary fibrosis. www.thelancet.com/respiratory Vol 5 January 2017

PIPF-012 study

The additional data supporting this variation come from Study PIPF-012 which was a single-arm, Phase IIIb, multicenter, long-term, open-label, safety study in patients with IPF who completed one of the previous Phase III studies (PIPF-004, PIPF-006, or PIPF-016). There was no criterion on IPF severity for enrollment into this extension study. It is noted that after implementation for the Amendment 2 pulmonary function tests were no longer collected in this study and therefore these results are not available for all patients. The target maintenance dose in this study was 2403 mg/day – the same as used in pivotal studies.

The applicant presented the results of decline in FVC volume over 180 weeks in the subgroup of patients with advanced and non-advanced diseases. Information on survival was also provided.

A total of 609 patients were enrolled into study PIPF-012, of which 596 treated patients (187 patients with advanced IPF and 409 patients with non-advanced IPF) had baseline FVC and/or DLco values at the time of enrollment into PIPF-012and were eligible for inclusion in the post-hoc analysis of efficacy by IPF severity (non-advanced vs. advanced). Patients from the PIPF-016 study were not included in the analysis due to a lack of available FVC follow-up data due to implementation of Global Amendment 2. Similar as in pivotal studies the majority of patients were over 65 and male. The median age in both groups was 69 years of age. In relation to patients with advanced IPF the mean percent predicted FVC was 59.8% (range 22- 125) and the mean percent of DLCO was 29.2% (range 13-45) at baseline. It is noted that the duration of treatment was significantly shorter in patients with advanced IPF as compare to those with non-advanced IPF, i.e. the mean duration of treatment 28.2 months in the advanced IPF group and 41.4 months in the non-advanced IPF group. The applicant stated that reason for this is a higher rate of mortality among advanced IPF patients.

The results of the post-hoc analysis of Study PIPF-012 study indicated that the annual rate of FVC decline (slope) in pirfenidone treated patients in the advanced IPF group was similar to the decline in the non-advanced group (-141.5 mL/year and -153.5 mL/year, respectively). However, all-cause mortality rate over 180 weeks was lower among patients with non-advanced IPF (49/409; 12.0%) compared to patients with advanced IPF (52/187; 27.8%).

In both groups mortality was much higher than in the pivotal trials. Mortality was higher in the advanced group due to the natural history of IPF, compared to the non-advanced group, and in both groups higher in the second and third year than in the first year. This is not unexpected as the result of the ongoing progression, pirfenidone at its best can only slow down progression.

MA29957 study

Further data supporting the proposed changes to the indication come from MA29957 study which was a Phase IIb, multicenter, randomized, double-blind, placebo-controlled of the efficacy, safety, and tolerability of combination treatment of **pirfenidone with added sildenafil** in patients with advanced IPF and at risk of Group 3 PH who had been on pirfenidone treatment in a dose range of 1602-2403 mg/day for ≥12 weeks with demonstrated tolerability. In this study eligible patients were randomly assigned in a 1:1 ratio to receive 1 year (52 weeks) of treatment with either oral sildenafil (20 mg) or matching placebo TID while they continued to take pirfenidone.

This study was focusing on the effect of sildenafil on pulmonary hypertension (group 3 i.e. secondary to pulmonary disease) as the primary and secondary endpoints investigated in the study were typical for studies investigating treatments for pulmonary hypertension. The primary endpoint of this study was the combined endpoint of relevant decline in 6MWD of ≥15% from baseline, respiratory-related non-elective hospitalization, or all-cause mortality. There were a number of secondary endpoints in this study including the assessment of individual components of the primary endpoint. Changes from

baseline in pulmonary function tests (PFT) results such changes in DLco (% predicted), changes in FVC (% predicted) and changes in FVC in ml were investigated as a secondary endpoint which was not included in the multiplicity control strategy.

Although the MAH acknowledged that study MA29957 was not designed to demonstrate a benefit of pirfenidone monotherapy in adult patients with advanced IPF, in support of this application the applicant is presenting the results of annual rate of decline in FVC volume in the comparator arm (i.e pirfenidone plus placebo arm). The results of the pirfenidone plus sildenafil arm was not considered to be relevant for this variation by the applicant and therefore these results were not discussed in detail in this report.

89 out of 177 patients randomised into the MA29957 study were included in the pirfenidone plus placebo arm. The median age of patients was 70.0 years in the pirfenidone plus sildenafil group and 69 in the pirfenidone plus placebo group. The majority of patients were male, White, and not Hispanic or Latino.

The primary endpoint of this study was the combined endpoint of relevant decline in 6MWD of ≥15% from baseline, respiratory-related non-elective hospitalization, or all-cause mortality.

The primary endpoint of this study was not met although as stated by the applicant these results are not relevant for this submission.

In study MA29957, 89 patients treated with Esbriet monotherapy had a similar decline in FVC as Esbriet-treated patients in the post-hoc analysis of the pooled phase 3 trials PIPF-004, PIPF-006, and PIPF-016. The annual rate of FVC decline from baseline to Week 52 among patients in the pirfenidone with added placebo group was -93 mL (SE: 46.4).

A total of 37 patients (41.6%) completed the double-blind treatment period. This was generally comparable with the pirfenidone+ sildenafil group.

However, discontinuation is much higher than in the pivotal studies PIPF-004 and PIPF-006, in which discontinuation was 4.6% and 19.9%, respectively. Main reasons for early discontinuation were the occurrence of adverse events (32.6%), death (14.6%), and withdrawal of consent (5.6%). Patients with advanced IPF and risk of PH have a higher a priori risk of death i.e. 25% of the discontinuations. These differences can be mostly explained by the difference in severity of the underlying disease, i.e., a higher disease burden in patients with advanced IPF at risk of grade 3 PH.

2.4.4. Conclusions on the clinical efficacy

The post-hoc analyses of patients with more advanced functional impairment from the pooled Phase III studies, the post-hoc analyses from patients with advanced disease from the open-label PIPF-012 study, and the changes in functional parameters observed in MA29957 (patients with advanced IPF and Group 3 PH) are generally consistent across the different data sources and suggest a therapeutic benefit of pirfenidone in patients with advanced IPF is comparable to that observed in patients with mild to moderate IPF. The annual FVC decline was lower in the pirfenidone treated patients as compared patients on placebo regardless of the disease status.

The decline in FVC observed over time in MA29957 (~100 mL) was lower than the average annual rate of decline of approximately 200 mL seen in untreated patients in the previous Phase III studies. This is consistent with the slowing of IPF.

progression in patients with advanced IPF treated with pirfenidone in the pooled Phase III studies.

2.5. Clinical safety

Introduction

The clinical safety profile of pirfenidone in advanced IPF patients described in this SCS is primarily based on pooled safety data concerning treatment-emergent adverse events

(TEAEs) from:

1. the control arm in the Phase IIb Study MA29957 (also called SP-IPF), a multicenter, randomized, double-blind, placebo-controlled, 52-week, international study of the efficacy, safety, and tolerability of combination treatment with sildenafil and pirfenidone in patients with advanced IPF and at risk of Group 3 pulmonary hypertension (PH), who had been on pirfenidone treatment taken three times daily (TID) for ≥12 weeks, in a dose range of 1602-2403 mg/day, for at least 4 weeks prior to the first screening visit.
2. the pivotal Phase III Studies (PIPF-004, PIPF-006 and PIPF-0016) in patients with advanced and non-advanced IPF. PIPF-004 and PIPF-006 supported the original EU Marketing Authorization Application (MAA) received for Esbriet (pirfenidone) on 28 February 2011 (EU/1/11/667/001-003 - EMEA/H/C/2154). PIPF-0016 was submitted on 3 July 2014 as part of a Type II variation to support labelling amendments (EMEA/H/C/2154/II/0021).
3. the long-term safety Study PIPF-012 of pirfenidone. PIPF-012 was the open-label, extension study for patients completing PIPF-004, PIPF-006, and PIPF-0016. PIPF-012 also supported the original EU Marketing Authorization for Esbriet (pirfenidone) in 2011 and the Type II variation EMEA/H/C/2154/II/0021.
4. In addition, ancillary safety information from Study WB29908 (PIPF-025, PASSPORT), a post-authorization safety study (PASS) of Esbriet evaluating long-term safety of Esbriet in a real-world setting, is also provided. This study was conducted at the request of the Committee for Medicinal Products for Human Use (CHMP) and was a follow-up measure to the EU marketing authorization received for Esbriet in 2011.Study WB29908 collected data from patients across the spectrum of IPF disease severity, including patients with advanced IPF. Regular reports for Study WB29908 were submitted to EMA with annual Periodic Safety Update Report (PSUR) submissions. The first interim report was included with PSUR #3 (EMEA/H/C/002154/ PSU/005; 22 October 2012). The eighth and final report was included with PSUR #7 (PSUSA/00002435/201702; 28 April 2017).

Pooling

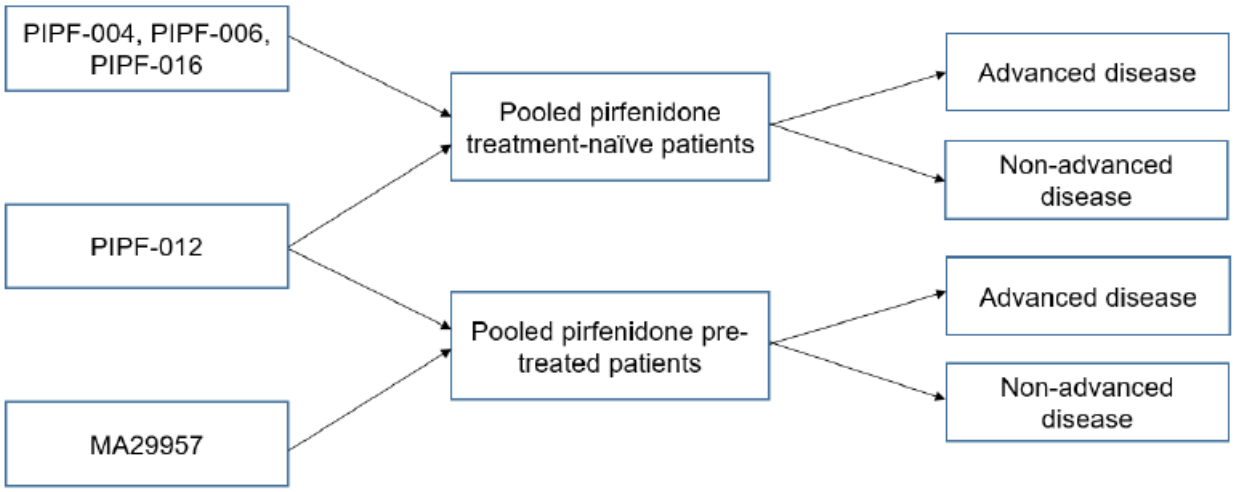
Data from Study MA29957, in patients with advanced IPF treated with pirfenidone, were integrated with data from three double-blind, placebo-controlled studies of pirfenidone in IPF (PIPF-004, PIPF-006, and PIPF-016), and with long-term, follow-up Study PIPF-012. The pivotal Phase III trials (PIPF-004, PIPF-006, and PIPF-016) enrolled pirfenidone treatment-naïve patients with advanced and non-advanced IPF.

Study PIPF-012 enrolled both pirfenidone treatment-naïve and pre-treated patients with advanced and non-advanced IPF. Study MA29957 only enrolled pirfenidone pre-treated patients with advanced IPF. In order to control for potential confounders caused by prior exposure to pirfenidone, the analysis of these studies is based on safety data pooled separately for pirfenidone treatment-naïve patients and pre-treated patients.

This allows also to explain the differences between the safety profile of pre-treated and treatment-naïve patients observed in previous studies (e.g., PIPF-012), where some common events (e.g., nausea) were observed at a higher frequency in treatment-naïve patients.

Figure 2 below shows how the patient populations have been pooled. Of note, patients who were treated with 1197 mg/d in PIPF-004 and enrolled in PIPF-012, are considered pre-treated for this analysis.

Figure 2 Pooling Strategy Scheme



The safety data of pooled naïve patients and pooled pre-treated patients were then compared between patients with advanced and non-advanced IPF, where advanced IPF is defined as below:

1. In Studies PIPF-004, PIPF-006, and PIPF-016 only patients with forced vital capacity less than 50% (FVC<50%) and/or carbon monoxide diffusing capacity at screening less than 35% (DLco<35%) predicted value were enrolled

All patients enrolled in Study MA29957 had advanced IPF and were at risk for group 3 PH. For MA29957, advanced IPF was defined as measurable carbon monoxide diffusing capacity at screening of less than or equal to 40% (DLco≤40%) predicted value

Study WB29908 (PIPF-025, PASSPORT) was not included in the integrated pooled population as this study reported adverse drug reactions (ADRs) while the pivotal trials and Study MA29957 reported adverse events (AEs). The outcomes for patients with advanced IPF enrolled in Study WB29908 have instead been discussed separately.

The studies in the pooled analysis were conducted over a period of more than 10 years, and were conducted for different periods of follow-up and duration. As such, direct comparison of frequency of AEs between studies would be inappropriate.

For this analysis, exposure-adjusted data have instead been used to account for the differences in study duration and follow-up.

In Studies PIPF-004, PIPF-006, PIPF-016 and PIPF-012, MedDRA version 11.0 was used, whereas in Study MA29957, MedDRA version 23.0 was used. The Sponsor acknowledges that different MedDRA versions were used in the different studies.

Table 16 below presents the number of pirfenidone treatment-naïve and pre-treated patients from each study contributing to the comparison of the safety profile between advanced IPF disease and non-advanced IPF disease.

Table 16 Number of patients from each clinical trial contributing to the comparison between advanced IPF disease and non-advanced IPF disease

Study	Treatment-Naïve Patients (1) (N=894)		Pre-Treated Patients (2) (N=414)	
	Non-advanced (3) n (%)	Advanced (4) n (%)	Non-advanced (3) n (%)	Advanced (4) n (%)
PIPF-004 treated with Pirfenidone 2403 mg/day	159 (17.8)	15 (1.7)	86 (20.8)	41 (9.9)
PIPF-004 treated with Pirfenidone 1197 mg/day	NA	NA	52 (12.6)	16 (3.9)
PIPF-004 treated with Placebo who moved into 012	100 (11.2)	36 (4.0)	NA	NA
PIPF-006 treated with Pirfenidone 2403 mg/day	165 (18.5)	6 (0.7)	87 (21.0)	43 (10.4)
PIPF-006 treated with Placebo who moved into 012	84 (9.4)	51 (5.7)	NA	NA
PIPF-016 treated with Pirfenidone 2403 mg/day	209 (23.4)	69 (7.7)	NA	NA
PIPF-012 treated with Pirfenidone 2403 mg/day	184 (20.6)	87 (9.7)	**225 (54.3)**	**100 (24.2)**
MA29957 treated with Pirfenidone 2403 mg/day	NA	NA	**0**	**89 (21.5)**
Total	717 (80.2)	177 (19.8)	225 (54.3)	189 (45.7)

(1) Treatment-naive patients treated with Pirfenidone were enrolled in PIPF-004, PIPF-006 and PIPF-016 and those enrolled in PIPF-012 who received placebo

Patient exposure

Exposure to Study Treatment

Of the pirfenidone treatment-naïve patients from the pooled population, the median treatment duration was roughly 4 months longer in patients with non-advanced IPF than patients with advanced IPF (16.4 months and 12.2 months respectively).

Pirfenidone pre-treated patients from the pooled population remained on treatment longer than their treatment-naïve counterparts, which is likely due to the design of Study PIPF-012 where patients remained on pirfenidone for up to 80 months, much longer than any of the other studies reported here. For pre-treated patients with non-advanced IPF, median treatment duration was more than 25 months longer than pre-treated patients with advanced IPF (41.7 months and 16 months respectively.

Table 17 Duration of treatment

	Treatment-Naïve Patients (1) (N=894)		Pre-Treated Patients (2) (N=414)	
	Non-advanced (3) n = 717 n (%)	Advanced (4) n = 177 n (%)	Non-advanced (3) n = 225 n (%)	Advanced (4) n = 189 n (%)
Duration of treatment (months)				
n observed	717	177	225	189
Mean (std)	21.5 (17.97)	19.9 (18.24)	43.9 (24.00)	20.8 (18.87)
Median	16.4	12.2	41.7	15.3
Q1 - Q3	12.0 - 21.6	11.7 - 21.8	25.8 - 63.9	6.6 - 25.8
Min - Max	0 - 79	0 - 79	0 - 80	0 - 79
Time from diagnosis to treatment (years)				

Adverse events

Analysis of Adverse Events in Pirfenidone Treatment-Naïve

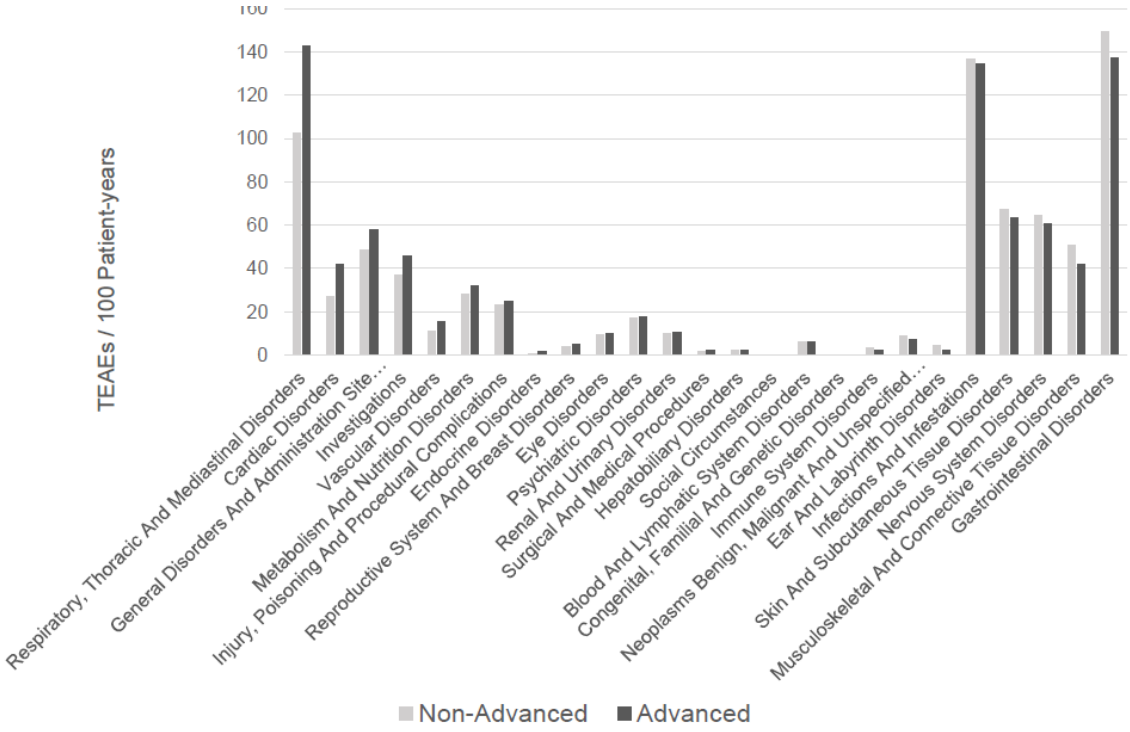
Patients from the Pooled Population

Overall, similar rates of TEAEs per 100 PY were observed in treatment-naïve patients from the pooled population with advanced IPF compared to treatment-naïve patients with non-advanced IPF (816.7 and 868.5 respectively;)

When analyzing TEAEs by SOC, two SOCs showed a higher TEAE rate (defined as ≥10/100 PYs) in advanced patients: respiratory, thoracic and mediastinal disorders; and cardiac disorders.

The exposure-adjusted TEAE rate is similar between advanced and non-advanced patients across all remaining SOCs.

Figure 3 Distribution of TEAEs by SOC in Treatment-Naïve Patients with Advanced or Non-Advanced IPF



IPF=idiopathic pulmonary fibrosis; SOC=system organ class; TEAE=treatment emergent adverse event.

Adverse Events in Treatment-Naïve Patients from the Pooled Population by Preferred Term within the SOC: Respiratory, Thoracic, and Mediastinal Disorders

The exposure-adjusted event rate difference between advanced and non-advanced treatment-naïve patients from the pooled population observed in the SOC respiratory, thoracic and mediastinal disorders was primarily driven by the PT idiopathic pulmonary fibrosis, along with other events (e.g., dyspnoea, PH, hypoxia) that are commonly associated with an aggravation of the patient's underlying condition. For all

reports of IPF, the investigator's verbatim terms were reviewed and in all cases referred to IPF progression, IPF exacerbation, IPF aggravation, worsening or end stage IPF.

Table 18 Exposure-Adjusted Event Rate by Preferred Term within the SOC: Respiratory, Thoracic, and Mediastinal Disorders

TEAE	Treatment Naïve (N=894)				
	Non-Advanced IPF (N=717)		Advanced IPF (N=177)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	167	13.00	82	27.93	14.93
Dyspnoea	171	13.31	67	22.82	9.51
Pulmonary Hypertension	41	3.19	36	12.26	9.07
Hypoxia	26	2.02	22	7.49	5.47

Adverse Events in Treatment-Naïve Patients from the Pooled Population by Preferred Term within the SOC: Cardiac Disorders

The exposure-adjusted event rate difference between advanced and non-advanced treatment-naïve patients observed in the SOC cardiac disorders is mainly driven by the PT atrial fibrillation and tachycardia

Out of 15 events of atrial fibrillation, 7 events were serious (6 events were assessed as not-related to pirfenidone and 1 event was assessed as related to pirfenidone by the investigator) and none had a fatal outcome. Atrial arrhythmias are the most commonly seen arrhythmias in patients with IPF.

Supraventricular tachycardia and multifocal atrial tachycardia are known to be cardiac manifestations of IPF.

Table 19 Exposure-Adjusted Event Rate by Preferred Term within the SOC: Cardiac Disorders

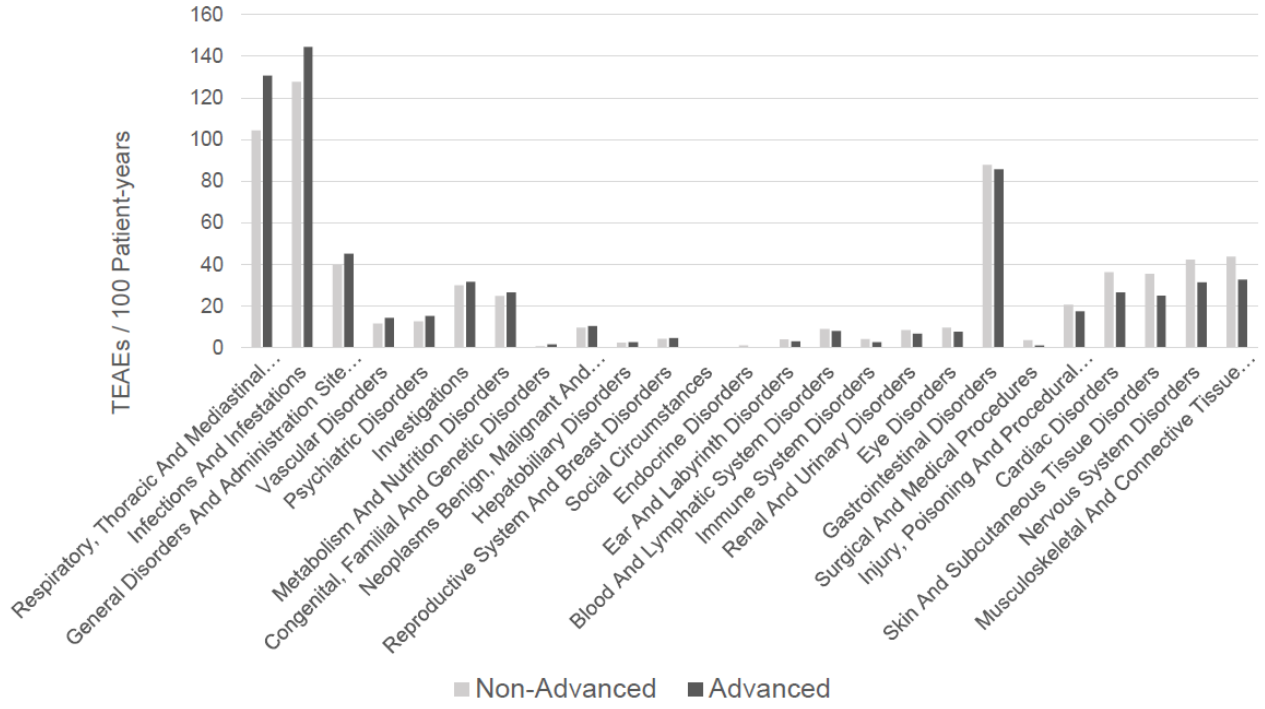
TEAE	Treatment Naïve (N=894)				
	Non-Advanced IPF		Advanced IPF		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Atrial Fibrillation	30	2.34	15	5.11	2.77
Tachycardia	14	1.09	10	3.41	2.32

Analysis of Adverse Events in Pre-treated Patients from the Pooled Population

Overall, similar AE rates per 100 PY were observed between advanced and nonadvanced Patients.

When analyzing TEAEs by SOC, 2 SOCs showed a higher TEAE rate (defined as >10/100 PYs) in advanced patients: respiratory, thoracic and mediastinal disorders; and infections and infestations.

Figure 4 Distribution of TEAEs by SOC in Pre-treated Patients with Advanced or Non-Advanced IPF



IPF=idiopathic pulmonary fibrosis; SOC=system organ class; TEAE=treatment emergent adverse event.

Adverse Events in Pre-Treated Patients from the Pooled Population by Preferred Term within the SOC: Respiratory, Thoracic, and Mediastinal Disorders

The exposure-adjusted event rate difference between pre-treated patients with advanced IPF and non-advanced IPF observed in SOC respiratory, thoracic, and mediastinal disorders is primarily driven by the PT IPF along with other events associated with an aggravation of the patient's underlying condition.

Table 20 Exposure-Adjusted Event Rate by Preferred Term within the SOC: Respiratory, Thoracic, and Mediastinal Disorders

TEAE	Pre-Treated (N=414)				
	Non-Advanced IPF (N=225)		Advanced IPF (N=189)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	119	14.46	119	36.27	21.81
Dyspnoea	131	15.92	83	25.30	9.38
Respiratory Failure	9	1.09	14	4.27	3.18
Pulmonary Hypertension	33	4.01	20	6.10	2.09

IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; PY=patient

Adverse Events in Pre-Treated Patients from the Pooled Population by Preferred Term within the SOC: Infections and Infestations

The exposure-adjusted event rate difference between advanced and non-advanced pre-treated patients observed in SOC infections and infestations is mainly due to the PT representing respiratory tract infections (i.e., lower respiratory tract infection, bronchitis, upper respiratory tract infection, respiratory tract infection, and pneumonia;), and thus might be attributed to the higher severity of the underlying disease (Odashima et al. 2020; Mostafaei et al. 2021).

All eight events of orchitis occurred in a single patient; they were all non-serious and were assessed as not-related to study treatment by the investigator.

Table 21 Exposure-Adjusted Event Rate by Preferred Term within the SOC: Infections and Infestations

TEAE	Pre-Treated (N=414)				
	Non-Advanced IPF (N=225)		Advanced IPF (N=189)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Lower Respiratory Tract Infection	35	4.25	45	13.72	9.47
Bronchitis	169	20.54	83	25.30	4.76
Upper Respiratory Tract Infection	169	20.54	83	25.30	4.76
Respiratory Tract Infection	21	2.55	20	6.10	3.55
Orchitis			8	2.44	2.44
Pneumonia	51	6.20	27	8.23	2.03

IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; PY=patient years; SOC=system organ class; TEAE=treatment-emergent adverse event.

Common adverse events

Common Adverse Events in Treatment-Naïve Patients with Advanced IPF

Among pirfenidone-naïve patients, all PTs that had a rate difference greater than 5 when comparing the rates in patients in with advanced IPF compared to non-advanced IPF; can all be attributed to the higher severity of the advanced underlying disease (i.e., IPF, bronchitis, dyspnoea, pneumonia, pulmonary hypertension, weight decreased, decreased appetite, oedema peripheral, and hypoxia)

Table 22 Common TEAEs in Treatment-Naïve Patients based on rate in Advanced IPF (rate ≥5/100 PY)

TEAE by PT	Treatment-Naïve Patients (N=894)				
	Non-Advanced IPF (N=717)		Advanced IPF (N=177)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Nausea	378	29.43	89	30.31	0.88
Idiopathic Pulmonary Fibrosis	167	13.00	82	27.93	14.93
Bronchitis	200	15.57	78	26.57	11
Dyspnoea	171	13.31	67	22.82	9.51
Cough	289	22.50	57	19.41	–3.09
Diarrhoea	309	24.06	56	19.07	–4.99
Rash	297	23.12	55	18.73	–4.39
Headache	260	20.24	53	18.05	–2.19
Upper Respiratory Tract Infection	338	26.31	52	17.71	–8.6
Fatigue	243	18.92	52	17.71	–1.21
Nasopharyngitis	229	17.83	48	16.35	–1.48
Dyspepsia	166	12.92	38	12.94	0.02
Pneumonia	80	6.23	37	12.60	6.37
Pulmonary Hypertension	41	3.19	36	12.26	9.07
Weight Decreased	78	6.07	35	11.92	5.85
Sinusitis	145	11.29	34	11.58	0.29
Dizziness	218	16.97	34	11.58	–5.39
Decreased Appetite	59	4.59	29	9.88	5.29
Back Pain	97	7.55	28	9.54	1.99
Anorexia[1]	88	6.85	28	9.54	2.69
Oedema Peripheral	51	3.97	27	9.20	5.23
Vomiting	171	13.31	26	8.86	–4.45

TEAE by PT	Treatment-Naïve Patients (N=894)				
	Non-Advanced IPF (N=717)		Advanced IPF (N=177)		Rate Difference
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Photosensitivity Reaction	112	8.72	25	8.51	–0.21
Stomach Discomfort	70	5.45	24	8.17	2.72
Constipation	86	6.70	23	7.83	1.13
Hypoxia	26	2.02	22	7.49	5.47
Insomnia	91	7.08	22	7.49	0.41
Abdominal Pain Upper	70	5.45	20	6.81	1.36
Gastroesophageal Reflux Disease	97	7.55	19	6.47	–1.08
Syncope	44	3.43	18	6.13	2.7
Hypertension	28	2.18	18	6.13	3.95
Atrial Fibrillation	30	2.34	15	5.11	2.77

Common Adverse Events in Pre-Treated Patients with Advanced IPF

Most of the common TEAEs observed in pre-treated patients with advanced IPF occurred at a rate similar to what is observed in pre-treated patients with non-advanced IPF. The common TEAEs with a rate difference greater than 5 in pirfenidone pre-treated patients with advanced IPF compared to non-advanced IPF (i.e., IPF, dyspnea, and lower respiratory tract infection) can all be attributed to the advanced nature of the underlying disease.

Table 23 Common TEAEs in Pre-Treated Patients with Advanced IPF (rate >5/100 PY)

TEAE by PT	Pre-Treated Patients (N=414)				
	Non-Advanced IPF (N=225)		Advanced IPF (N=189)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	119	14.46	119	36.27	21.81
Bronchitis	169	20.54	83	25.30	4.76
Dyspnoea	131	15.92	83	25.30	9.38
Upper Respiratory Tract Infection	169	20.54	83	25.30	4.76
Cough	144	17.50	54	16.46	–1.04
Diarrhoea	109	13.25	52	15.85	2.6
Lower Respiratory Tract Infection	35	4.25	45	13.72	9.47
Nausea	126	15.31	38	11.58	–3.73
Oedema Peripheral	52	6.32	37	11.28	4.96
Nasopharyngitis	148	17.99	35	10.67	–3.73
Fatigue	78	9.48	32	9.75	0.27
Urinary Tract Infection	59	7.17	30	9.14	1.97
Constipation	42	5.10	28	8.54	3.44
Pneumonia	51	6.20	27	8.23	2.03
Back Pain	59	7.17	27	8.23	1.06
Headache	75	9.11	26	7.93	–1.18
Vomiting	66	8.02	24	7.32	–0.7
Pulmonary Hypertension	33	4.01	20	6.10	2.09
Dizziness	71	8.63	20	6.10	–2.53
Respiratory Tract Infection	21	2.55	20	6.10	3.55
Decreased Appetite	30	3.65	18	5.49	1.84
Hypotension	15	1.82	18	5.49	3.67
Sinusitis	75	9.11	17	5.18	–3.93

IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; PT=preferred term; PY=patient years; TEAE=treatment-emergent adverse event

Serious adverse event/deaths/other significant events

DEATHS

Pulmonary fibrosis is a progressive disease that steadily worsens over time. The median survival of patients ranges from 2.5 years to 3.5 years. Accordingly, a higher rate of fatal TEAEs has been observed in both treatment-naïve and pre-treated patients with advanced IPF, as described in the following sections.

Table 24 Exposure adjusted rates for Adverse Events leading to death occurring in patients treated with Pirfenidone in studies PIPF-004, PIPF-006, PIPF-012, PIPF-016 and MA29957

	Treatment-Naïve Patients (1) (N=894)				Pre-Treated Patients (2) (N=414)			
	Non-advanced (3) n = 717		Advanced (4) n = 177		Non-advanced (3) n = 225		Advanced (4) n = 189	
System Organ Class Preferred Term	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)
Total number of AEs	48	3.74	19	6.47	37	4.50	61	18.59
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
Total number of AEs	31	2.41	16	5.45	26	3.16	40	12.19
IDIOPATHIC PULMONARY FIBROSIS	22	1.71	14	4.77	18	2.19	32	9.75
RESPIRATORY FAILURE	6	0.47			3	0.36	2	0.61
ACUTE RESPIRATORY FAILURE	2	0.16	1	0.34	2	0.24	2	0.61
HYPOXIA	1	0.08	1	0.34	1	0.12		
ACUTE RESPIRATORY DISTRESS SYNDROME					1	0.12		
DYSPNOEA							3	0.91
PNEUMOTHORAX							1	0.30
PULMONARY MASS					1	0.12		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)								
Total number of AEs	9	0.70			2	0.24	1	0.30
LUNG CANCER METASTATIC	2	0.16						
BLADDER CANCER	1	0.08						
BLADDER NEOPLASM	1	0.08						
LARGE CELL CARCINOMA OF THE RESPIRATORY TRACT STAGE UNSPECIFIED	1	0.08						
OESOPHAGEAL CANCER METASTATIC	1	0.08						
PANCREATIC CARCINOMA METASTATIC	1	0.08						
SMALL CELL LUNG CANCER METASTATIC	1	0.08						
SMALL CELL LUNG CANCER STAGE UNSPECIFIED	1	0.08						
BREAST CANCER METASTATIC					1	0.12		
LUNG NEOPLASM MALIGNANT					1	0.12	1	0.30
CARDIAC DISORDERS								
Total number of AEs	5	0.39			2	0.24	7	2.13
MYOCARDIAL INFARCTION	2	0.16			1	0.12		
ARRHYTHMIA	1	0.08						
ATRIAL FIBRILLATION	1	0.08						
CARDIAC FAILURE CONGESTIVE	1	0.08						
ACUTE MYOCARDIAL INFARCTION					1	0.12		
CARDIAC ARREST							4	1.22
CARDIO-RESPIRATORY ARREST							2	0.61
CARDIOGENIC SHOCK							1	0.30
INFECTIONS AND INFESTATIONS								
Total number of AEs	3	0.23	2	0.68	3	0.36	7	2.13
LOBAR PNEUMONIA	1	0.08						
PNEUMONIA	1	0.08	2	0.68	2	0.24	4	1.22
PNEUMONIA INFLUENZAL	1	0.08						
PNEUMOCYSTIS JIROVECI PNEUMONIA					1	0.12		
PNEUMONIA BACTERIAL							1	0.30
SEPSIS							1	0.30
SEPTIC SHOCK							1	0.30

System Organ Class Preferred Term	Treatment-Naïve Patients (1) (N=894)				Pre-Treated Patients (2) (N=414)			
	Non-advanced (3) n = 717		Advanced (4) n = 177		Non-advanced (3) n = 225		Advanced (4) n = 189	
	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
Total number of AEs					1	0.12	1	0.30
DEATH					1	0.12		
SUDDEN CARDIAC DEATH							1	0.30
NERVOUS SYSTEM DISORDERS								
Total number of AEs					2	0.24	4	1.22
CEREBROVASCULAR ACCIDENT					2	0.24	1	0.30
ANOXIC ENCEPHALOPATHY							1	0.30
CEREBRAL HAEMORRHAGE							1	0.30
SEIZURE							1	0.30
RENAL AND URINARY DISORDERS								
Total number of AEs					1	0.12		
RENAL FAILURE					1	0.12		
VASCULAR DISORDERS								
Total number of AEs			1	0.34			1	0.30
AIR EMBOLISM							1	0.30
AORTIC ANEURYSM			1	0.34				

(1) Treatment-naive patients treated with Pirfenidone were enrolled in PIPF-004, PIPF-006 and PIPF-016 and those enrolled in PIPF-012 who received placebo

Table 25 Exposure adjusted rates for Related Adverse Events leading to death occurring in patients treated with Pirfenidone in studies PIPF-004, PIPF-006, PIPF-012, PIPF-016 and MA29957

System Organ Class Preferred Term	Treatment-Naïve Patients (1) (N=894)				Pre-Treated Patients (2) (N=414)			
	Non-advanced (3) n = 717		Advanced (4) n = 177		Non-advanced (3) n = 225		Advanced (4) n = 189	
	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)
Total number of AEs	6	0.47	2	0.68	3	0.36	2	0.61
INFECTIONS AND INFESTATIONS								
Total number of AEs	2	0.16			1	0.12		
LOBAR PNEUMONIA	1	0.08						
PNEUMONIA	1	0.08						
PNEUMOCYSTIS JIROVECI PNEUMONIA					1	0.12		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
Total number of AEs	2	0.16	2	0.68				
ACUTE RESPIRATORY FAILURE	1	0.08						
IDIOPATHIC PULMONARY FIBROSIS	1	0.08	1	0.34				
HYPOXIA			1	0.34				
CARDIAC DISORDERS								
Total number of AEs	1	0.08			1	0.12		
ARRHYTHMIA	1	0.08						
MYOCARDIAL INFARCTION					1	0.12		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)								
Total number of AEs	1	0.08					1	0.30
SMALL CELL LUNG CANCER STAGE UNSPECIFIED	1	0.08						
LUNG NEOPLASM MALIGNANT							1	0.30
NERVOUS SYSTEM DISORDERS								
Total number of AEs					1	0.12	1	0.30

(1) Treatment-naive patients treated with Pirfenidone were enrolled in PIPF-004, PIPF-006 and PIPF-016 and those enrolled in PIPF-012 who received place

System Organ Class Preferred Term	Treatment-Naïve Patients (1) (N=894)				Pre-Treated Patients (2) (N=414)			
	Non-advanced (3) n = 717		Advanced (4) n = 177		Non-advanced (3) n = 225		Advanced (4) n = 189	
	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)
CEREBROVASCULAR ACCIDENT					1	0.12		
SEIZURE							1	0.30

Deaths in Treatment-Naïve Patients from the Pooled Population

The only AE leading to death with an exposure-adjusted rate >1/100 PYs higher in treatment-naïve patients with advanced IPF compared to treatment-naïve patients with non-advanced IPF was IPF. This is an expected finding taking into consideration the higher severity of the underlying IPF.

Table 26 TEAEs Leading to Death More Frequently in Treatment-Naïve Patients with Advanced vs. Non-Advanced IPF

TEAEs leading to death	Pre-Treated Patients (N=414)				
	Non-Advanced IPF (N=225)		Advanced IPF (N=189)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	22	1.71	14	4.77	3.06

TEAEs Leading to Death Observed Only in Treatment-Naïve Patients with Advanced IPF

An isolated TEAE with fatal outcome was observed in treatment-naïve patients with advanced IPF in the SOC cardiac disorders. The TEAE was assessed as not related to study treatment by the Investigator.

Table 27 TEAEs Leading to Death Observed only in Treatment-Naïve Patients with Advanced IPF

TEAEs leading to death	Treatment-Naïve Patients (N=894)			
	Non-Advanced IPF (N=717)		Advanced IPF (N=177)	
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)
Aortic Aneurysm	0	0	1	0.34

Deaths in Pre-Treated Patients from the Pooled Population

The TEAEs leading to death in pre-treated patients with an exposure-adjusted rate of >1/100 PYs higher in advanced patients compared to non-advanced patients were IPF and cardiac arrest.

Both of these TEAEs appear related to the higher severity of the underlying advanced IPF (Kreuter et al. 2016). A deeper analysis showed that none of the 4 TEAEs of cardiac arrest were attributed as related to pirfenidone by the investigator.

Table 28 TEAEs Leading to Death More Frequently in Pre-Treated Patients with Advanced vs. Non-Advanced IPF

TEAEs leading to death	Pre-Treated Patients (N=414)				
	Non-Advanced IPF (N=225)		Advanced IPF (N=189)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	18	2.19	32	9.75	7.56
Cardiac Arrest	0	0	4	1.22	1.22

IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; PT=preferred

TEAEs leading to death observed only in Pre-Treated Patients with advanced IPF

All the observed AEs appear related to the underlying advanced IPF and associated co-morbidities (**Table 29**; Kreuter et al. 2016). Only 3 AEs leading to death occurred in more than a single case. All of them (4 events of cardiac arrest, 3 events of dyspnea, and 3 events of cardio-respiratory arrest) were assessed as not-related to pirfenidone by the investigator.

Table 29 AEs Leading to Death Observed in Pre-Treated Patients with Advanced IPF, not Non-Advanced IPF

AEs leading to death	Pre-Treated Patients (N=414)			
	Non-Advanced IPF (N=225)		Advanced IPF (N=189)	
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)
Cardiac Arrest	0	NA	4	1.22
Dyspnoea	0	NA	3	0.91
Cardio-Respiratory Arrest	0	NA	2	0.61
Cardiogenic Shock	0	NA	1	0.30
Pneumonia Bacterial	0	NA	1	0.30
Sepsis	0	NA	1	0.30
Anoxic Encephalopathy	0	NA	1	0.30
Cerebral Haemorrhage	0	NA	1	0.30
Seizure	0	NA	1	0.30
Sudden Cardiac Death	0	NA	1	0.30
Air Embolism	0	NA	1	0.30
Pneumothorax	0	NA	1	0.30
Septic Shock	0	N/A	1	0.30

AE=adverse event; IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; NA=not applicable; PT=preferred term; PY=patient years.

Source:

SERIOUS ADVERSE EVENTS

Serious Adverse Events in Treatment-Naïve Patients

When analyzing STEAEs by SOC, there were 3 SOCs that showed a higher rate of serious TEAEs (defined as a difference >5/100 PY) in treatment-naïve patients with advanced IPF as compared to treatment-naïve patients with non-advanced IPF: respiratory, thoracic and mediastinal disorders; cardiac disorders; infections and infestations. The exposure-adjusted rate of STEAEs was similar for all remaining SOCs across treatment-naïve patients with advanced IPF and treatment-naïve patients with non-advanced IPF.

Figure 5 Distribution of Serious TEAEs by SOC in Treatment-Naïve Patients with Advanced or Non-Advanced IPF

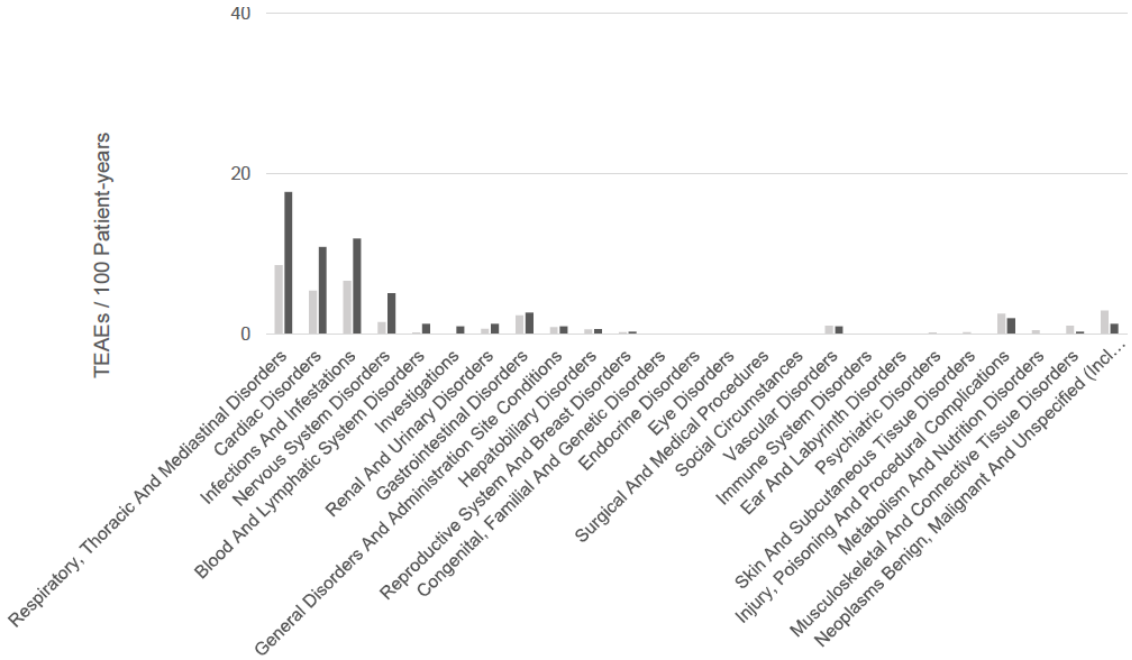


Table 30 Exposure adjusted rates for Related Serious Adverse Events occurring in patients treated with Pirfenidone in studies PIPF-004, PIPF-006, PIPF-012, PIPF-016 and MA29957

	Treatment-Naïve Patients (1) (N=894)				Pre-Treated Patients (2) (N=414)			
	Non-advanced (3) n = 717		Advanced (4) n = 177		Non-advanced (3) n = 225		Advanced (4) n = 189	
System Organ Class Preferred Term	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)
Total number of AEs	46	3.58	24	8.17	27	3.28	7	2.13
INFECTIONS AND INFESTATIONS								
Total number of AEs	9	0.70	2	0.68	4	0.49	1	0.30
PNEUMONIA	4	0.31	1	0.34	2	0.24		
DIVERTICULITIS	2	0.16						
LOBAR PNEUMONIA	2	0.16						
GASTROENTERITIS	1	0.08					1	0.30
BRONCHITIS			1	0.34				
PNEUMOCYSTIS JIROVECI PNEUMONIA					1	0.12		
PNEUMONIA PNEUMOCOCCAL					1	0.12		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS								
Total number of AEs	9	0.70	9	3.07	6	0.73	1	0.30
IDIOPATHIC PULMONARY FIBROSIS	3	0.23	5	1.70	2	0.24		
ACUTE RESPIRATORY FAILURE	2	0.16	1	0.34	1	0.12		
PULMONARY EMBOLISM	2	0.16			1	0.12		
PLEURAL EFFUSION	1	0.08						
RESPIRATORY FAILURE	1	0.08	1	0.34	1	0.12		
HAEMOPTYSIS			1	0.34				
HYPOXIA			1	0.34				
PNEUMONIA ASPIRATION					1	0.12		
PNEUMOTHORAX							1	0.30
CARDIAC DISORDERS								
Total number of AEs	5	0.39	1	0.34	1	0.12		

	Treatment-Naïve Patients (1) (N=894)				Pre-Treated Patients (2) (N=414)			
	Non-advanced (3) n = 717		Advanced (4) n = 177		Non-advanced (3) n = 225		Advanced (4) n = 189	
System Organ Class Preferred Term	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)
ANGINA PECTORIS	2	0.16						
ARRHYTHMIA	1	0.08						
CORONARY ARTERY DISEASE	1	0.08						
SICK SINUS SYNDROME	1	0.08						
ATRIAL FIBRILLATION			1	0.34				
MYOCARDIAL INFARCTION					1	0.12		
GASTROINTESTINAL DISORDERS								
Total number of AEs	5	0.39	3	1.02	6	0.73		
DIVERTICULAR PERFORATION	2	0.16						
COLITIS	1	0.08						
COLONIC POLYP	1	0.08						
PANCREATITIS ACUTE	1	0.08						
CONSTIPATION					1	0.12		
DIVERTICULUM					1	0.12		
GASTROINTESTINAL HAEMORRHAGE			1	0.34				
GASTROOESOPHAGEAL REFLUX DISEASE			1	0.34				
HAEMORRHOIDS					1	0.12		
NAUSEA			1	0.34				
PANCREATITIS					1	0.12		
RECTAL POLYP					1	0.12		
VOMITING					1	0.12		
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)								
Total number of AEs	4	0.31			1	0.12	1	0.30

System Organ Class Preferred Term	Treatment-Naïve Patients (1) (N=894)				Pre-Treated Patients (2) (N=414)			
	Non-advanced (3) n = 717		Advanced (4) n = 177		Non-advanced (3) n = 225		Advanced (4) n = 189	
	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)
BLADDER CANCER	1	0.08						
COLON CANCER STAGE II	1	0.08						
OVARIAN CANCER RECURRENT	1	0.08						
SMALL CELL LUNG CANCER STAGE UNSPECIFIED	1	0.08						
LUNG NEOPLASM MALIGNANT							1	0.30
PROSTATE CANCER METASTATIC					1	0.12		
HEPATOBILIARY DISORDERS								
Total number of AEs	3	0.23	2	0.68				
BILIARY DYSKINESIA	1	0.08						
CHOLECYSTITIS	1	0.08						
HEPATITIS	1	0.08						
CHOLECYSTITIS ACUTE			1	0.34				
CHOLELITHIASIS			1	0.34				
SKIN AND SUBCUTANEOUS TISSUE DISORDERS								
Total number of AEs	3	0.23						
PHOTOSENSITIVITY REACTION	2	0.16						
RASH	1	0.08						
NERVOUS SYSTEM DISORDERS								
Total number of AEs	2	0.16	2	0.68	6	0.73	2	0.61
CEREBROVASCULAR ACCIDENT	1	0.08			3	0.36		
CHRONIC INFLAMMATORY DEMYELINATING POLYRADICULONEUROPATHY	1	0.08						
CENTRAL NERVOUS SYSTEM LESION					1	0.12		

System Organ Class Preferred Term	Treatment-Naïve Patients (1) (N=894)				Pre-Treated Patients (2) (N=414)			
	Non-advanced (3) n = 717		Advanced (4) n = 177		Non-advanced (3) n = 225		Advanced (4) n = 189	
	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)
CEREBRAL ARTERY OCCLUSION			1	0.34				
CONVULSION							1	0.30
DEMYELINATING POLYNEUROPATHY					1	0.12		
SEIZURE							1	0.30
SYNCOPE			1	0.34	1	0.12		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
Total number of AEs	1	0.08	1	0.34				
CHEST PAIN	1	0.08	1	0.34				
INJURY, POISONING AND PROCEDURAL COMPLICATIONS								
Total number of AEs	1	0.08						
INCISIONAL HERNIA, OBSTRUCTIVE	1	0.08						
INVESTIGATIONS								
Total number of AEs	1	0.08	3	1.02				
LIVER FUNCTION TEST ABNORMAL	1	0.08						
ALANINE AMINOTRANSFERASE INCREASED			1	0.34				
ASPARTATE AMINOTRANSFERASE INCREASED			1	0.34				
WEIGHT DECREASED			1	0.34				
METABOLISM AND NUTRITION DISORDERS								
Total number of AEs	1	0.08			1	0.12	2	0.61
HYPOVOLAEMIA	1	0.08						
CACHEXIA					1	0.12	1	0.30
DEHYDRATION							1	0.30
PSYCHIATRIC DISORDERS								

System Organ Class Preferred Term	Treatment-Naïve Patients (1) (N=894)				Pre-Treated Patients (2) (N=414)			
	Non-advanced (3) n = 717		Advanced (4) n = 177		Non-advanced (3) n = 225		Advanced (4) n = 189	
	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)	Event count	Rate (incidence rate/100 patient years)
Total number of AEs	1	0.08						
SUICIDAL IDEATION	1	0.08						
RENAL AND URINARY DISORDERS								
Total number of AEs	1	0.08						
RENAL FAILURE ACUTE	1	0.08						
BLOOD AND LYMPHATIC SYSTEM DISORDERS								
Total number of AEs			1	0.34				
COAGULOPATHY			1	0.34				
EAR AND LABYRINTH DISORDERS								
Total number of AEs					1	0.12		
VERTIGO					1	0.12		
ENDOCRINE DISORDERS								
Total number of AEs					1	0.12		
ADRENAL MASS					1	0.12		

Serious TEAEs in Treatment-Naïve Patients within the SOC: Respiratory, Thoracic, and Mediastinal Disorders

The higher rate of STEAEs observed in treatment-naïve patients with advanced IPF for the SOC respiratory, thoracic and mediastinal disorders was primarily driven by the PTs IPF and hypoxia.

This is an expected finding considering the higher severity of advanced IPF.

Table 31 Exposure-Adjusted STEAE Rate within the SOC: Respiratory, Thoracic, and Mediastinal Disorders

STEAE	Treatment-Naïve Patients (N=894)				
	Non-Advanced IPF (N=717)		Advanced IPF (N=177)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	63	4.90	36	12.26	7.36
Hypoxia	2	0.16	5	1.70	1.54

IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; PT=preferred

Serious TEAEs in Treatment-Naïve Patients within the SOC: Cardiac Disorders

The higher rate of STEAEs in the SOC cardiac disorders observed in treatment-naïve patients with advanced IPF is mainly driven by the PTs atrial fibrillation, acute myocardial infarction, and angina pectoris.

Cardiovascular disorders were the most frequent seen in a study with 272 patients investigating the impact of comorbidities in IPF.

Table 32 Exposure-Adjusted STEAE Rate within the SOC: Cardiac Disorders

STEAE	Treatment-Naïve Patients (N=894)				
	Non-Advanced IPF (N=717)		Advanced IPF (N=177)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Atrial Fibrillation	14	1.09	7	2.38	1.29
Acute Myocardial Infarction	3	0.23	4	1.36	1.13
Angina Pectoris	4	0.31	4	1.36	1.05

Serious TEAEs in Treatment-Naïve Patients within the SOC: Infections and Infestations

The higher rate of STEAEs observed in naïve advanced IPF patients observed for the SOC infections and infestations is mainly due to PTs representing respiratory tract infections (i.e., pneumonia, bronchitis) and appears related to the higher severity of the underlying disease.

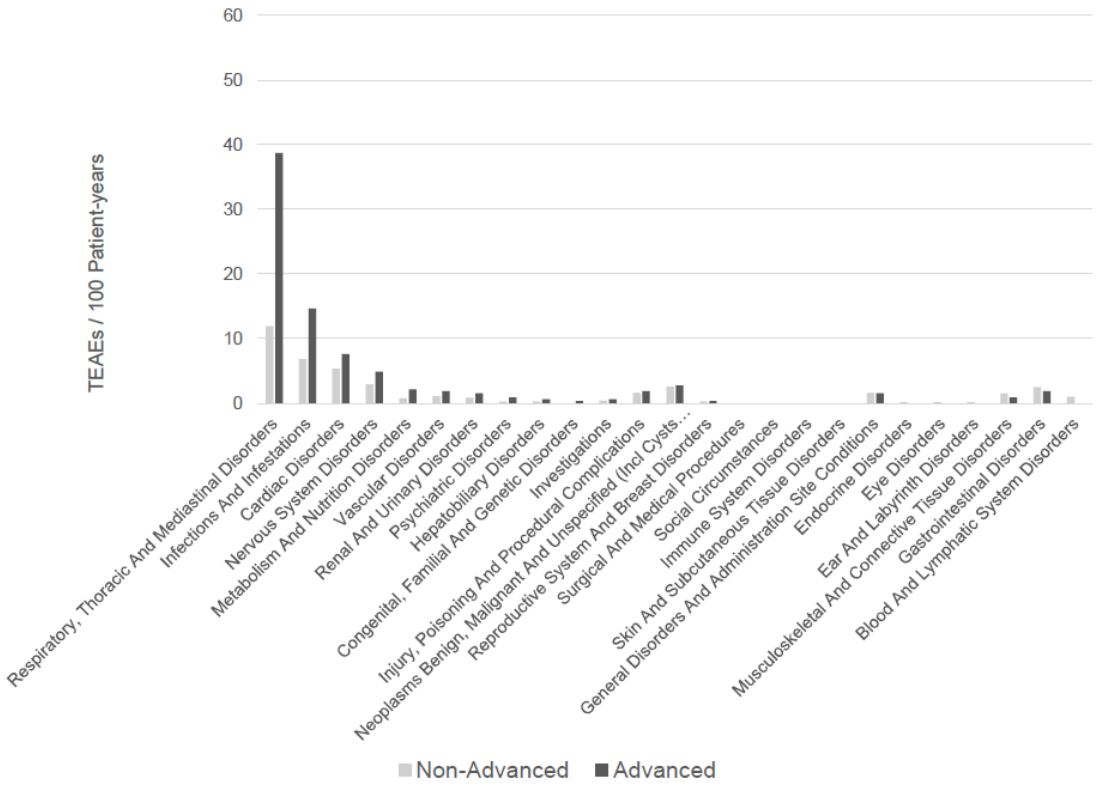
Table 33 Exposure-Adjusted STEAE Rate within the SOC: Infections and Infestations

STEAE	Treatment-Naïve Patients (N=894)				
	Non-Advanced IPF (N=717)		Advanced IPF (N=177)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Pneumonia	37	2.88	18	6.13	3.25
Bronchitis	13	1.01	8	2.72	1.71

Serious Adverse Events in Pre-Treated Patients

When analyzing STEAEs by SOC, there were 2 SOCs that showed a higher rate of serious TEAEs (defined as a difference >5/100 PY) in pre-treated patients with advanced IPF as compared to pre-treated patients with non-advanced IPF: respiratory, thoracic and mediastinal disorders; and infections and infestations. The exposure-adjusted rate of serious TEAEs was similar for all remaining SOCs across pre-treated patients with advanced IPF and pre-treated patients with non-advanced IPF.

Figure 6 Distribution of STEAEs by SOC in Pre-Treated Patients with Advanced or Non-Advanced IPF



Serious TEAEs in Pre-Treated Patients within the SOC: Respiratory, Thoracic, and Mediastinal Disorders

The higher rate of STEAEs observed in pre-treated patients with advanced IPF for the SOC respiratory, thoracic and mediastinal disorders was primarily driven by the PT IPF, along with other events associated with an aggravation of the patient's underlying condition.

Table 34 Exposure-Adjusted STEAE Rate within the SOC: Respiratory, Thoracic, and Mediastinal

STEAE	Pre-Treated Patients (N=414)				
	Non-Advanced IPF (N=225)		Advanced IPF (N=189)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	53	6.44	79	24.08	17.64
Respiratory Failure	5	0.61	10	3.05	2.44
Dyspnoea	5	0.61	9	2.74	2.13
Acute Respiratory Failure	3	0.36	5	1.52	1.16

IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; PT=preferred

Serious TEAEs in Pre-Treated Patients within the SOC: Infections and Infestations

The higher rate of STEAEs observed in advanced, pre-treated patients for the SOC infections and infestations is mainly resultant of PT representing respiratory tract infections (i.e., pneumonia and

bronchitis) which might be attributed to the higher severity of the underlying disease (Odashima et al. 2020; Mostafaei et al. 2021).

Table 35 Exposure-Adjusted STEAE Rate within the SOC: Infections and Infestations

STEAE	Pre-Treated Patients (N=414)				
	Non-Advanced IPF (N=225)		Advanced IPF (N=189)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Pneumonia	20	2.43	16	4.88	2.45
Bronchitis	9	1.09	8	2.44	1.35

IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; PT=preferred term; PY=patient years; SOC=system organ class; STEAE=serious treatment emergent adverse event.

SEVERE TEAES

Severe TEAEs with Highest Exposure-Adjusted Rate in Treatment-Naïve Patients from the Pooled Population with IPF

Severe TEAEs (i.e., TEAEs of Grade 3 and higher) with an exposure-adjusted rate >1/100 PYs higher in treatment-naïve patients with advanced IPF than in treatment-naïve patients with non-advanced IPF are shown in **Table 36** below. All these events appear directly or indirectly related to the severity of the underlying advanced IPF.

An example of AE indirectly related to the severity of the underlying disease is syncope, which is a symptom of several disorders likely to occur more frequently in patients with advanced IPF, e.g. PH and cardiac disorders (Galiè et al. 2015). Of the 10 severe syncope events, 9 were assessed as not-related, and 1 as related by the Investigator.

Table 36 Exposure-Adjusted Severe TEAE Rate in Treatment-Naïve Patients with IPF

Severe TEAE	Treatment-Naïve Patients (N=894)				
	Non-Advanced IPF (N=717)		Advanced IPF (N=177)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	62	4.83	37	12.6	7.77
Hypoxia	3	0.23	12	4.09	3.86
Syncope	3	0.23	10	3.41	3.18
Pneumonia	26	2.02	15	5.11	3.09
Bronchitis	10	0.78	10	3.41	2.63
Atrial Fibrillation	6	0.47	7	2.38	1.55
Dyspnoea	15	1.17	8	2.72	1.55
Acute Myocardial Infarction	2	0.16	4	1.36	1.2

IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; PT=preferred term; PY=patient years; TEAE=treatment-emergent adverse event.

Severe TEAEs with Higher Exposure-Adjusted Rate in Pre-Treated Patients with advanced IPF

Severe TEAEs with an exposure-adjusted rate >1/100 PYs higher in pre-treated patients with advanced IPF than in pre-treated patients with non-advanced IPF are shown in **Table 37** below. The majority of these TEAEs appear related to the severity of the underlying advanced IPF. The difference in the rate of pulmonary embolism between advanced and non-advanced patients is minimal. All 5 events of pulmonary embolism were assessed as not related by the Investigator and no fatal outcomes were reported.

Table 37 Exposure-Adjusted Severe TEAE Rate in Pre-Treated Patients with IPF

Severe TEAE	Pre-Treated Patients (N=414)				
	Non-Advanced IPF (N=225)		Advanced IPF (N=189)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	42	5.1	72	21.95	16.85
Dyspnoea	16	1.94	24	7.32	5.38
Pneumonia	11	1.334	14	4.27	2.93
Respiratory Failure	5	0.61	9	2.74	2.13
Fatigue	3	0.36	8	2.44	2.08
Pulmonary Hypertension	6	0.73	7	2.13	1.4
Cardiac Arrest	0	N/A	4	1.22	1.22
Acute Respiratory Failure	1	0.12	4	1.22	1.1
Pulmonary Embolism	4	0.49	5	1.52	1.03

TEAEs That Occurred Only in Patients with Advanced IPF Regardless of Prior Pirfenidone Treatment (≥3 events)

None of the TEAEs occurring only in patients with advanced IPF were serious events. The 8 events of orchitis all occurred in the same patient, none were serious events, and all were assessed as not related to

pirfenidone by the Investigator. The TEAE N-terminal prohormone brain natriuretic peptide increased may be explained by the higher severity of the underlying advanced IPF.

Rash is a well-known ADR associated with pirfenidone; the 3 events of rash papulosquamous reported in patients with advanced IPF are a specific subtype of rash and appear to be a random finding, as rash follicular and rash pustular were reported only in patients with non-advanced IPF.

Table 38 TEAEs that Occurred in Patients with Advanced IPF Regardless of Prior Pirfenidone Treatment (≥3 events)

Preferred Term	Treatment-Advanced IPF		Pre-treated Advanced IPF	
	n	rate (incidence rate/100PY	n	rate (incidence rate/100PY
Orchitis	0	N/A	8	2.44
Rash Papulosquamous	3	1.02	0	N/A
N-terminal Prohormone Brain Natriuretic Peptide Increased	0	N/A	3	0.91

TEAES OF SPECIAL INTEREST

TEAEs of Special Interest in Treatment-Naïve Patients

In the pirfenidone treatment-naïve patients, the exposure-adjusted event rates of TEAEs, serious TEAEs, severe TEAEs, TEAEs leading to death and TEAEs leading to treatment discontinuation was higher in patients with advanced IPF than in patients with non-advanced IPF.

The rates of gastrointestinal (GI) disorder, photosensitivity, rash, dizziness, and fatigue are similar across advanced and non-advanced patients.

The rate of weight decreased was higher in advanced IPF patients than in non-advanced IPF patients. Weight decrease is a known ADR of pirfenidone, and could occur more frequently in advanced IPF patients due to additional factors such as prolonged physical inactivity (which leads to loss of muscle mass), or to loss of appetite due to worsening of the underlying disease or depression (Britze et. al. 2017; Torrisi et al. 2018).

TEAEs of Special Interest in Pre-Treated Patients

The exposure-adjusted event rate of serious TEAEs, severe TEAEs, TEAEs leading to death and TEAEs leading to treatment discontinuation is higher in pre-treated patients with advanced IPF compared to non-advanced patients. These differences are driven by SOCs and are discussed in the previous sections.

The rates of GI disorder, photosensitivity, rash, dizziness, weight decreased and fatigue are similar in patients with advanced and non-advanced IPF.

*Table 39 Summary of Safety Profile **of any** (Exposure) Adjusted of adverse event of specific interest in Patients Treated with Pirfenidone in Studies PIPF- 004, PIPF-006, PIPF-012, PIPF-016, and MA29957 – **Treatment naïve population***

	Non-Advanced		**Advanced**		
	Event count	**Rate incidence**	**Event count**	**Rate incidence**	**Rate difference**
GI disorder	1921	149.56	403	137.26	-12.30
Photosensitivity	191	14.87	42	14.30	-0.57
Rash	462	35.97	95	32.36	-0.61

Dizziness	218	16.97	34	11.58	-5.39
Weight decreased	78	6.07	35	11.92	5,85
Fatigue	243	18.92	52	17.71	-1.21

*Table 40 Summary of Safety Profile **of any** (Exposure) Adjusted of adverse event of specific interest in Patients Treated with Pirfenidone in Studies PIPF- 004, PIPF-006, PIPF-012, PIPF-016, and MA29957 –**Pre-treated population***

	Non-Advanced N=		**Advanced** N=		
	Event count	**Rate incidence**	**Event count**	**Rate incidence**	**Rate difference**
GI disorder	723	87.86	281	85.66	-2.20
Photosensitivity	55	6.68	21	6.40	-0.28
Rash	124	15.07	30	9.14	-5.93
Dizziness	71	8.63	20	6.10	-2.53
Weight decreased	49	5.95	16	4.88	-1.07
Fatigue	78	9.48	32	9.75	0.27

Laboratory findings

The applicant clarified that an analysis of laboratory data were not provided because all laboratory abnormalities considered clinically significant by the investigators were collected as adverse events (AEs) and presented with the rest of the safety assessment in the submitted Summary of Clinical Safety. In addition, many years of post-marketing signal detection activities has not identified any evidence suggesting that patients with advanced IPF are more prone to laboratory abnormalities than patients with non-advanced IPF.

Safety in special populations

No new data was submitted. This was considered acceptable by the CHMP.

Safety related to drug-drug interactions and other interactions

No new data was submitted. This was considered acceptable by the CHMP.

Discontinuation due to adverse events

Table 41 Frequency of Treatment Emergent Adverse Events leading to treatment discontinuation occurring in patients treated with Pirfenidone in studies PIPF-004, PIPF-006, PIPF-012, PIPF-016 and MA29957

System Organ Class Preferred Term	Treatment-Naïve Patients (1) (N=894) Non-advanced (3) n = 717 n (%)	 Advanced (4) n = 177 n (%)	Pre-Treated Patients (2) (N=414) Non-advanced (3) n = 225 n (%)	 Advanced (4) n = 189 n (%)
Total Number Of TEAEs	175	71	103	88
Patients With At Least One TEAE	173 (24.1)	70 (39.5)	103 (45.8)	87 (46.0)

TEAEs leading to Withdrawal of Treatment in Treatment-Naïve Patients

Idiopathic pulmonary fibrosis and pneumonia are the only TEAEs leading to discontinuation showing a rate difference higher than 1 TEAE/100 PYs in patients with advanced IPF compared to patients with non-advanced IPF. Both events are expressions of the higher severity of the underlying advanced IPF.

Table 42 TEAEs Leading to Withdrawal of Treatment in Treatment-Naïve Patients

TEAEs leading to discontinuation	Treatment-Naïve Patients (N=894)				
	Non-Advanced IPF (N=717)		Advanced IPF (N=177)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	35	2.72	19	6.47	3.75
Pneumonia	1	0.08	5	1.7	1.62

IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; PT=preferred term; PY=patient years; TEAE=treatment-emergent adverse event.

Source: SP-IPF_Filing_Tab_2_2_9.

TEAEs leading to Withdrawal of Treatment in Pre-Treated Patients

Idiopathic Pulmonary Fibrosis is the only TEAE leading to discontinuation which shows a rate difference higher than 1 TEAE/100 PYs in pre-treated advanced IPF patients. This is clearly related to the higher severity of the advanced IPF.

Table 43 TEAEs Leading to Withdrawal of Treatment in Pre-Treated Patients

TEAEs leading to discontinuation	Pre-Treated Patients (N=414)				
	Non-Advanced IPF (N=225)		Advanced IPF (N=189)		Rate Differences
	n	rate (incidence rate/100PY)	n	rate (incidence rate/100PY)	
Idiopathic Pulmonary Fibrosis	35	4.25	33	10.06	5.81

IPF=idiopathic pulmonary fibrosis; N=number of patients; n=number of events; PT=preferred

Post marketing experience

Esbriet capsules were first granted marketing approval in the EU on 28 February 2011, which marks the IBD. Esbriet capsules were approved in the United States (U.S.) on 15 October 2014 and Esbriet film-coated tablets were approved on 11 January 2017. Esbriet® film-coated tablets were also approved in the EU (24 April 2017), Canada (2 June 2017), Australia (23 October 2017), and Switzerland (8 November 2017). As of the DLP of this PBRER (27 February 2021), Esbriet® capsules have been approved in 70 countries worldwide and Esbriet film-coated tablets have been approved in more than 50 countries worldwide.

The cumulative worldwide exposure to pirfenidone is estimated at 254,983 patient-equivalents and 175,311 patient-years.

The last safety review for Esbreit was performed the 14th PSUR (data lock point 27 February 2021). In this PSUR the risk-benefit balance of medicinal products containing pirfenidone was considered to remain unchanged.

Study WB29908, PIPF-025

The trial title: post-authorisation safety study of Esbriet (pirfenidone): a prospective observational registry to evaluate long-term safety in a real-world setting (PASSPORT)

Study design

This product registry was a multicenter, long-term, prospective, observational study evaluating the long-term safety in patients who were prescribed Esbriet. Patients received Esbriet at the discretion of their physicians, and were followed through the registry for 2 years after they began treatment with Esbriet under real-world conditions.

This registry complied with the requirement of a PASS, and as a post-authorization commitment, was approved by the CHMP.

This registry was conducted in accordance with the protocol and all applicable laws and regulations, including Good Pharmacoepidemiology Practices, the ethical practices having their origination in the

Declaration of Helsinki, and applicable national guidelines (ISPE 2007, Declaration of Helsinki 2008). This study was conducted and closely monitored by the MAH, or designee, with oversight by a project-specific SAB.

Setting

The registry's planned enrollment was 1000 Esbriet-treated patients from approximately 100 pulmonary clinics throughout selected EU Member States. Enrollment was completed with a total of 1009 patients who received treatment with Esbriet.

Treating physicians collected pre-specified data, specifically serious and non-serious adverse drug reactions of special interest (ADRSI) or of relevance to the investigators, at baseline and every 3 months thereafter for the duration of the patients' participation in study. Each patient was followed until discontinuation of the study or up to a maximum of 2 years. The MAH also closely monitored the retention of patients and undertook all reasonable efforts to minimize loss to follow-up for the entire duration of the registry.

Patients

In the European Union, Esbriet is indicated for the treatment of mild-to-moderate IPF in adults. Consequently, the protocol did not encourage the use of Esbriet for any other condition or for use in pediatric patients. However, if a physician in collaboration with the patient and/or legal representative made an independent clinical decision to prescribe Esbriet outside the terms of the SmPC and the patient met the other protocol inclusion/exclusion criteria, then the patient was permitted to be included in the registry.

Variables

The primary variables in this study were safety variables. Only adverse drug reactions (ADRs), both serious and non-serious, were collected in this study to enable evaluation of the long-term safety of Esbriet. An ADR was defined as a noxious and unintended response to a medicinal product related to any dose in which a causal relationship between the medicinal product and the adverse event (AE) was at least a reasonable possibility.

Important potential and identified risks were monitored as adverse drug reactions of special interest (ADRSIs) while on this study. 'Other ADRs' were also collected at the discretion of the principle investigator. Corresponding serious ADRs of special interest (SADRSIs) and 'other SADRs' were also monitored

The important identified risks were:

1. Photosensitivity reactions and skin rashes
2. Abnormal liver function tests
3. Dizziness
4. Weight loss
5. Gastrointestinal symptoms
6. Fatigue
7. Angioedema

The important potential risks were:

8. Falls
9. Drug interactions (including smoking, Ciprofloxacin, Warfarin)
10. Increased platelet counts
11. Specific cardiac events (including supraventricular tachyarrhythmia, atrioventricular block and sick sinus syndrome, ventricular arrhythmia, bundle branch block, and aortic or pulmonic valvular incompetence)
12. Blood dyscrasias (specifically agranulocytosis, leukopenia, and neutropenia)
13. Severe skin reactions

PASSPORT pre-specified 12 patient subgroups with missing safety information, based on patient information obtained at the time of screening. One of 12 pre-specified patient subgroups was the use in patients with advanced stages of IPF (baseline FVC <50%).

Results in patients with patients with advanced stages of IPF (baseline FVC <50%):

144 patients were in advanced stages of IPF (baseline FVC <50%).

ADRSIs: 91 patients had 213 events (serious and non-serious). Most of these events were in the special interest categories of GI symptoms, photosensitivity reactions and skin rashes, fatigue and weight loss.

Other ADRs: 55 patients had 82 events, predominantly non-serious events already listed in the SmPC. These events included decreased appetite and respiratory events associated with the underlying disease (dyspnoea and cough); 1 patient each had pulmonary embolism, IPF, productive cough and respiratory failure.

SADRSI: 9 patients had 13 events; one patient had a report of blood dyscrasias (mentioned previously) and the remaining events were predominantly gastrointestinal symptoms.

SADR: none

Other SADRs: gastric ulcer, pneumonia, decreased appetite, IPF, pulmonary embolism, and respiratory failure

Death: 1 patient died from pneumonia (already mentioned).

The MAH concluded that no new signals were observed for patients with advanced stages of IPF and the observed events in this subgroup are consistent with the known profile of Esbriet or related to the underlying disease in the target elderly population with IPF.

2.5.1. Discussion on clinical safety

The safety data for pirfenidone when used in patients with advanced IPF come from studies PIPF-004, PIPF-006, PIPF-016, MA29957, PIPF-012 and PIPF-025. PIPF-004, PIPF-006 and PIPF-016 were double-blind, placebo-controlled, PIPF-012 was an open label extension study, PIPF-025 was a post-authorization safety study performed in a real-world setting. Finally, MA29957 study was performed in patients with the risk of pulmonary hypertension.

The safety data from 5 studies were pooled.

The data from study MA29957, in patients with advanced IPF treated with pirfenidone, were integrated with data from three double-blind, placebo-controlled studies of pirfenidone in IPF (PIPF-004, PIPF-006, and PIPF-016), and with long-term, follow-up Study PIPF-012.The safety profile of pirfenidone when used in patients with advanced IPF disease was compared to patients with non-advanced IPF disease. The safety data from 5 pooled studies were presented separately for pirfenidone treatment-naïve and pre-treated patients.

The studies in the pooled analysis were conducted over a period of more than 10 years, and were conducted for different periods of follow-up and duration. As such, direct comparison of frequency of AEs between studies was impossible therefore the exposure-adjusted data have been used to account for the differences in study duration and follow-up.

The Applicant provided the safety set for the treatment naïve and pre-treated population separately, based on the knowledge that gastro-intestinal events are more frequently observed in early stage of treatment, possibly leading to early drop out.

Pooling strategy

The pooling of the studies PIPF004, PIPF006 and PIPF016 is justified as they were conducted in a comparable time frame and used the same in and exclusion criteria. These studies primarily included patients with mild to moderate diseases.
Pooling of study MA29957 into this dataset was however considered to be problematic as this study included only pre-treated, advanced patients and it comprises a specific patient group at risk of pulmonary hypertension.

In addition, in study MA29957, adverse events were encoded using MedDRA version 23 instead of MedDRA version 11 in the other studies. The applicant considers that evaluation according these different MedDRA versions will have minimal impact (if any) on relevant outcomes as the safety analyses is analysed at system organ class [SOC] level, followed by an investigation of preferred term [PT] reported with higher frequency in advanced IPF. Although some uncertainties regarding the comparability of the MedDRA versions remain, this explanation is accepted.

Tolerability in the advanced population (advanced IPF patients on pirfenidone as compared to non-advanced IPF patients on pirfenidone-data from studies of PIPF-004, PIPF-006, PIPF-016, MA29957 and PIPF-012)

Duration of exposure

In general, the median duration of treatment was longer for patients with non-advanced IPF as compared to those with advanced IPF. In the treatment-naïve group of patients the median duration of treatment in patients with advanced IPF was 12 months whereas in the pre – treated group of advanced IPF patients the median duration of treatment was 15.3 months (based on the data from 5 pooled studies).

In study PIPF-025 patients were followed through the registry for 2 years after they began treatment with Esbriet under real-world conditions.

Summary of adverse events- exposure adjusted rate incidence.

Generally, the advanced population showed a higher incidence of rated adjusted adverse events (AE., SAE, AE's leading to discontinuation) in the summary of adverse events in both the treatment naïve and pre-treated population. This consideration applies to the summary of any-cause AEs, as well to the summary of the drug-related AEs. These differences between the advanced and non-advanced group are likely related to the severity of the disease rather than a difference in tolerance of pirfenidone as discussed below.

Common adverse events

Treatment-naïve patients

Overall, similar rates of TEAEs per 100 PY were observed in treatment-naïve patients from the pooled population with advanced IPF compared to treatment-naïve patients with non-advanced IPF (816.7 and 868.5 respectively;)

When analyzing TEAEs by SOC, two SOCs showed a higher TEAE rate (defined as ≥10/100 PYs) in advanced patients: respiratory, thoracic and mediastinal disorders; and cardiac disorders.

In relation to SOC respiratory, thoracic and mediastinal disorders the difference between group was driven primary by PT idiopathic pulmonary fibrosis, along with other events (e.g., dyspnea, PH, hypoxia) that are commonly associated with an aggravation of the patient's underlying condition.

In relation to cardiac disorders the following PTs were more frequently reported in patients with advanced IPF: atrial fibrillation and tachycardia. Out of 15 events of atrial fibrillation, 7 events were serious (6 events were assessed as not-related to pirfenidone and 1 event was assessed as related to pirfenidone by the investigator. Although these differences could be related to the severity of the disease the applicant was requested to discuss AEs within the SOC of cardiac disorders by comparing the frequency of these events in patients with advanced IPF receiving pirfenidone to those receiving placebo. The requested discussion was provided and it is discussed below.

Pre-treated patients

Overall, similar AE rates per 100 PY were observed between advanced and non-advanced patients in the pre-treated group (675.2 and 673.1, respectively).

When analyzing TEAEs by SOC, 2 SOCs showed a higher TEAE rate (defined as >10/100 PYs) in advanced patients: respiratory, thoracic and mediastinal disorders; and infections and infestations.

SOC respiratory, thoracic, and mediastinal disorders is primarily driven by the PT IPF along with other events associated with an aggravation of the patient's underlying condition such as dyspnoea, respiratory failure and pulmonary hypertension. In addition, lower respiratory tract infection, bronchitis, upper respiratory tract infection, respiratory tract infection, and pneumonia occurred with the higher rate in patients with advanced IPF in the pre-treated group. The applicant was requested to discuss AEs within the SOC infections and infestations by comparing the frequency of these events in patients with advanced IPF receiving pirfenidone to those receiving placebo and the outcome is discussed below.

For the related TEAEs differences between advanced vs non-advanced patients were seen for treatment-naïve patients in SOC Respiratory, thoracic and mediastinal disorders, driven by IPF, PH and dyspnea, and Soc Metabolism and nutrition disorders, driven by PTs decreased appetite and anorexia.

IPF, PH and dyspnea are typical events for IPF and indeed it can be assumed that they are more related the progression of severity of the disease rather than to the treatment.

Decreased appetite and anorexia are well known ADRs of pirfenidone.

Tolerability in the advanced population (advanced IPF patients on pirfenidone as compared to advanced IPF patients on placebo- data from studies PIPF-004, PIPF-006 and PIPF-016)

As the safety profile of pirfenidone in advanced IPF and non-advanced IPF is being compared, it cannot be fully distinguished whether the observed differences are attributable to the higher severity of the underlying disease (as it is claimed by the applicant) or if there are differences in safety profile of pirfenidone when used in advanced IPF patients.

Theoretically patients with more advanced IPF and therefore with a worse clinical status could be more prone to development of some AEs compared to mild or moderate IPF patients.

Therefore, the applicant was requested to discuss the safety profile of pirfenidone in advanced IPF patients and present an additional analysis by comparing the frequency of AEs in patients with advanced IPF on pirfenidone to those on placebo (**based on the data from studies PIPF-004, PIPF-006 and PIPF-016**). The safety data from MA29957 study were not included in this pooled analysis as characteristics of patients included in this study were different.

The applicant provided the requested analysis:

In six SOCs the TEAE frequency (defined as ≥5) was higher in the pirfenidone arm with advanced patients (≥ 5%) compared to placebo; nervous system disorders; gastrointestinal (GI) disorders; infections and infestations; skin and subcutaneous tissue disorders; cardiac disorders; metabolism and

nutrition disorders. Of these, the SOCs cardiac disorder, metabolism and nutrition disorders were also higher when comparing the non-advanced with advanced population.

When looking on PTs level the events that were higher in the advanced population treated with pirfenidone were already listed as very common or common ADRs in the current Esbriet SmPC

PTs that were higher in the advanced population treated with pirfenidone compared to the advanced population treated with placebo and to the non-advanced population treated with pirfenidone and not listed in the SmPC are pneumonia and bronchitis.

Pneumonia was higher in the advanced patients on pirfenidone compared to those placebo as well as to non-advanced patients. As clarified by the applicant, although the PT pneumonia was higher in the pifenidone arm, the PT lobar pneumonia, pneumonia mycoplasmal and tracheobronchitis was higher in the placebo arm, more or less balancing the difference in the PT pneumonia. The incidence in bronchitis was higher in the prifidone arm, but only one of these reports was serious and deemed related by the investigator. These observations are not considered to be reliable evidence for amending the Product information.

In the SOC nervous system disorders, peripheral neuropathy was higher in the advanced population treated with pirfenidone. When compared to the non-advanced population, in the treatment naïve patient the incidence was higher as well (2.8 % and 0.8%, respectively), but in the pre- treated patients not (0% and 3.1%, respectively). These are only considered to be as a weak signal and therefore no amendments to the product information was considered necessary.

In the SOC cardiac disorders, the higher frequency observed in the pirfenidone arm versus the placebo arm was driven by small differences across several PTs, with bradycardia being the only PT with a difference higher than 3%. None of the three reports of bradycardia was assessed as serious or related to pirfenidone by the investigator. Because the frequency is also higher in the advanced group than in the non-advanced population, there seems a higher risk for cardiac disorders. While a difference compared to non-advanced patients might be explained by a difference in severity of the disease, the difference with placebo could indicate a possible treatment related effect however due to a small number of events no firm conclusion could be made in this regard. No amendments to the product information was considered necessary however as agreed with the applicant AEs within the SOC Cardiac disorders in patients advanced IPF will continue to be monitored via routine pharmacovigilance and the data presented in the in PSURs.

Serious adverse event/deaths/other significant events

Deaths

In studies PIPF-004, PIPF-006, PIPF-012, PIPF-016 and MA29957 80 deaths were reported in the pooled advanced IPF group and 85 deaths were reported in pooled non-advanced IPF group. In general, the Exposure adjusted rate for Adverse Events leading to death was higher in the advanced IPF group (6.47 /100 patient years in Treatment-Naïve Patients and 18.59/100 patient years in Pre-Treated Patients) as compared to the non-advanced IPF group 3.74/100 patient years in Treatment-Naïve Patients and 4.50/100 patient years in Pre-Treated Patients). The difference is particularly high for Pre-Treated Patients.

This finding is not unexpected as pulmonary fibrosis is a progressive disease that steadily worsens over time. The median survival of patients with IPF ranges from 2.5 years to 3.5 years and therefore more fatal TEAEs has been observed in patients with advanced IPF. The most common adverse events leading to death were observed within the SOC of respiratory, thoracic and mediastinal disorders. AEs leading to death with the higher exposure-adjusted rate in the advanced IPF group was IPF and cardiac arrest (seen in pre-treated patients and associated with respiratory failure).

Serious adverse events

- **Advanced IPF patients on pirfenidone as compared to non-advanced IPF patients on pirfenidone (data from studies of PIPF-004, PIPF-006, PIPF-016, MA29957 and PIPF-012)**

SAEs were also reported with the higher rate in patients with advanced IPF as compared to patients with non-advanced IPF (58.92/100 patient years in Treatment-Naïve Patients and 82.91/100 patient years in pre-treated patients in the advanced IPF group as compared to 36.59/100 patient years in treatment-naïve patients and 41.68/100 patient years in Pre-Treated Patients in the non-advanced IPF group).

When analyzing STEAEs by SOC, there were 3 SOCs that showed a higher rate of serious TEAEs (defined as a difference >5/100 PY) in patients with advanced IPF as compared to patients with non-advanced IPF: respiratory, thoracic and mediastinal disorders; cardiac disorders; infections and infestations.

The higher rate of STEAEs observed with advanced IPF for the SOC respiratory, thoracic and mediastinal disorders was primarily driven by IPF and hypoxia (for treatment-naïve patients) and IPF, Respiratory Failure, Dyspnoea and Acute Respiratory Failure (for pre-treated patients).

- **Advanced IPF patients on pirfenidone as compared to advanced IPF patients on placebo- pooled safety data from studies PIPF-004, PIPF-006 and PIPF-016**

One SOC, cardiac disorders, showed a frequency of serious TEAEs higher than 3% in the pirfenidone arm, however due to small number of events no firm conclusion could be made. The PTs within the SOC Cardiac disorders in patients with advanced IPF will be monitored by the applicant as disused above**.**

Severe adverse events

- **Advanced IPF patients on pirfenidone as compared to non-advanced IPF patients on pirfenidone**

The exposure-adjusted rate of severe TEAEs such as idiopathic pulmonary fibrosis, dyspnoea, pneumonia, respiratory failure, fatigue, pulmonary hypertension, cardiac arrest, acute respiratory failure, pulmonary embolism hypoxia, syncope, bronchitis, atrial fibrillation and acute myocardial infarction was higher in advanced IPF patients as compared to non-advanced IPF patients.

It is claimed that these TEAEs are indirectly or directly related to the severity of the underlying disease, which can be agreed.

For related severe TEAEs, PTs with a difference of >1/100PY between advanced vs non-advanced patients were seen for IPF (treatment-naïve patients) and fatigue (pre-treated patients).

- **Advanced IPF patients on pirfenidone as compared to advanced IPF patients on placebo- pooled safety data from studies PIPF-004, PIPF-006 and PIPF-016)**

In the comparison between advanced patients receiving pirfenidone as compared to those on placebo the cardiac disorders and injury, poisoning and procedural complications SOCs showed a frequency of severe TEAEs 3% or higher in the pirfenidone arm than in the placebo arm. Again as discussed above for the severe TEAEs, the imbalance between pirfenidone and placebo in this SOC is driven by small differences across several PTs, the main one being the PT Angina pectoris. In the SOC injury, poisoning and procedural complications, the imbalance between pirfenidone and placebo is driven by small differences across several PTs, with none showing a difference higher than 2%. The reported PTs are animal bite, fall, rib fracture, and stent occlusion, and no consistent pattern is observed.

TEAEs of Special Interest

The rates of TEAEs of special interest such as gastrointestinal (GI) disorder, photosensitivity, rash, dizziness, and fatigue were similar across advanced and non-advanced patients. The rate of weight decreased was higher in advanced IPF patients than in non-advanced IPF patients. In the comparison between advanced patients receiving pirfenidone as compared to those on placebo the frequencies of GI disorders, photosensitivity, rash, weight decreased, and fatigue are higher in the pirfenidone arm versus placebo and they are listed in the current Esbriet SmPC.

Although initially not defined as AESI, extra attention lays on the SOC of hepatobiliary disorders because of the known effects of pirfenidone on the liver. Exposure-adjusted rates of TEAEs within the SOC of hepatobiliary disorders are comparable between advanced and non-advanced patients, as well as between treatment-naïve and pre-treated patients. Underlying PTs are slightly different between the four groups, with cholelithiasis having the highest incidence in all groups. The minor differences between the advanced and non-advanced population are considered not clinically relevant.

Safety in patients with advanced IPF and risk of pulmonary hypertension (study MAA29957).

Patients with IPF and PH have been shown to have markedly higher 1-year mortality rates than IPF patients without PH. In Study MA29957, 18/89 (20.2%) patients in the pirfenidone group had died from all causes. This was higher than the rate from the pooled Phase III studies (4.4%), indicating that the patients in study MAA29957 may differ from the other advanced patients. Whether patients with use advanced IPF and risk for group 3 PH have a different, possibly more severe/serious safety profile than patients with advanced IPF without PH was explored by the applicant. In the SOCs vascular disorders and respiratory, thoracic and mediastinal disorders, infections and infestations and cardiac disorders, higher exposure-adjusted rates in severe or serious TEAEs or TEAEs leading to death were consistently observed in study MA29957 compared to study PIPF-012. However, these differences can be mostly explained by the difference in severity of the underlying disease, i.e., a higher disease burden in patients with advanced IPF at risk of grade 3 PH.

Laboratory findings

Originally no discussion was provided by the applicant in relation to the frequency of laboratory findings in patients with advanced IPF as compared to patients with non-advanced IPF. The applicant clarified that an analysis of laboratory data were not provided because all laboratory abnormalities considered clinically significant by the investigators were collected as adverse events (AEs) and presented with the rest of the safety assessment in the submitted Summary of Clinical Safety. In addition, many years of post-marketing signal detection activities has not identified any evidence suggesting that patients with advanced IPF are more prone to laboratory abnormalities than patients with non-advanced IPF.

Nevertheless, the requested analysis was performed. Six parameters showed a frequency of lab shifts ≥5% in the pirfenidone arm compared to the placebo arm. Of the six parameters showing differences in grade shifts between the pirfenidone and placebo arms, two (alanine amino transferase and Gamma-glutamyl-transferase increases) are listed in the SmPC for Esbriet, one (protein) is likely due to the very small dataset and three (lymphocytes, platelets, and hypophosphatemia) are not confirmed by the box plot analysis and the cumulative experience.

Post marketing data

Esbriet capsules were first granted marketing approval in the EU on 28 February 2011, which marks the IBD. Esbriet capsules were approved in the United States (U.S.) on 15 October 2014 and Esbriet film-coated tablets were approved on 11 January 2017. Esbriet film-coated tablets were also approved

in the EU (24 April 2017), Canada (2 June 2017), Australia (23 October 2017), and Switzerland (8 November 2017). As of the DLP of this PBRER (27 February 2021), Esbriet capsules have been approved in 70 countries worldwide and Esbriet film-coated tablets have been approved in more than 50 countries worldwide.

The cumulative worldwide exposure to pirfenidone is estimated at 254,983 patient-equivalents and 175,311 patient-years.

The last safety review for Esbriet was performed the 14th PSUR (data lock point 27 February 2021).

The safety data on the use of the product in advanced stages of IPF also come from Study WB29908, PIPF-025. Study WB29908 was a multicenter, long-term, prospective, observational study evaluating the long-term safety in patients who were prescribed Esbriet. Patients received Esbriet at the discretion of their physicians, and were followed through the registry for 2 years after they began treatment with Esbriet under real-world conditions.

This registry complied with the requirement of a PASS, and as a post-authorization commitment, was approved by the CHMP.

In Study WB29908 144 patients in advanced stages of IPF (baseline FVC <50%) were included. In this study 91 patients with advanced stages of IPF had 213 events adverse drug reactions of special interest (ADRSIs) (serious and non-serious). Most of these events were in the special interest categories of GI symptoms, photosensitivity reactions and skin rashes, fatigue and weight loss. 55 patients with advanced stages of IPF had 82 other adverse drug reactions, predominantly non-serious events already listed in the SmPC. These events included decreased appetite and respiratory events associated with the underlying disease (dyspnoea and cough); 1 patient each had pulmonary embolism, IPF, productive cough and respiratory failure. 9 patients with advanced stages of IPF had 13 serious adverse drug reactions of special interest: one patient had a report of blood dyscrasias (mentioned previously) and the remaining events were predominantly gastrointestinal symptoms.

The first interim report was of this study was included with PSUR #3 (EMEA/H/C/002154/ PSU/005; 22 October 2012). The eighth and final report was included with PSUR #7 (PSUSA/00002435/201702; 28 April 2017). In the assessment report circulated during this procedure, the PRAC assessor concluded that no new safety signals were identified in this study. In addition, it was agreed that the safety profile of pirfenidone when used in patients with advanced stages of IPF was consistent with the known safety profile of Esbriet.

2.5.2. Conclusions on clinical safety

No new safety issues were identified compared between the non-advanced and advanced population. Agreed updates to the safety information are in 4.4. of the SmPC that Esbriet is essentially Sodium free and that exposure-adjusted analyses of pooled clinical trials in IPF confirmed that the safety and tolerability profile of Esbriet in IPF patients with advanced disease (n=366) is consistent with that established in IPF patients with non-advanced disease (n=942).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

As part of the proposed extension of indication in this variation the MAH had submitted an updated RMP version 12, dated 26 November 2021, following the request to delete severe skin reactions an important potential risk, following the PSUR assessment. At this stage in the product life-cycle with cumulative post-marketing experience it was considered that the safety specification can be further updated to remove the following safety concerns:

-Gastrointestinal symptoms

-Risk of medication error in patients transferring between capsules and tablets,

-Patients with QT prolongation,

-Patients with underlying specific cardiac events.

There were some additional editorial changes requested for Part V and Part VI of the RMP. The MAH submitted an updated RMP vs 12.1 addressing all issues raised in the Request for Supplementary Information.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 12.1 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 12.1 with the following content:

Safety concerns

Table 44 Summary of Safety Concerns

Summary of safety concerns	
Important identified risks	• Photosensitivity reaction and rash • DILI
Important potential risks	None
Missing information	None

DILI = drug-induced liver injury.

Pharmacovigilance plan

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

Risk minimisation measures

Table 45 Summary Table of Pharmacovigilance Activities and Risk Minimization Activities by Safety Concern

• **Safety Concern**	• **Risk Minimization Measures**	• **Pharmacovigilance Activities**
• Photosensitivity reaction and rash	• **Routine risk minimization measures:** • ***Routine risk communication:*** • **SmPC:** • Section 4.2 (Posology and method of administration) • Section 4.4 (Special warnings and precautions for use) • Section 4.8 (Undesirable effects) • ***Patient Information Leaflet:*** • *Section 2 What you need to know before you take Esbriet – Warnings and Precautions* • *Section 3 How to take Esbriet – Dose reduction due to side effects*	• **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**
•	• **Additional risk minimization measures:** • Safety Checklist: • A Safety Checklist about monitoring and management of photosensitivity reaction and rash was made available to be distributed at the time of initial launch and with launch of any new formulation to all local medical staff involved in managing patients with IPF. It requests reporting of all clinically-significant ADRs of photosensitivity reaction and rash to the MAH, where an association is suspected.	
• DILI	• **Routine risk minimization measures:** • ***Routine risk communication:*** • **SmPC:**	• **Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:**

• **Safety Concern**	• **Risk Minimization Measures**	• **Pharmacovigilance Activities**
	• Section 4.2 (Posology and method of administration) • Section 4.3 (Contraindications) • Section 4.4 (Special warnings and precautions for use) • Section 4.8 (Undesirable effects) • ***Patient Information Leaflet:*** • *Section 2 What you need to know before you take Esbriet – Warnings and Precautions* • *Section 3 How to take Esbriet – Dose reduction due to side effects* • *Section 4 Possible side effects* •	A Guided Questionnaire will be used to follow-up incoming reports of DILI. A cumulative medical review of spontaneous reports is carried out at least quarterly. The outcome of these reviews is included in the PBRERs. Reporting of any findings to regulatory
	• If a patient exhibits an aminotransferase elevation >3 to $<5\times$ ULN without bilirubin elevation and without symptoms or signs of DILI after starting pirfenidone therapy, other causes should be excluded, and the patient monitored closely. Discontinuation of other medicines associated with liver toxicity should be considered. If clinically appropriate, the dose of pirfenidone should be reduced or interrupted. Once liver function tests are within normal limits pirfenidone may be re-escalated to the recommended daily dose if tolerated. • DILI • Uncommonly, elevations in AST and ALT were associated with concomitant bilirubin increases. Cases of severe DILI, including isolated cases with fatal outcome, have been reported post-marketing (see Section 4.8 of the Esbriet SmPC).	

• **Safety Concern**	• **Risk Minimization Measures**	• **Pharmacovigilance Activities**
	• In addition to the recommended regular monitoring of liver function tests, prompt clinical evaluation and measurement of liver function tests should be performed in patients who report symptoms that may indicate liver injury, including fatigue, anorexia, right upper abdominal discomfort, dark urine, or jaundice. • If a patient exhibits an aminotransferase elevation \> 3 to < 5 × ULN accompanied by hyperbilirubinaemia or clinical signs or symptoms indicative of liver injury, pirfenidone should be permanently discontinued and the patient should not be rechallenged. • If a patient exhibits an aminotransferase elevation to ≥ 5 × ULN, pirfenidone should be permanently discontinued and the patient should not be rechallenged.	
	• Pirfenidone has not been studied in individuals with severe hepatic impairment and pirfenidone must not be used in patients with severe hepatic impairment (see Section 4.3 of the Esbriet SmPC). • **Other risk minimization measures beyond the Product Information:** • **Pack size**: None • **Medicine's legal status:** Pirfenidone is a prescription only medicine. • **Additional risk minimization measures:** • <u>Safety Checklist:</u> • A Safety Checklist about monitoring and management of DILI is to be distributed to all local	

• Safety Concern	• Risk Minimization Measures	• Pharmacovigilance Activities
	medical staff involved in managing patients with IPF, and may be re-distributed in case of further updates or launch of new formulations. It requests HCPs to report all clinically-significant ADRs of liver-related abnormalities to the MAH.	

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.4, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons:

The Marketing Authorization Holder (MAH) considers it justified not conducting User Consultation for the Package Leaflet for this variation because:

- No significant changes impacting the readability of the package leaflet have been made.
- The new additions to the text follow the same structure and use similar descriptions and terminology as used in the approved package leaflet.
- The target group of users will be almost identical between the approved indication (mild to moderate IPF patients) and the applied indication (all IPF patients), with no significant difference in age or safety profile.
- Moreover, no change to posology is proposed in this application

According to the European Commission Guidance document, "Guidance concerning consultation with target patient groups for the package leaflet", user consultation should be considered where significant changes are made to the package leaflet through a variation procedure or Article 61(3) of Directive 2001/83/EC update procedure.

This type II variation seeks to amend the currently authorized indication of Esbriet (pirfenidone) to cover treatment of all adult patients with idiopathic pulmonary fibrosis (IPF). The current authorised indication is restricted to the treatment of adults with mild to moderate IPF. User consultation was conducted in the context of the initial Esbriet Marketing Authorisation Application, which sought approval for the treatment of adult patients with IPF.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Idiopathic Pulmonary Fibrosis (IPF) is a devastating disease of unknown aetiology characterised by fibrosis of the lung interstitium, decrease in lung volume, and progressive pulmonary insufficiency typically leading to death (Lynch and Toews 1998).

IPF is recognized by the American Thoracic Society (ATS), European Respiratory Society (ERS), Japanese Respiratory Society (JRS), and the Latin American Thoracic Association (ALAT) as a distinct form of interstitial lung disease (ILD), defined by a constellation of clinical, histopathologic, and radiologic features (Raghu et al. 2018, Raghu et al. 2011, and ATS/ERS 2002) and is also categorized as the most common histopathologic form of idiopathic interstitial pneumonia (Katzenstein and Myers 1998).

3.1.2. Available therapies and unmet medical need

Currently, two antifibrotic drugs, pirfenidone and nintedanib, have been shown to slow IPF progression (Oldham & Collard 2017) which led to their regulatory approvals across major geographies for the treatment of IPF. Pirfenidone was approved in the European Union (EU) in 2011, followed by nintedanib four years later in 2015. Both drugs were approved in the United Stated (US) in 2014. In contrast to the US and many other countries, pirfenidone in the EU is only authorised in the treatment of mild to moderate IPF. With this submission, the Marketing Authorization Holder (MAH) seeks to extend the EU indication for pirfenidone to include patients with advanced IPF.

The Official ATS/ERS/JRS/ALAT Statement (2015) rated several treatment options, without a distinction for the severities of IPF.

3.1.3. Main clinical studies

No new pivotal data were provided with this application.

Utilising the data from the original pivotal trials investigating Esbriet as a treatment for IPF, as well as from study MA29957, a recently completed Phase 2 study in patients with advanced IPF, the applicant has performed **retrospective post-hoc analyses** to compare the efficacy and safety profile of Esbriet in patients with mild to moderate IPF versus patients with more advanced IPF.

For the purpose of the post-hoc efficacy analyses of Studies PIPF-004, PIPF-006, PIPF-016 and PIPF-012 advanced IPF was defined as patients with an FVC <50% predicted and/or DLco <35% predicted at baseline. As a consequence, all other patients were defined as having non-advanced IPF. In study MA29957 advanced IPF was defined as a measurable DLco >40% AND Risk of Group 3 PH.

Data from the following studies has been used for the assessment of the efficacy in patients with advanced IPF:

- Pooled Phase III studies (PIPF-004/006/016): A total of 623 patients were treated with pirfenidone and 624 with placebo. Among the 1247 patients, 1077 patients were categorized as having non-advanced IPF and 170 patients had advanced IPF.

- PIPF-012 study: total 596 patients had available FVC or DLco data in Study PIPF-012. Of these, 187 patients were classified as advanced IPF and 409 patients as non-advanced IPF.
- MA29957 study: A total of 89 patients received pirfenidone with added placebo.

3.2. Favourable effects

Based on the results of the post-hoc analysis of PIPF-004/006/016 studies a similar treatment effect of pirfenidone was observed in patients with advanced as compared to patients with non-advanced IPF. The annual FVC decline was lower in the pirfenidone treated patients as compared patients on placebo regardless of the disease status. Among patients with advanced IPF, the annual FVC decline was significantly lower with pirfenidone versus placebo (150.9 mL vs 277.6 mL; nominal p=0.0035). Among patients with non-advanced IPF, annual FVC decline was also significantly lower with pirfenidone versus placebo (128.7 mL vs. 216.7 mL; nominal p=0.0001). The provided annual rates of % predicted change in FVC were in line with the FVC changes in mL.

In relation to all-cause mortality assessment among patients with advanced IPF, less patients died in the pirfenidone group as compared to the placebo group. The percentage of patients with advanced IPF who died from any cause was 4.4% (4/90) in the pirfenidone subgroup compared with 15.0% (12/80) with placebo over 52 weeks of treatment.

The results of the 6MWT confirmed the observation made for FVC that there is a treatment effect of pirfenidone in both non-advanced and advanced patient compared to respective placebo groups. For UCSD SOBQ score, there was a consistent effect of pirfenidone in reducing the worsening of dyspnoea in both populations compared to the greater deterioration in the placebo group. In summary, the secondary endpoint support the results of the primary endpoints.

The results of the post-hoc analysis of Study PIPF-012 indicated that the annual rate of FVC decline (slope) in pirfenidone treated patients in the advanced IPF group was similar to the decline in the non-advanced group (-141.5 mL/year and -153.5 mL/year, respectively). All-cause mortality rate over 180 weeks was lower among patients with non-advanced IPF (49/409; 12.0%) compared to patients with advanced IPF (52/187; 27.8%).

In study MA29957, 89 patients treated with Esbriet monotherapy had a similar decline in FVC as Esbriet-treated patients in the post-hoc analysis of the pooled phase 3 trials PIPF-004, PIPF-006, and PIPF-016. ACM was 20.2%.

3.3. Uncertainties and limitations about favourable effects

The provided analyses were made post-hoc and are thus posed to bias. However, from a clinical point of view the drug effect in different stages of severity and the clinical endpoints can be considered reasonably justified. Analyses of secondary endpoints support to the observed results and the totality of data make the risk of a chance finding negligible.

3.4. Unfavourable effects

Exposure-adjusted analyses of pooled clinical trials in IPF confirmed that the safety and tolerability profile of Esbriet in IPF patients with advanced disease (n=366) is consistent with that established in IPF patients with non-advanced disease (n=942). Adverse events that were higher in the advanced population treated with pirfenidone and can be considered ADRs are already listed as very common or common ADRs in the current Esbriet SmPC.

3.5. Uncertainties and limitations about unfavourable effects

IPF is a disease with high morbidity. The morbidity increases upon progression of the diseases. In the SOCs vascular disorders and respiratory, thoracic and mediastinal disorders, infections and infestations and cardiac disorders, higher exposure-adjusted rates in severe or serious TEAEs or TEAEs leading to death were consistently observed in study MA29957 compared to study PIPF-012.

These differences can however be mostly explained by the difference in severity of the underlying disease, i.e., a higher disease burden in patients with advanced IPF at risk of grade 3 PH. The small difference in the SOC cardiac disorders as compared to placebo is noted but all serous or severe cases were considered to be not related to pirfenidone by the investigator and following continued post-marketing monitoring by the MAH no signal of a safety profile in these patient subgroups different from the known safety profile had emerged. AEs within the SOC Cardiac disorders will continue to be monitored by the applicant in PSURs.

3.6. Effects Table

Table 46 Effects Table for Esbriet which is indicated in adults for the treatment of idiopathic pulmonary fibrosis (IPF)."

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
FVC Volume	FVC Volume (mL) Change with Linear Slope Through Month 12 of Study Treatment	ml	Advanced IPF Pirfenidone 2403 mg/day: -150.9 [30.24]	Advanced IPF Placebo: -277.6 [33.53]	Difference in Mean: 126.71 [43.09] Relative difference in mean: 45.6% P-value (nominal): 0.0035 **Methodological limitation:** -the inclusion/exclusion criteria used in the post-hoc analyses of the pooled pivotal studies define only a narrow subset of all patients with advanced IPF and may not be generalizable to a broader population of patients with more advanced IPF -the post-hoc analyses are not under type I error control and therefore cannot be considered as providing confirmatory evidence	Pooled Studies PIPF-004/-006/-016 post-hoc analyses
Mortality rate	All-cause mortality	%	4.4	15.0	Uncertainties: Post-hoc definition of population, no guideline available for definition - Post-hoc analyses, possible selection bias	
FVC Volume	Annual rate of FVC decline (slope)	ml	Advanced IPF Pirfenidone 2403 mg/day: (-141.5 mL/year)	No placebo group	**Methodological limitation:** not possible distinguish the treatment effect of pirfenidone from the natural course of disease using the single arm data provided from the PIPF-012 study	Study PIPF-012 post-hoc analyses
FVC Volume	Annual rate of FVC decline from baseline to Week 52	ml	Advanced IPF Pirfenidone 2403 mg/day: -93 mL (SE: 46.4).	No comparator group	**Methodological limitation:** not possible distinguish the treatment effect of pirfenidone from the natural course of disease using the single arm data provided from the MA29957 study	MA29957 study
Unfavourable Effects						
TEAEs	exposure-adjusted TEAEs per 100 PY		Treatment-naïve patients: Advanced IPF 816.7/100 patient years	No placebo group		Pooled analysis of PIPF-004, PIPF-006, PIPF-016, MA29957, PIPF-012 and PIPF-025

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
			Treatment-naïve Non- Advanced IPF 868.5/100 patient years Pre-treated patients Advanced IPF 675.2/100 patient years Pre-treated patients Non-Advanced IPF 673.1/100 patient years			
STEAEs	exposure-adjusted STEAEs per 100 PY		Treatment-naïve patients: Advanced IPF 58.92/100 patient years Treatment-naïve Non- Advanced IPF 36.59/100 patient years Pre-treated patients Advanced IPF 82.91/100 patient years Pre-treated patients Non-Advanced IPF 41.68/100 patient years	No placebo group		Pooled analysis of PIPF-004, PIPF-006, PIPF-016, MA29957, PIPF-012 and PIPF-025

Safety

Effect	Short Description	Unit	Non-advanced (n= 717)	Advanced (n= 177)	Uncertainties/ Strength of evidence	References
Unfavourable Effects						
AE	Exposure adjusted adverse events rate	n/100 PY	266.57	264.98	Pooled safety data base of the treatment naïve population. No data is available making a comparison with placebo.	
Serious AE			3.58	8.17		
AE leading to discontinuation			5.76	6.47		

Effect	Short Description	Unit	Non-advanced (n= 717)	Advanced (n= 177)	Uncertainties/ Strength of evidence	References
Death			0.47	0.68		
Weight decreased			4.36	8.51		

Notes: The summarised AE are the drug related adverse events.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Based on the results of the provided post-hoc analysis a similar treatment effect of pirfenidone was observed in patients with advanced IPF as compared to patients with non-advanced IPF.

The difference in annual FVC decline between pirfenidone and placebo is considered relevant. Even a stable response can be considered of high clinical relevance for patients because IPF is a fatal disease with progressive deterioration of lung tissue. Hence preservation of slowing decline of pulmonary function, FVC and diffusion capacity, can be considered as one of main goals of treatment of IPF. The difference in mortality in the advanced IPF patients of 10.6% between the pirfenidone and placebo also clearly indicates a relevant benefit.

No new safety signals were identified in the pooled analysis of PIPF-004, PIPF-006, PIPF-016, MA29957, PIPF-012 and PIPF-025 studies. The safety data of pirfenidone when used in patients in advanced stages of IPF was investigated also in the PAS study (WB29908). This study corroborated that the safety profile of pirfenidone when used in patients with advanced stages of IPF was consistent with the known safety profile of Esbriet. Previously reported adverse events associated with the use of pirfenidone are gastro intestinal events, photosensitivity, rash, weight decrease, and fatigue while the hepatic function has to be monitored frequently as advised in the SmPC. These events are considered to be manageable in the overall IPF population proposed to be included in the label with the established risk minimisation measures. Based on a consistent difference between the pirfenidone arm versus the placebo arm for AEs in the SOC Cardiac disorders, the applicant will monitor post-marketing AEs within the SOC Cardiac disorders in patients advanced IPF and presented them in the PSUR.

3.7.2. Balance of benefits and risks

Considering the clinical benefit demonstrated for patients in advanced stages of the disease and the manageable risk profile of Esbriet a positive B/R can be concluded.

3.8. Conclusions

The overall B/R of Esbriet is positive.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of 'advanced' idiopathic pulmonary fibrosis (IPF) by the deletion of the current qualifier 'mild to moderate', based on the results from Study MA29957; this is a 52-week Phase IIb, multicentre, randomised, double-blind, placebo-controlled clinical trial in IPF patients with advanced lung function impairment (DLco < 40% of predicted) and at high risk of grade 3 pulmonary hypertension, and additional analyses performed on the original pivotal trials for pirfenidone in IPF.
As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated. In addition, the MAH took the opportunity to include information in section 4.4 of the SmPC related to the content of sodium per Esbriet capsule and tablet. The Package Leaflet is updated in accordance. Version 12.1 of the RMP has also been submitted.

The variation leads to amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Esbriet-H-C-2154-II-0074'

Attachments

1. SmPC and Package Leaflet (changes highlighted), as a relevant example with changes highlighted as adopted by the CHMP on 23 February 2023.