EMA/286537/2021
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Esbriet

International non-proprietary name: pirfenidone

Procedure No. EMEA/H/C/002154/II/0069

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	23 Jan 2021	23 Jan 2021	☐
☐	CHMP Rapporteur Assessment Report	19 Mar 2021	19 Mar 2021	☐
☐	CHMP Co-Rapporteur Assessment Report	19 Mar 2021	19 Mar 2021	☐
☐	PRAC Rapporteur Assessment Report	25 Mar 2021	19 Mar 2021	☐
☐	PRAC members comments	29 Mar 2021	29 Mar 2021	☐
☐	Updated PRAC Rapporteur Assessment Report	30 Mar 2021	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	09 Apr 2021	09 Apr 2021	☐
☐	CHMP members comments	12 Apr 2021	12 Apr 2021	☐
☐	Updated CHMP Rapporteur(s) (Joint) Assessment Report	15 Apr 2021	15 Apr 2021	☐
☒	Request for supplementary information	22 Apr 2021	22 Apr 2021	☐

Procedure resources	
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List of abbreviations

AE adverse event
ATS American Thoracic Society
BTD Breakthrough Therapy Designation
cHP chronic hypersensitivity pneumonitis
CSR clinical study report
COMP Committee for Orphan Medicinal Products
EMA European Medicines Agency
ERS European Respiratory Society
FDA Food and Drug Administration
FVC forced vital capacity
GCP Good Clinical Practice
HPRA Health Products Regulatory Authority
IIP idiopathic interstitial pneumonia
IIS investigator initiated study
ILD interstitial lung disease
IPAF interstitial pneumonia with autoimmune features
IPF idiopathic pulmonary fibrosis
MCID minimal clinically important difference
MDT multidisciplinary team
MMF mycophenolate mofetil
OS overall survival
PF-ILD progressive fibrosing ILD
PFS progression-free survival
SAE serious adverse event
SAP statistical analysis plan
SCE summary of clinical efficacy
SCS summary of clinical safety
SD standard deviation
sNDA supplementation New Drug Application
SSc-ILD systemic sclerosis interstitial lung disease
TEAE treatment-emergent adverse events
UILD unclassifiable interstitial lung disease
6MWD 6 minute walking distance

1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Roche Registration GmbH submitted to the European Medicines Agency on 5 January 2021 an application for a variation.

The following changes were proposed:

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 the treatment of unclassifiable interstitial lung disease (UILD) for Esbriet; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11.0 of the RMP has also been submitted.

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

Information relating to orphan designation

On 21 May 2020, the Sponsor requested Orphan Drug Designation from the EMA for the treatment of UILD. On 6 October 2020, the Sponsor attended an oral explanation before the Committee for Orphan Medicinal Products (COMP) to discuss the application. On 7 October 2020, the Sponsor withdrew the application prior to the final opinion.

Orphan market exclusivity of Esbriet for "Treatment of idiopathic pulmonary fibrosis" (based on designation EU/3/04/241) expired on 02 Mar 2021.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

N/A

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.

Derogation(s) of market exclusivity

N/A

Protocol assistance

The MAH did not seek Protocol assistance at the CHMP.

2. Recommendations

Based on the review of the submitted data, this application regarding the following change:

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 the treatment of unclassifiable interstitial lung disease (UILD) for Esbriet; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 11.0 of the RMP has also been submitted.

☐is recommended for approval.

☐is not recommended for approval.

☒is subject to a request for supplementary information (please refer to the RSI section <and the proposed Changes to the Product Information in a separate document>) before a recommendation can be made.

The responses timetable to the Request for Supplementary Information will be[1] [2]:

☐ 30 days (15 days to assess with clock-stop, 8 days to assess with immediate responses)

☒ 60 days (36 days to assess)

Grounds for refusal

n/a

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

3. EPAR changes

This section will be completed by the PL at the time of CHMP Opinion.

[1] Instructions to assessor: please select one of the two options. If no option is selected, a default 30-day assessment timetable will be applied.
[2] Note to MAH: this timetable refers to the assessment of the responses to the RSI and is determined by the Rapporteur/assessor; it does not refer to the clock-stop necessary for the preparation and submission of the responses which is determined by the MAH and communicated to the Procedure Assistant upon receipt of the assessment report.

4. Scientific discussion

4.1. Introduction

The purpose of this application is to extend the license for pirfenidone to include the use of pirfenidone for the treatment of patients with unclassifiable interstitial lung disease (UILD). The data supporting this application are based on the results from Study MA39189, a Phase II double-blind, placebo-controlled trial evaluating the efficacy and safety of pirfenidone in patients with UILD.

4.1.1. Problem statement

Disease or condition

Interstitial lung disease (ILD) represents a group of diffuse pulmonary parenchymal disorders that are classified together based on specific clinical, radiological, and histopathological features; many of these disorders are associated with significant morbidity and mortality. Approximately 10% of patients evaluated by multi-disciplinary teams (MDT) have characteristics that do not allow them to be classified as a specific subset of ILD (Skolnik and Ryerson 2016). This "unclassifiable ILD" (UILD) population has emerged as a formal medical entity with an established definition for diagnosis of fibrotic ILD.

State the claimed the therapeutic indication

The applicant is proposed the following indication:

Esbriet is indicated in adults for the treatment of unclassifiable interstitial lung disease (UILD).

Epidemiology

The 2002 American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus statement on idiopathic interstitial pneumonias (IIPs) identified unclassifiable ILD as an area requiring further study, but resisted the creation of a formal disease category. Indeed, little is known about the prevalence, characteristics, and outcomes of patients with unclassifiable ILD. In the study performed by Guler and colleagues it was estimated that the prevalence of unclassifiable interstitial lung disease within patients with interstitial lung disease is around 11.9% (95% confidence interval, 8.5–15.6%), with lower prevalence in centers that reported use of a formal multidisciplinary discussion of cases (9.5% vs. 14.5%).

Aetiology and pathogenesis

Diffuse (interstitial) lung disease includes a wide variety of relatively uncommon conditions presenting with characteristic clusters of clinical features and marked by an immune response. There are over 200 specific diffuse lung diseases, many of unknown etiology including unclassifiable ILD. Both environmental and genetic factors are believed to contribute to the development of diffuse lung disease.

Clinical presentation, diagnosis <and stage/prognosis

The clinical features of UILD are similar to other types of fibrotic ILDs (Guler et al. 2018):

Relatively consistent burden of dyspnea, cough, and functional limitation prompts patients to seek medical attention and thus patients have a similar ILD severity at the time of diagnosis;

UILD patients can display clinical, radiological, and histopathological features that also occur in other ILDs and idiopathic interstitial pneumonias (IIPs), but their combination, in any given patient, does not allow assigning a specific diagnosis either due to inadequate or discrepant findings;

In terms of disease behavior and prognosis, a considerable proportion of patients with UILD will progress and the impact on patient survival appears to be at a level between the survival of IPF and non-IPF ILD patients, with 2-year survival rates ranging from 70 to 76% (Guler and Ryerson 2018).

Guler SA, Ellison K, Algamdi M, Collard HR, Ryerson CJ. Heterogeneity in unclassifiable interstitial lung disease: a systematic review and metaanalysis. Ann Am Thorac Soc 2018;15:854–863.

Management

There is a lack of standard of care for patients with UILD. Moreover, most drugs currently used to treat UILD, such as the corticosteroids prednisone, prednisolone and methylprednisolone, and immune-suppressants including MMF and azathioprine, have not been subjected to rigorous clinical testing.

In May 2020, the CHMP approved Ofev (nintedanib) in adults for the treatment of other chronic fibrosing interstitial lung diseases (ILDs) with a progressive phenotype. The application was based on a single pivotal trial of 52-week duration that included 663 patients including 114 (17%) of patients with unclassifiable ILD.

The overall study population showed an improvement of the rate of FVC decline compared to placebo 0f 107 mL/year and was supported with a numerically lower proportion of patients with acute ILD exacerbations, and risk of FVC decline ≥ 10% predicted or death (HR 0.66 95% CI 0.53, 0.83, p=0.0003).

For the subgroup of patients with an unclassifiable disease, the mean (95% CI) annual rate of FVC decline was 68·3 [−31·4 to 168·1]ml; no other outcome measures are specifically reported for this subgroup [Wells 2020]

4.1.2. About the product

Pirfenidone (ESBRIET®) is an orally active, small molecule that has been shown to exert both antifibrotic and anti-inflammatory properties in a variety of animal models and in vitro systems.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).

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

No scientific advice was requested in the context of this variation.

The applicant had previous regulatory interactions with the FDA and EMA.

4.1.4. General comments on compliance with GCP

The Clinical trial was 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.

A request for GCP inspection has been adopted for the following clinical study MA39189. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the LoQ and will be needed by Day 91.

4.2. Non-clinical aspects

No new clinical data have been submitted in this application, which is considered acceptable.

4.2.1. Ecotoxicity/environmental risk assessment

An updated Environmental Risk Assessment for pirfenidone to account for UILD use is provided under Module 1.6.1.

Phase-1 PEC_{SW} and action limit using the default FPEN

The maximum daily dose (MDD) for Pirfenidone is 2403 mg. The Phase-1 predicted environmental concentration for surface water (PECSW) while using the default fraction of market penetration (FPEN) of 0.01 (1% of the population) is calculated as follows:

PEC_{SW} = MDD × FPEN ÷ (default wastewater per inhabitant × default dilution)

= 2,403,000 µg/d × 0.01 ÷ (200 l/d × 10)

= 12.0 µg/l

Using the default FPEN of 0.01, the Phase-1 PEC is greater than the EMA (2006) Guideline [2] action limit of 0.01 µg/l.

A refined fraction of market penetration ($F_{PEN\text{-}REFINED}$) based on prevalence is presented below.

Phase-1 PEC and action limit using a refined $F_{PEN\text{-}REFINED}$

In the EMA Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00) the PECSW ultimately depends on MDD and FPEN, which is an estimate of the fraction of the population using a given medicine. The default FPEN is 0.01 or 1% of the population, however, the FPEN may be refined based on published epidemiology data.

Prevalence for IPF and UILD

IPF prevalence in existing ERA by HLS in 2009 [ERA submitted for initial MAA]

At the time of the environmental risk assessment (ERA) by HLS in 2009 [6] Pirfenidone was indicated for the treatment of idiopathic pulmonary fibrosis (IPF), a certain proportion of all interstitial lung diseases (ILD).

HLS estimated an IPF prevalence of 30 per 100,000 inhabitants and used a FPEN-REFINED of 0.0003 to calculate the PEC_{SW}. This resulted in a PEC_{SW} of 0.360 mg/l [6]:

PEC_{SW} = MDD × $F_{PEN\text{-}REFINED}$ ÷ (default wastewater per inhabitant × default dilution)

= 2,403,000 µg/d × 0.0003 ÷ (200 l/d × 10)

= 0.360 µg/l

Updated assessment of IPF prevalence

According to Orphanet [9] the IPF prevalence in Europe is 11.5 per 100,000. However, taking a prevalence of ILD (all types) of 97.9 per 100,000 subjects over the age of 15 as described by Duchemann et al., 2017 [1] and a proportion of IPF of ILD of 32% as described by Kreuter et al., 2015 [8], this results in a IPF prevalence of 31.3 per 100,000, which is almost equal to the existing assessment of 2009.

UILD prevalence

Taking a prevalence of ILD (all types) of 97.9 per 100,000 subjects over the age of 15 as described by Duchemann et al., 2017 [1] and a proportion of unclassifiable interstitial lung disease (UILD) of ILD of 24% as described by (Hyldgaard et al., 2017 [7], this results in a UILD prevalence of 23.5 per 100,000.

Combined IPF and UILD prevalence

The combined prevalence for IPF (31.3 per 100,000) and UILD (23.5 per 100,000) is 54.8 per 100,000, which results in a $F_{PEN\text{-}REFINED}$ of 0.000548 which is used in the calculation for a refined PEC_{SW}.

Refined Phase-1 PEC_{SW}

The refined Phase-1 PEC using the combined IPF and UILD prevalence of 54.8 per 100,000 ($F_{PEN\text{-}REFINED}$ = 0.000548) is calculated as follows:

PEC_{SW} = MDD × $F_{PEN\text{-}REFINED}$ ÷ (default wastewater per inhabitant × default dilution)

= 2,403,000 µg/d × 0.000548 ÷ (200 l/d × 10)

= 0.659 µg/l

The combined PEC_{SW} for both indications, IPF and UILD, amounts to 0.659 µg/l. This is about a factor 1.8 higher than the PEC_{SW} of 0.360 mg/l in the existing ERA of 2009 [6].

As a result the applicant used this refined, higher, PEC_{SW} value of 0.659 µg/l to adapt the ERA Phase 2 Tier.

Phase 2, Tier A assessment

The EMA Phase 2 Tier A basic dataset is complete (cf. [6]). Hence, the initial risk estimations for surface water, groundwater and sewage treatment as well as the consideration of additional criteria for possible referral to compartmental assessment in Phase 2 Tier B can be performed.

Surface water risk assessment

Chronic ecotoxicity and surface water PNEC. Chronic ecotoxicity tests were performed with Pirfenidone according to OECD guidelines 201, 211 and 210 with algae, daphnids and fish, respectively [6]. The surface water PNEC is calculated as the lowest of the three chronic surface water ecotoxicity NOEC values divided by an assessment factor of 10 [2]. In the case of Pirfenidone, with NOEC values of 18.3 mg/l for the algae, 94.0 mg/l for the daphnids and 10.6 mg/l for the fish [6] , the fish early life stage NOEC of 10.6 mg/l (i.e. 10600 µg/l) drives the PNEC:

$PNEC_{SW}$ = 10600 µg/l ÷ 10 = 1060 µg/l

The surface water PEC÷PNEC risk characterisation ratio is

0.659 µg/l ÷ 1060 µg/l = 0.00062

Conclusion. In view of the PEC÷PNEC risk characterisation ratio of 0.00062 based on Phase 2 Tier A procedures, there is no concern for risk caused by Pirfenidone to surface waters.

Groundwater risk assessment

The groundwater PEC is approximated as the surface water PEC divided by 4:

PEC_{GW} = 0.659 µg/l ÷ 4 = 0.165 µg/l

The groundwater PNEC is approximated as the chronic ecotoxicity NOEC for daphnids of 94.0 mg/l (i.e. 94000 µg/l) [6] divided by an assessment factor of 10:

$PNEC_{GW}$ = 94000 µg/l ÷ 10 = 9400 µg/l

The groundwater PEC÷PNEC risk characterisation ratio is

0.165 µg/l ÷ 9400 µg/l = 0.000018

Conclusion. In view of the PEC÷PNEC risk characterisation ratio of 0.000018, there is no concern for risk caused by Pirfenidone to groundwater.

Sewage treatment risk assessment

The sewage works PEC is approximated as the Pirfenidone surface water PEC multiplied by 10 (the default surface water dilution factor used in the PECSW calculation):

PEC_{STP} = 0.659 µg/l × 10 = 6.59 µg/l = 0.00659 mg/l

An activated sludge respiration inhibition test according to OECD 209 over 3 hours was performed in compliance with GLP [6], which resulted in an NOEC of 100 mg/l.

The bacterial PNEC for sewage treatment is calculated as the activated sludge respiration inhibition NOEC divided by an assessment factor of 10 [2]:

$PNEC_{bacteria,\ sewage\ treatment}$ = 100 mg/l ÷ 10 = 10 mg/l

Hence, the sewage works PEC÷PNEC risk characterisation ratio is

0.00659 mg/l ÷ 10 mg/l = 0.00066

Conclusion. In view of the PEC÷PNEC risk characterisation ratio of 0.00066 there is no evidence for risk caused by Pirfenidone to sewage treatment.

Additional decision criteria for in-depth compartmental investigations in Phase 2 Tier B

Lipophilicity – bioconcentration assessment. The n-octanol/water partition coefficient $logK_{OW}$ of Pirfenidone determined in compliance with GLP following OECD guideline 107 is 0.9 [6]. As the $logK_{OW}$ is <3, following the EMA 2006 Guideline [2] a bioaccumulation assessment is not required.

K_{OC} – soil fate and effects assessment. Adsorption and desorption constants to the organic carbon fraction in four soils and one activated sewage sludge were determined following OECD guideline 106 using ^{14}C-labelled Pirfenidone [6]. The highest observed soil desorption coefficient was 79.8 l/kg. The experimental data show that Pirfenidone does not adsorb to organic substrates. Based on the observed K_{OC} values, Pirfenidone can be classified as highly mobile in soils and sewage sludges according to the McCall [9] classification scheme.

The observed K_{OC} values are well below the threshold of 10'000 l/kg in the EMA 2006 ERA Guideline. Hence, no consideration of the soil compartment through landspreading of sewage sludge is necessary for Pirfenidone.

Sediment chronic effects and risk assessment

Sediment PEC. As more than 10% of applied radioactivity was registered in the sediment after 13 days (cf. [6]) a sediment PEC for Pirfenidone is calculated and compared with a sediment PNEC.

The sediment PEC is derived using Eq. 14–17 as well as default values of the EMA Draft Guidance Document of 2018 [3]. The sediment PEC is based on adsorption to suspended solids. In view of many default values, this PEC ultimately depends on the organic-carbon/water distribution coefficient (KOC) and on the surface water PEC (PECSW). The PEC for the wet sediment (PECSED) is calculated by using the maximum KOC in soil (i.e. 79.8 l/kg) as a worst case [3]:

$PEC_{SED} = (K_{SUSP\text{-}WATER} / RHO_{SUSP}) \times PEC_{SW} \times 1000$

$= ((Fwater_{SUSP} + (Fsolid_{SUSP} \times Kp_{SUSP} \times RHO_{SOLID} \times 10\text{-}3)) / RHO_{SUSP}) \times PEC_{SW} \times 1000$

$= ((Fwater_{SUSP} + (Fsolid_{SUSP} \times Foc_{SUSP} \times Koc_{SOIL} \times RHO_{SOLID} \times 10\text{-}3)) / RHO_{SUSP}) \times PEC_{SW} \times 1000$

$= ((0.9 + (0.1 \times 0.1 \times 79.8\ l{\cdot}kg\text{-}1 \times 2.5\ kg{\cdot}m\text{-}3 \times 10\text{-}3)) / 1.15\ kg{\cdot}m^{-3}) \times 0.000659\ mg{\cdot}l^{-1} \times 1000$

= 0.0017 mg/kg wet weight

The PEC for the dry sediment (PEC_{SED_DW}) is calculated as follows [3]:

PEC_{SED_DW} = PEC_{SED} × 4.6 = 0.0017 mg/kg × 4.6 = 0.0076 mg/kg dry weight

Chronic sediment ecotoxicity and sediment PNEC. The sediment PNEC is derived from a chronic sediment ecotoxicity test with larvae of the midge Chironomus riparius, following OECD guideline 218 and performed in compliance with GLP [6]; the organic carbon (OC) content of the artificial sediment was not determined in the 2009 study; hence a worst-case value of 0.1% was assumed. The overall NOEC for both endpoints emergence ratio and development rate was 495 mg Pirfenidone/kg sediment (dry weight).

Results from sediment toxicity tests should be recalculated into a standard sediment with an organic carbon content of 10% (fraction of 0.1) according to Eq. 18 of the EMA Draft Guidance Document of 2018 [3]. Since the organic carbon (OC) content of the artificial sediment was not determined in the 2009 study, a worst-case value of 0.1% was assumed; i.e. NOECST SED equals the NOECTEST SED:

$NOEC_{ST\ SED}$ = $NOEC_{TEST\ SED}$ × ($Foc_{ST\ SED}$ ÷ $Foc_{TEST\ SED}$)

= 495 mg/kg × (0.1 ÷ 0.1) = 495 mg/kg standard sediment

With one single chronic NOEC available, according to the EMA Draft Guidance Document of 2018 [3] the deterministic sediment PNEC is derived by dividing the NOEC by an assessment factor of 100.

$PNEC_{ST\ SED}$ = $NOEC_{ST\ SED}$ ÷ 100 = 495 mg/kg ÷ 100 = 4.95 mg/kg standard sediment

The sediment PEC÷PNEC risk characterisation ratio is:

PEC_{SED_DW} ÷ $PNEC_{ST\ SED}$ = 0.0076 mg/kg ÷ 4.95 mg/kg = 0.0015

Conclusion. In view of the PEC÷PNEC risk characterisation ratio of 0.0015, there is no concern for risk caused by Pirfenidone to sediments.

4.2.2. Discussion on non-clinical aspects, ERA

The pharmacologically active ingredient Pirfenidone (RO0220912-000) was assessed for its potential environmental risk arising from the extended medical use, 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} = 0.659	$PNEC_{SW}$ = 1060	0.00062	>1
Groundwater	PEC_{GW}= 0.165	$PNEC_{GW}$= 9400	0.000018	>1
STP	PEC_{SW} = 6.59	$PNEC_{bacteria,\ STP}$ = 10,000	0.00066	>0.1
Sediment	PEC_{SED}= 0.0076 mg/kg dw	$PNEC_{SED}$= 4.95 mg/kg	0.0015	>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.

The Expert has signed and dated the updated ERA and a CV has been provided.

Table 1 ***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)	0.659	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.

There is no additional environmental concerns raised with respect to the use of Pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF) and unclassifiable interstitial lung disease (UILD).

4.2.3. Conclusion on the non-clinical aspects, ERA

Based on the updated data submitted in this application, the new/extended indication does 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.

4.3. Clinical aspects

4.3.1. 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.

Table 2 Tabular overview of clinical studies

5.3.5 Efficacy and Safety Studies								
MA39189	Synopsis: Module 2.7.6 CSR: Module 5.3.5.1	Primary: rate of decline in FVC by handheld spirometry Secondary: change in FVC by site spirometry, DLco, 6MWD, PFS, all-cause and respiratory hospitalization, and PROs Safety Exploratory: role of MMF treatment in ILD, biomarkers associated with fibrosis and ILD	Phase II, multicenter, international, double-blind, two-arm, randomized, placebo-controlled	Pirfenidone: 2403 mg orally daily (3×267 mg capsules [801 mg] TID)	Double-blind treatment period: 253 patients (127 in pirfenidone arm, 126 in placebo arm) Safety follow-up period: 204 patients	Patients with UILD	24-week double-blind treatment period Additional 12-month safety follow-up period	Complete; Full Report

CHMP comment:

A request for GCP inspection has been adopted for the following clinical study MA39189. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the LoQ and will be needed by Day 91 (MO).

4.3.2. Pharmacokinetics

No new data were provided

4.3.3. Pharmacodynamics

No new data were provided

4.3.4. PK/PD modelling

No new data were provided

4.3.5. Discussion on clinical pharmacology

No new data were provided

4.3.6. Conclusions on clinical pharmacology

No new clinical pharmacology information were provided with this submission. PK data were not collected in MA39189 study. The applicant has not provided any discussion whether the PK and PD profile in patients unclassifiable interstitial lung disease (UILD) is expected to be similar as compared to IPF patients **(OC).**

4.4. Clinical efficacy

4.4.1. Dose response study(ies)

CHMP comment

No dose finding study was performed for the treatment of unclassifiable interstitial lung disease (UILD). In study MA39189 pirfenidone was given in the same dose as it is currently approved for the treatment of mild to moderate idiopathic pulmonary fibrosis. The applicant should discuss and justify why the dose approved currently for the treatment of IPF was considered appropriate for patients with UILD **(OC).**

4.4.2. Main study(ies)

MA39189

Title of Study

Multicenter, International, Double-Blind, Two-Arm, Randomized, Placebo-Controlled, Phase II Trial of Pirfenidone in Patients with Unclassifiable Progressive Fibrosing ILD

Methods

This was a multicenter, international, double-blind, two-arm, randomized, placebo-controlled, Phase II study with an open-label extension in patients with fibrosing ILD who could not be classified with moderate or high confidence into any other category of fibrosing ILD by MDT review ("UILD"). Eligible patients were randomly assigned in a 1:1 ratio, on a double-blind basis using a stratified algorithm, to receive either pirfenidone (801 mg three times daily [TID]) or placebo. The randomized patients were stratified by concomitant MMF treatment (yes/no) and the presence/absence of IPAF as defined by the MDT.

- **Washout period**

After providing informed consent, patients were required to taper and/or discontinue all prohibited medications in the 28 days prior to the start of screening during the washout period. If a prohibited medication had to be tapered, the process had to start early enough so that the patient discontinued the medication in the 28 days prior to the start of screening.

- **Screening**

After they completed the washout period, patients entered screening, which lasted up to 21 days. During screening, patients were evaluated for eligibility based on the inclusion and exclusion criteria. Patients not taking a prohibited medication forwent the washout period and directly entered screening.

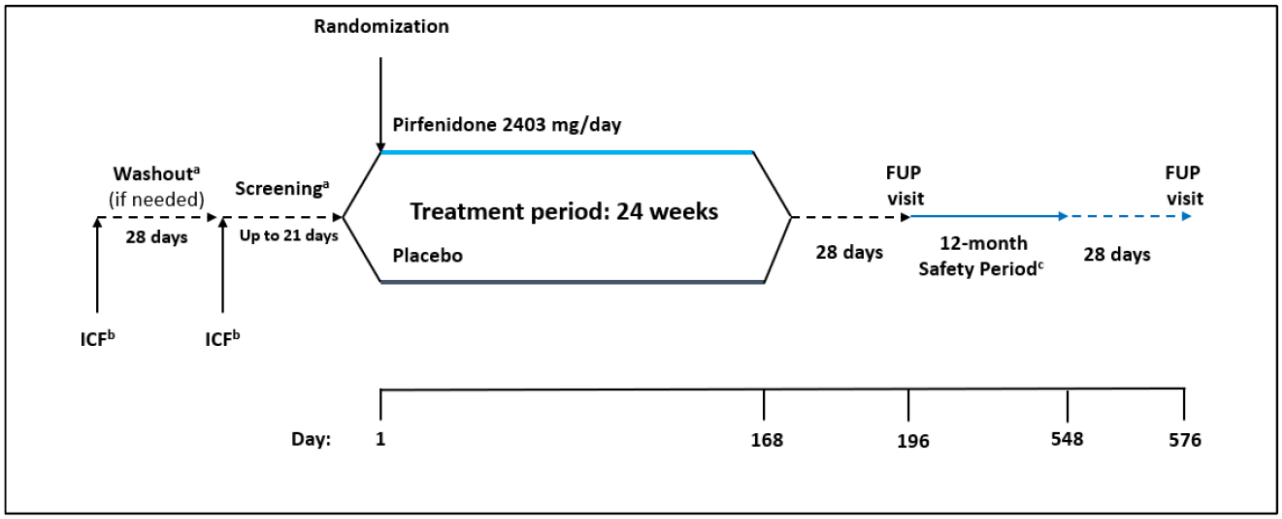
- **Double-blind treatment period- 24 weeks**

Following treatment initiation, the daily dosage was titrated to the full dosage of 9 capsules per day over a 14-day period. After the titration period, trial treatment continued through Week 24, and monitoring was conducted by monthly trial visits for safety and efficacy. Patients remained on a stable maintenance dose for the duration of the treatment period unless the dose was reduced, or dosing was interrupted to manage an adverse event (AE). Any patient with an actual or anticipated interruption of trial treatment for a period of ≥28 consecutive days was reported by written communication; however, per protocol, it was supposed to be reported by telephone to Roche's Medical Monitor or designee to discuss the circumstances of the case. Once the patient restarted trial treatment, the dose had to be re-titrated over 14 days

- **Safety follow up -12 months**

After patients completed the double-blind treatment period and the follow-up visit at Week 28, the Sponsor offered patients the option to receive open-label pirfenidone within the trial protocol in a safety follow-up period of up to 12 months. During the safety follow-up period, patients were evaluated by the investigator at monthly visits for the first 6 months and approximately every 3 months thereafter until the end of the safety follow-up period. A final follow-up visit was performed at the end of the safety period, 28 days after the last open-label dose.

Figure 1 ***Trial design***



FUP = follow-up; ICF = Informed Consent Form

*Table 3****: Titration Schedule in Double-Blind Treatment Period and Open-Label Safety Follow-Up Period***

Treatment Days	Dosage
Days 1 through 7	One capsule 3 times daily with meals
Days 8 through 14	Two capsules 3 times daily with meals
Day 15 onwards	Three capsules 3 times daily with meals

Patients received open-label pirfenidone during safety follow-up period of up to 12 months. A final follow-up visit was performed at the end of the safety period, 28 days after the last open-label dose.

CHMP comment

The applicant submitted one study (MA39189) investigating the use of pirfenidone in patients with fibrosing ILD that, following MDT review, could not be classified with either high or moderate confidence as a specific idiopathic interstitial pneumonia or other defined ILD.

MA39189 study had a 24 weeks double-blind treatment period and 12 months safety follow-up in which patients were receiving open-label pirfenidone. No spirometry or other efficacy assessments were conducted during the 12-month safety follow-up.

There are no EU guidelines on the clinical investigation of medicinal products for the treatment of ILD. Nevertheless, taking into consideration previous regulatory decisions it is considered that the duration of the double-blind treatment period is too short **(MO).** It is noted that PIPF-004 and PIPF-006 studies supporting the idiopathic pulmonary fibrosis indication had 72 weeks double-blind treatment periods. Studies INPULSIS-1, INPULSIS-2, INBUILD and SENSCIS investigating nintedanib in various ILD indications had 52 weeks double-blind treatment periods.

Study participants

Main inclusion criteria:

- Were ≥18–85 years of age
- **Had confirmed fibrosing ILD that, following MDT review, could not be classified with either high or moderate confidence as a specific idiopathic interstitial pneumonia or other defined ILD** (e.g., chronic hypersensitivity or CTD-ILD)
- Had **progressive disease** as considered by the investigator using the following definition:
- Patient deterioration within the last 6 months, which was defined as:
    - A rate of decline in FVC >5% OR
    - Significant symptomatic worsening not due to cardiac, pulmonary, vascular, or other causes
- Had extent of fibrosis >10% on HRCT (visual scoring) within the last 12 months
- Had FVC ≥45% of predicted value
- Had DLco ≥30% of predicted value
- Had forced expiratory volume in 1 second (FEV1)/FVC ratio ≥0.7
- Had 6MWD ≥150 meters

As stated above the study enrolled patients with confirmed fibrosing ILD that, following MDT review, could not be classified with either high or moderate confidence as a specific idiopathic interstitial pneumonia or other defined ILD.

The levels of confidence were defined as follows:

High confidence: a specific diagnosis is highly likely (i.e., usual interstitial pneumonia pattern on high-resolution computed tomography [HRCT] in the case of IPF)

Moderate confidence: the MDT arrives at a "working diagnosis" of a particular ILD, which is sufficient to lead to a specific therapeutic strategy (i.e., antifibrotic therapy in the case of IPF, immunosuppressive therapy in the case of CTD-ILD)

Low confidence: the MDT may have a suspicion of a particular ILD but considers the available evidence insufficient to inform the therapeutic strategy

The following patient populations (non-exhaustive list) were therefore eligible for enrollment:

- Patients with "UILD"
- Patients who fulfilled research classification criteria for IPAF (Fischer et al. 2015)
- Patients with low confidence diagnosis of NSIP, cHP, CTD-ILD, etc.

CHMP comment:

The 2002 ATS/ERS classification proposed an "unclassifiable" category of IIP, acknowledging that a final diagnosis may not be achieved in all cases.

MA39189 study enrolled patients patients with confirmed fibrosing ILD that, following MDT review, could not be classified with either high or moderate confidence as a specific idiopathic interstitial pneumonia or other defined ILD. The inclusion criteria to the study were very broad as not only patients with "UILD" diagnosis or who fulfilled research classification criteria for IPAF could be enrolled, but also those with low confidence diagnosis of specific ILDs including NSIP, cHP, CTD-ILD. The applicant should further justify these inclusion criteria and present the efficacy data after exclusion of patients with any diagnosis of specific ILDs **(OC)**. It is noted that in this study, the MDT discussion was mandatory before the qualifying diagnosis of uILD can be made. This is supported. On the other hand, a surgical lung biopsy was not required to be performed. This is considered as a limitation, although it is acknowledged that some patients are unable or unwilling to undergo lung biopsy.

As postulated by Guler and colleagues, there are likely important differences in patients with interstitial lung disease who are unclassifiable despite a surgical lung biopsy and patients who are unclassifiable in the absence of a surgical biopsy. Therefore, the applicant is requested to further discuss the efficacy results separately in patients with and without lung biopsy **(OC).** The reasons why lung biopsy was not performed should be presented and discussed by the applicant **(OC).**

All enrolled patients had to have extent of fibrosis >10% on HRCT and progressive disease as considered by the investigator. Progressive disease was defined based on the presence of a decline in FVC % (>5%) within the last 6 months or significant symptomatic worsening not due to cardiac, pulmonary, vascular, or other causes. In patients with IPF, a decline in FVC of ≥10% over 12 months is generally taken to indicate progressive disease.

The applicant is proposing the following indication: *Esbriet is indicated in adults for the treatment of unclassifiable interstitial lung disease (UILD).* This indication is not supported as the pivotal study was only enrolling patients with progressive disease and this need to be reflected in the text of the indication **(MO).**

Further, the study population was limited to patients with baseline DLCO ≥30% and FVC ≥45%. The applicant should discuss whether this criteria be reflected in the text of the indication. It is noted that currently Esbriet is indicated the treatment of **mild to moderate** IPF only **(MO).**

Main exclusion Criteria

- Had a diagnosis with moderate or high confidence of NSIP and any ILD with an identifiable cause such as CTD-ILD, cHP, or others
- Had diagnosis of IPF independent of the confidence level
- Had history of unstable angina or myocardial infarction during the previous 6 months
- Had received treatment with high-dose systemic corticosteroids (i.e., >15 mg/d of prednisolone or equivalent) or any immunosuppressant other than MMF at least 4 weeks prior to screening. Patients being treated with MMF had to be receiving stable doses that were expected to remain stable throughout the trial and were started ≥3 months prior to screening
- Had previously been treated with pirfenidone or nintedanib
- Had been treated with N-acetyl-cysteine (NAC) for fibrotic lung disease at any time within 4 weeks of the screening period
- Had received drug treatment for any type of pulmonary hypertension (e.g., sildenafil, endothelin receptor antagonist)
- Had significant co-existent emphysema (extent greater than extent of fibrosis on HRCT within the last 12 months)
- Had significant other organ comorbidity, including hepatic or renal impairment
- Had predicted life expectancy <12 months or were on an active transplant waiting list

- **Had used any tobacco product in the 12 weeks prior to the start of screening, or were unwilling to abstain from their use through to the follow-up** visit (comment Phase I interaction study that found that pirfenidone exposure was 50% lower in smokers compared with non-smokers).
- Had engaged in illicit drug or alcohol abuse within 12 months prior to screening, according to the investigator's judgment
- Had planned major surgery during the trial
- Had history of angioedema
- Used fluvoxamine concomitantly
- Had clinical evidence of any active infection, which, according to the investigator's judgment, could have interfered with trial conduct or measurement of pulmonary function or have affected the course of the ILD
- Had any history of hepatic impairment, elevation of transaminase enzymes, or confirmation of any of the following liver function test (LFT) criteria above the specified limits:
    - Total bilirubin above the upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) or alanine aminotransferase
    - (ALT) >1.5 × ULN
    - Alkaline phosphatase >2.0 × ULN
    - Creatinine clearance <30 mL/min, calculated with the Cockcroft-Gault formula
- Had any serious medical condition, clinically significant abnormality on an electrocardiogram (ECG) at screening, or laboratory test results (hematology, serum chemistry, and urinalysis) that, in the opinion of the investigator, could have posed an additional risk to the patient following the administration of trial treatment
- Had ECG results that indicated a heart rate corrected QT interval (corrected using Fridericia's formula [QTcF]) ≥500 ms at screening or had a family or personal history of long QT syndrome.

CHMP comment:

The main exclusion criterion in the study was a clinical diagnosis of IPF (independent of the confidence level) and patients with any diagnosis of specific ILDs (with moderate or high confidence).

Treatments

Dosage and Administration

The study treatment included pirfenidone and matching placebo administered at a daily dose of 2403 mg. This dose was administered orally in the form of three 267-mg capsules (801 mg) TID with food, at the same times each day.

Criteria for Dose Modification or Withdrawal from Treatment

Patients had to remain on a stable maintenance dose for the duration of the treatment period unless the dose was reduced, or dosing was interrupted to manage an AE. Any patient with an actual or anticipated interruption of trial treatment for a period of ≥28 consecutive days was reported by written communication; however, per protocol, it was supposed to be reported by telephone to Roche's Medical Monitor or designee to discuss the circumstances of the case. Once the patient restarted trial treatment, the dose had to be retitrated over 14 days.

Concomitant medications

Concomitant therapy included any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient from the washout

period until 28 days after the last dose of trial treatment. All such medications were reported to the investigator and recorded on the concomitant medications eCRF.

All protocol-allowed medications taken by the patient for concomitant disease(s) were continued as necessary during the study and were recorded on the eCRF. Treatments prescribed to patients were adapted according to the local standard-of-care practice.

Use of the following therapies was prohibited during the study, and these therapies were tapered and/or discontinued in the 28 days prior to screening:

- Investigational therapy other than trial treatment
- High-dose systemic corticosteroids (15 mg/d of prednisolone or equivalent) for more than 28 days
- Immunosuppressive therapies (e.g., azathioprine)
- Treatment with NAC for fibrotic lung disease at any time within 4 weeks of the screening period; intermittent use of NAC for other conditions was permitted
- Fluvoxamine and other cytochrome P450 1A2 inhibitors
- Cytochrome P450 1A2 inducers

If down titration of prohibited therapy was required, it had to be done during the 28-day washout period.

CHMP comment:

In the study patients were randomised in a 1:1 ratio to pirfenidone and matching placebo administered at a daily dose of 2403 mg. Patients had to remain on a stable maintenance dose for the duration of the treatment period unless the dose was reduced, or dosing was interrupted to manage an AE. In the trial, patients could use concomitant therapy with MMF (MMF treatment includes mycophenolate mofetil/sodium or mycophenolic acid). As MMF may have an effect on the disease course of unclassifiable ILD, patients were stratified according to whether they received concomitant MMF treatment during the trial.

High dose systemic corticosteroids (15 mg/d of prednisolone or equivalent) for longer than 28 days, Immunosuppressive therapies (e.g. azathioprine), treatment with NAC for fibrotic lung disease, CYP1A2 inhibitors and inducers were not allowed in the study.

Objectives

Primary Efficacy Objective
To evaluate the efficacy of pirfenidone vs. placebo on lung function parameters

Secondary Efficacy Objective
To evaluate the efficacy of pirfenidone vs. placebo from baseline (Day 1) until Week 24 on other functional parameters, outcomes, and PROs

Safety Objective (From Baseline to Week 28)
To evaluate the safety of pirfenidone vs. placebo

Exploratory Objectives

To evaluate the role of MMF treatment in ILD

To evaluate potential biomarkers associated with fibrosis and ILD

Outcomes/endpoints

Primary endpoint

- Rate of decline in FVC measured in milliliters by daily handheld spirometer (daily home spirometry) over the 24-week, double-blind treatment period

Secondary Efficacy Objective

- Change in percent predicted FVC and in milliliters measured by spirometry during clinic visits (clinic spirometry)
- Categorical change in FVC of >5% (absolute change in percent predicted and relative change in milliliters), measured both by daily home spirometry as well as by spirometry during clinic visits (clinic spirometry)
- Categorical change in FVC of >10% (absolute change in percent predicted and relative change in milliliters), measured both by daily home spirometry as well as by spirometry during clinic visits (clinic spirometry)
- Change in percent predicted DLco
- Change in 6MWD in meters
- Change in UCSD-SOBQ score
- Change in Leicester Cough
- Change in cough score on a visual analog scale
- Change in total score and subscores of the SGRQ
- Non-elective hospitalization, both respiratory and all-cause
- Incidence of, and time to first, investigator-reported acute exacerbations (analogous to the methods described by Collard et al. 2016)
- PFS, defined as the time to the first occurrence of a >10% absolute decline in percent predicted FVC (measured during a clinic visit), a >50 m decline in 6MWD, or death
- PFS, alternatively defined as the time to the first occurrence of a >10% relative decline in FVC (measured during a clinic visit), non-elective respiratory hospitalization, or death
- Time to death from any cause
- Time to death from respiratory Diseases

Safety endpoints

- Nature, frequency, severity, and timing of treatment-emergent adverse events
- toDose reductions and treatment interruptions
- Clinical laboratory test results
- 12-lead ECGs

- Withdrawals from study treatment or
- study discontinuations

Handheld Spirometry

Because handheld spirometry has been shown to be feasible in patients with IPF and to have the potential to detect functional decline earlier (Russell et al. 2016; Johannson et al. 2017), it was decided to use handheld daily home spirometry as the primary outcome measure to assess the efficacy of pirfenidone over a 24-week period (Maher et al. 2017).

Each patient performed a single home spirometry reading at approximately the same time each day. For this purpose, each trial participant was provided with a portable handheld Micro Spirometer (CareFusion, Kent, England). The Micro Spirometer measured FEV1 and FVC by means of a turbine volume transducer and provided a digital readout registered in liters at body temperature and pressure saturated with water vapor. Each spirometer was factory calibrated. Blows were categorized by a spirometer-based algorithm as "rejected", "borderline accepted", or "accepted". Only "acceptable" blows were retained for analysis; blows that were shorter than 6 seconds or had a flow-change of 100 mL in the last 0.5 seconds were classified as acceptable blows. During the final analysis, after re-read, only 2 categories (acceptable or non-acceptable) were recorded. Coughing during the blow rendered a warning message of non-acceptable blow, which allowed the patient to perform another blow the same day. The handheld spirometry device had several built-in features to control for a good blow. Most of these controls measured intra-blow differences of blows performed on the same day. As only one blow was requested per day in this study (to avoid sheer stress, which is considered harmful in patients with fibrosis), these controls could not be activated, enabling undetected day-to-day variability and physiologically impossible values.

Training on how to use the device was provided at the screening visit, and refresher training was offered after Month 1, between Months 2 and 3, and between Months 4 and 5. Before implementation of handheld home spirometry in the study, all technical measures were taken into consideration for perfect device functionality, as per previous published data (Russell et al. 2016; Johannson et al. 2017). These measures included use of factory-calibrated spirometers, validated workflow of the device and software used, intensive training of patients to reduce variability, and retraining of patients with multiple missing values either by the investigator at the center or by a home nursing staff member. Data were downloaded by site staff at each site visit (every 4 weeks). Patients were blinded to daily home spirometry values. The Sponsor selected a healthcare company that was responsible for providing home nursing services for the participating sites. The vendor was responsible for ensuring that all home nursing professionals were licensed, qualified, and in good standing, as per applicable regulations.

CHMP comment:

The primary endpoint of this study was the rate of decline in FVC measured in milliliters by daily handheld spirometer (daily home spirometry) over the 24-week double-blind treatment period.

The applicant decided to use handheld daily home spirometry as opposed to spirometry performed during clinic visits as in previous studies (Russell et al. 2016; Johannson et al. 2017) home spirometry showed a good correlation with hospital-obtained readings. In addition it was believed that home spirometry has the potential to detect functional decline earlier. However, taking into consideration previous regulatory decisions and unproven advantages of home spirometry, it is considered that that the annual rate of decline in forced vital capacity (FVC) should have been selected as a primary endpoint in the study **(MO).**

Change in percent predicted FVC and in milliliters measured by spirometry during clinic visits was investigated as a secondary endpoint. However this endpoint and also all other secondary endpoints were not under type I error control. This is considered as another significant limitation of this study.

Further, it is important to highlight that the rate of decline in forced vital capacity (FVC) is only a surrogate endpoint and therefore it is considered that a positive trend in other endpoints investigating direct clinical effects (for example patients reported outcomes or survival) needs to be shown in the study. In the study patient-reported outcomes and survival were investigated; however, as stated these endpoints were not under type 1 error control.

As per the study protocol (version 3.0, schedule of assessments, footnote o), nursing visits to the patient's home were to occur at least three times during the trial for each subject "to provide handling evaluations and quality assurance for the daily spirometer assessments". Describe what was reviewed as part of these home visits, clarify if this occurred for all subjects as planned, and if issues with the conduct and quality of spirometry assessment were identified and documented through this process. If issues were identified through these home visits, clarify what actions were taken as a result **(OC).**

Sample size

The purpose of the trial was hypothesis generation regarding the efficacy of pirfenidone vs. placebo on lung function parameters on the basis of rate of decline in FVC, as measured by daily handheld spirometry.

A total sample size of approximately 250 patients was planned, and patients were to be randomized in a 1:1 ratio. The randomization was to be stratified by concomitant MMF treatment (yes/no) and the presence/absence of IPAF as defined by the MDT. The planned sample size was based on the statistical hypothesis of the primary endpoint and assumed 80% power and a two-sided significance level of 5% using a Student's t-test.

Based on historical data, it was assumed that FVC decline in the placebo arm would be 85 mL with a common standard deviation of 70 mL, which could be reduced to 60 mL with a common standard deviation of 70 mL in the pirfenidone arm. In this scenario, 125 patients per treatment arm would be needed to detect this treatment effect with 80% power.

These assumptions were further based upon the following considerations: in IPF, the annual rate of decline of FVC is approximately 200 mL. Owing to the fact that patients with unclassifiable ILD have rates of disease progression in the range of patients with IPF, albeit with a lower mortality rate (Ryerson et al. 2013), a similar decline rate of 200 mL/year, equivalent to a 100 mL decline over a treatment period of 24 weeks, can be expected. However, a yet unknown proportion of patients in this trial was to be treated concomitantly with MMF. In a previous study of CTD-ILD (Fischer et al. 2013), MMF was found to have beneficial effects on lung functions in these patients. While CTD-ILD is a distinct entity from the current trial population, both conditions may share some autoimmune features. Therefore, the applicant considered that assuming a smaller FVC decline of 85 mL in the placebo arm compared with 60 mL in the pirfenidone arm over the 24-week double-blind treatment period appeared justified. In addition, the

applicant considered that the potential confounding effect of concomitant MMF therapy in these patients justified stratification to ensure equal distribution of patients who receive and do not receive treatment with MMF.

CHMP comment

The sample size calculation is based on the primary efficacy endpoint and the assumptions appear reasonable, although the clinical relevance should be justified for treatment difference of FVC decline of 25 mL (OC). It is noted that the stated purpose of the trial was hypothesis generation.

Randomisation

Patients were randomly assigned in a ratio of 1:1 to receive either pirfenidone or placebo. The randomization process was conducted using a validated interactive voice or web-based response system (IxRS). To guard against systematic selection bias and to ensure comparability between treatment groups, randomization was stratified according to concomitant MMF treatment (yes/no) and presence/absence of IPAF as defined by the MDT.

Blinding (masking)

This was a double-blind study with an open-label extension. The investigational site personnel and the patients were blinded to treatment assignment following randomization. The iDMC and any personnel performing any interim analysis (as applicable) were unblinded to the treatment throughout the trial.
If unblinding was necessary for patient management (e.g., in the case of a serious adverse event [SAE] for which patient management could be affected by knowledge of treatment assignment), the investigator was able to break the treatment code by contacting the IxRS.

Statistical methods

Statistical Analysis Plan

The original SAP Version 1.0 was dated 05 JULY 2018. SAP Version 2.0 was dated 29 OCTOBER 2018: this version was used to perform the primary analysis of the study following the database lock on 03 MAR 2019.

The final version of the SAP (Version 3.0) was dated 17 JULY 2020. This version was used to perform the final analysis of the study following the database lock on 06 APR 2020. It incorporated additional analyses suggested by FDA on 08 NOV 2019 as part of Written Response feedback to the Sponsor on their proposal to support efficacy supplements for progressive fibrosing ILD (PF-ILD) or specific disease classifications within PF-ILD, such as UILD.

An overview of the statistical reporting and associated milestones for Study MA39189 is provided in Table 4:

Table 4 Overview of Statistical Reporting Performed for Study MA39189

Reporting Event or Milestone	Date	SAP Version Implemented	Comments
Initial SAP published	5 July 2018	1.0	Used for dry-run for primary analysis in Sept 2018
Updated SAP published	29 Oct 2018	2.0	For list of major changes, see Section 3.9.11.3
Primary analysis	DBL: 3 Mar 2019	2.0	Occurred when the 24-week double-blind period and the 4-week safety follow-up were completed
Post hoc analysis 1	Apr 2019	2.0	Additional reporting for primary CSR
FDA request	8 Nov 2019	--	FDA requested additional mixed modelling and tipping point analyses
Post hoc analysis 2	Dec 2019	--	New tables, figures, and listings produced for publication purposes
Final analysis	Final DBL: 6 Apr 2020	3.0	Occurred when the 12-month safety follow-up period was completed
Updated SAP published	17 July 2020	3.0	For list of major changes, see Section 3.9.11.3

CSR = clinical study report; DBL = database lock; FDA = U.S. Food and Drug Administration; SAP = statistical analysis plan; V = version

The following major changes were made in Versions 2.0 and 3.0 of the SAP:

Version	Date	Change number	Change description
2	08-Oct-2018	1	Clarification related to the aim and timeline of the primary analysis and final analysis of the study are included under section Outcome Measures.
2	08-Oct-2018	2	Week 28 is included in all descriptive efficacy tables.
2	08-Oct-2018	3	The safety follow-up period definition is changed as stated in section On-treatment Assessments (12-Month Safety Follow-up Period).
2	08-Oct-2018	4	Disposition is updated in section Patient Disposition.
2	08-Oct-2018	5	Details were added in order to analyze valid daily spirometry data in section Demographic and Baseline Characteristics.
2	08-Oct-2018	6	Additional analyses needed in the safety follow-up period based on safety follow-up population are presented under section Safety Follow-up analyses.
2	08-Oct-2018	7	Safety follow-up visits were included under section Visit Windows.
2	08-Oct-2018	8	Listings of stratification factors, separated types of adverse events and pregnancy data were removed from the corresponding sections.
3	18-Jun-2020	9	Categorical change of 5% and 10% for home FVC measurements deleted because of implausible data collected
3	18-Jun-2020	10	Restrict analysis of oxygen requirements to patients who had oxygen requirements
3	18-Jun-2020	11	Add information about sensitivity analyses performed for home FVC measurements in section Sensitivity Analyses
3	18-Jun-2020	12	Add correlation analysis for home FVC and site FVC measurements (Additional analyses after FDA feedback), see Exploratory Efficacy Endpoints
3	18-Jun-2020	13	Mixed model analysis added for home spirometry and site spirometry as sensitivity analysis in section Sensitivity Analyses
3	18-Jun-2020	14	Subgroup analysis for biopsy taken before randomization (yes/no) added
3	18-Jun-2020	15	Tipping point analysis added for various assumptions to impute missing values in section Sensitivity Analyses for missing data
3	18-Jun-2020	16	Safety tables added to compare study data with phase III studies in section Adverse events

Changes to the planned analyses

After the first database lock for the primary CSR on 28 FEBRUARY 2019, planned analyses on categorical change in FVC for home spirometry from the analysis plan were removed due to the unexpected nature of the data measured by home spirometry in terms of high variability and physiologically implausible FVC data points.

The following new or modified analyses were performed during the primary analysis (as per SAP Version 2.0 dated 29 OCTOBER 2018):

- Baseline characteristics (demographics, UILD disease characteristics, spirometry test history, 6MWT, and oxygen requirements) for MMF subgroup (yes/no)
- Test for normality (i.e., Shapiro-Wilks etc.) for checking model assumptions of primary analysis
- Box-plot of predicted 24-week decline for all patients in order to show outliers to be removed from sensitivity analysis
- Q-Q plot of 24 weeks decline for all patients in order to show graphically the deviation from normality assumption of the primary analysis model
- Sensitivity analysis of primary endpoint excluding patients with less than 10% of expected FVC values from home spirometry
- Correlation analysis of predicted 24-week declines for home and clinic spirometry
- Forest plot for sensitivity analysis of primary endpoint
- Forest plot for clinic FVC measures (secondary endpoint)
- Categorical change of 5% and 10% for clinic FVC in mL (relative change)

The following new or modified analyses were performed at the time of the final analysis, the changes implemented after the primary analysis (as per SAP Final Version 3.0; dated 17 JULY 2020):

- Mixed model analysis for home and site spirometry
- Fixed missing imputation based on placebo distribution
- Fixed missing imputation between Q1 and Q3 of placebo distribution
- Tipping point analysis with shifts

The following analyses were not performed during final analysis because of unexpected high variability of home spirometry measurements (as per SAP Final Version 3.0; dated 17 JULY 2020):

- Categorical change for home FVC
- Categorical change in FVC of >5% (absolute change in percent predicted and relative change in mL), measured by daily spirometry during clinic visits
- Categorical change in FVC of >10% (absolute change in percent predicted and relative change in mL), measured by daily spirometry during clinic visits

Independent Review Facility for Daily Home Spirometry Results

A handheld spirometry device was used by the patient to measure daily FVC at home. The following blow categories were collected for each daily measurement: Accepted, Rejected, Borderline Accepted. Only accepted blows were to be considered for analysis.

However, data collected by daily home spirometry was impacted by technical problems, such as physiologically implausible readings being classified as acceptable blows.

After primary analysis of study data, an external organization (eResearch Technology Inc.) was contracted to perform a blinded, manual re-assessment of the home spirometry data resulting in a modified flagging of acceptable daily FVC values.

Analysis Populations

The **intent-to-treat (ITT) population** was defined as all randomized patients. Patients in the ITT population were assigned to treatment arm as randomized (planned treatment). The ITT population was the primary analysis population for all efficacy analyses.

The **safety population** was defined as all patients with at least one intake of pirfenidone or placebo, i.e. at least one record in the drug-log of the double-blind period with a nonzero dose. Patients in the safety population were assigned to treatment arm according to the actual treatment they received.

For the 12-month safety follow-up period, the **safety follow-up population** was defined as all patients who received at least one dose of pirfenidone after the randomized treatment end plus 28 days.

Safety analyses for the 12-month follow-up period were performed from the date of the first pirfenidone drug intake during safety follow-up period up to the study completion/discontinuation visit.

A per-protocol population was not defined for this study.

Analysis of primary endpoint – rate of decline in FVC in mL measured by handheld spirometer over the 24-week double-blind treatment period

The primary analysis of the primary endpoint compared the mean estimated FVC decline in each treatment arm using a student's t-test with a two-sided significance level $\alpha=0.05$. Additionally, a two sample Wilcoxon test was used for treatment comparison: results of this test were of a descriptive nature only.

The mean estimated FVC decline for each treatment arm was calculated using the estimated FVC decline for each individual patient in that arm and was used as an estimate of the mean FVC decline. The estimated FVC decline for individual patients was obtained by applying a linear regression model to all data points collected for that patient during the 24-week double-blind treatment period:

$X_{it} = \alpha_i + \beta_i D_{it} + \mu_{it}$

where

X_{it} = the FVC measurements (mL) of patient i on day t, with i=1,…,N and t=1,…,T, N being the total number of patients randomized and T the total number of days with assessment.

D_{it} = study day t of patient i

α_i, β_i= intercept and slope of the individual linear regression of patient i

The time-adjusted decline for patient i was then obtained by estimating the patients' individual difference in predicted values between baseline and week 24 from the linear regression model. In a further step, the mean estimated FVC decline was obtained by taking the mean over all individual time-adjusted declines of all patients by treatment arm.

A summary table displaying the mean estimated FVC decline together with two-sided 95% confidence intervals based on percentiles of the t-distribution was provided by treatment arm.

The same analyses were performed by restricting the FVC decline values, as follows:

- Including patients with at least 3 site spirometry measurements
- excluding patients with a predicted FVC decline below -1000 mL or above 1000 mL
- excluding values with a difference +/-50% from corresponding baseline site spirometry

These analyses were applied once taking into account the old and once the new quality flag.
As a sensitivity analysis to the primary analysis (introduced in SAP version 3.0), the mean FVC decline over 24 weeks was also estimated using a random slope and intercept linear regression model, with absolute change in FVC (mL) as the outcome variable and assuming linear decline in lung function over time. The model included random coefficients for the slope and intercept, fixed effect terms for treatment and stratification factors (MMF treatment and IPAF). The model was applied once taking into account the old and once the new quality flag.

The statistical model was defined as follows:

$Y_{ijk} = (\alpha + a_i) + (\gamma + \beta_s T_k + g_i)\, t_{ij} + \beta g\, Cov1_i + \beta a\, Cov2_i + \varepsilon_{ij}$

- Y_{ijk} is the value measured for i^{th} patient at time j in treatment group k
- t_{ij} is the time of measurements for i^{th} patient at study day j
- $T_k = 0$ if patient is in Placebo group, and $T_k = 1$ if patient is in Pirfenidone group
- β_s is the effect of Pirfenidone on the slope
- α and γ are elements of the intercept and slope respectively
- a_i and g_i are random specific components of the intercept and slope for the i^{th} patient

- β_g , β_a are patient specific demographics' coefficients (strata)
- $Cov1_i$, $Cov2_i$ are covariates to be included for the i^{th} patient
- ε_{ij} is the random error for i^{th} patient at time j
- a_i and g_i are assumed to be normally distributed with mean 0 and arbitrary
- covariance matrix
- ε_{ij} are assumed to be independent and normally distributed with mean 0 and variance $\sigma\varepsilon_2$
- Within patient errors follow a random coefficient regression model with random effect for intercept and slope
- An unstructured variance-covariance structure was be used to model the within patient measurements
- The variance-covariance matrix, modeled to estimate the inter-individual variability, is considered to have a Variance-Components structure

Analysis of secondary endpoint – rate of decline in FVC in mL measured by spirometry during site visits over the 24-week double-blind treatment period

Spirometry was conducted at each site (clinic) visit during the double-blind treatment period (weeks 1, 4, 8, 12, 16, 20, 24) and at early treatment discontinuation visit occurring 28 days after the last dose of double-blind treatment.

The decline of FVC in mL measured by spirometry during site (clinic) visits was compared between the treatment arms in the same fashion as described for the primary endpoint. However, a Wilcoxon test was not planned for this endpoint.

The decline of FVC in mL measured by spirometry during site (clinic) visits was also compared between the treatment arms using the same random slope and random intercept linear regression model described for the primary endpoint, both with and without including the stratification factors as covariates. Note that analysis was introduced in SAP version 3.0.

The absolute change in percent predicted FVC measured by spirometry during site visits at week 24 was compared between the treatment arms using a rank analysis of covariance (ANCOVA). Change from baseline was used as the outcome variable and the standardized rank baseline value was included as a covariate.

Categorical changes in FVC (mL) measured during site (clinic) visits of >5% and >10% was compared between the treatment arms using a Cochran-Mantel- Haenszel test stratified by concomitant MMF medication use (Yes/No), and the presence/absence of IPAF as defined by the MDT.

Handling of missing data in the secondary endpoint

Three different approaches were introduced to evaluate the robustness of the analysis of the secondary endpoint to the missing at random (MAR) assumption in SAP version 3.0. Due to the low number, deaths and other intercurrent events were not considered in the multiple imputation analysis. No data was collected after treatment discontinuation.

<u>Fixed missing imputation based on Placebo distribution</u>

Missing data in both treatment groups was singly imputed by descriptive statistics derived from the distribution of the placebo group. For each visit the following descriptive statistics of FVC (mL) were calculated from the placebo group only: lower quartile, median, upper quartile.

For each of the 2 treatment groups 3 datasets with imputed missing values were created:

- Missing values imputed by median of placebo group for the respective visit
- Missing values imputed by lower quartile of placebo group for the respective visit
- Missing values imputed by upper quartile of placebo group for the respective visit

Then, within each of the 9 possible combinations of treatment group datasets two analyses were performed:

1. The mean FVC decline in the treatment arms was compared using a student's t-test. The mean FVC decline for each treatment arm was calculated using the estimated FVC decline for each individual patient, which was obtained by applying a linear regression model to the data over time of the respective patient.
2. The decline in FVC (mL) at week 24 was estimated from a random slope and intercept model. This model included fixed effects for treatment, the stratifying variables concomitant use of MMF and presence/absence of IPAF and treatment-by time interaction. Random effects were included for both time and intercept.

The difference between treatment groups was calculated together with the corresponding p-value.

A table presented the results from the two analyses: estimates for the placebo group, pirfenidone group and the comparison pirfenidone versus placebo together with the respective p-value for each of the 9 combinations of imputed values.

Fixed missing imputation between Q1 and Q3 of Placebo distribution

A tipping point sensitivity analysis was performed, where missing data of both treatment groups was imputed by values derived from the range between lower and upper quartile (Q1 – Q3) in the Placebo group at each visit. The aim of the tipping point approach was to assess how severe departures from MAR could be in order to reverse conclusions from the analysis of secondary endpoint under different assumptions for the decline after withdrawal of the randomized treatment.

100 datasets with imputed values were created for each treatment group. For the first dataset missing values in the respective treatment group were imputed by the lower quartile (Q1) of placebo group within each visit. In the second dataset, the missing values were imputed by Q1 plus the amount of 0.01 x (Q3 – Q1). The value added to Q1 was increased within each subsequent dataset by another amount of 0.01 x (Q3-Q1), so that in the last of the 100 dataset the amount of Q3 from the placebo group was imputed for missing values.

Then, for each of the 10000 combinations of datasets the decline in FVC (mL) at week 24 was estimated from a random slope model. This model included fixed effects for the stratifying variables concomitant use of MMF and presence/absence of IPAF and treatment-by-time interaction. Random effects were included for both time and intercept.

The difference between treatment groups was calculated together with the respective p-value.

A heat map displaying positive and negative outcome based on the p-values for the comparison pirfenidone versus placebo with green and red colors (green: < 0.05, red: > 0.05) was provided to illustrate the outcome of this analysis graphically. The robustness of the results was to be discussed based on the magnitude of deviations from MAR required to change the results.

Tipping point analysis with shifts

A tipping point sensitivity analysis using the Multiple Delta Adjustment Method was performed.

As a first step non-monotone missing data were imputed 100 times using MCMC (Markov Chain Monte Carlo) to generate 100 data sets of longitudinal spirometry data (FVC [mL]) with monotone missingness pattern (PROC MI). Such a missingness pattern is the pre-requisite for subsequently applying sequential imputation and means that once a patient has a missing FVC value at a particular time point, FVC values at all subsequent time points also have missing values. The seed in PROC MI number was set to 1234.

Once the monotone missing pattern was created, the tipping point analysis for the longitudinal FVC data was based on the Multiple Delta Adjustment Method. Data in each of the 100 generated datasets with the monotone missingness pattern was imputed once (under MAR) by using sequential regression. A delta adjustment was added to each imputed value. The value of each delta adjustment was given by shift parameters S1 and S2 for the 2 treatments.

For patients with more than one monotone missing visit, multiple adjustments must be applied and since the imputation method is sequential, the effect of the adjustments was cumulative. S1 and S2 therefore

represent the slope of a linear adjustment over time. This step was repeated for a variety of combinations of S1 and S2.

For each combination of shift values S1 and S2 the 100 complete data sets were analyzed using the statistical model as described above. The estimate of treatment difference at week 24 was derived. Rubin's rules were used to combine the results from the analyses for each pair of S1 and S2 (PROC MIIANALYZE). Point estimates for the comparison pirfenidone versus placebo and respective p-values were reported for selected combinations of S1 and S2 in a cross-table.

The following combinations of S1 and S2 were applied:

• S1 (Pirfenidone): -130, -125,-120,-115,-110,-105,-100,-95,-90,-85,-80,-75,-70,-65,-60,- 55,-50,-45,-40,-35,-30,-25,-20,-15,-10,-5,0, 5, 10

• S2 (Placebo): -40,-35,-30,-25,-20,-15,-10,-5,0, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120.

A heat map displaying positive and negative outcome based on the p-values for the comparison pirfenidone versus placebo with green and red colors (green: < 0.05, red: > 0.05) was provided to illustrate the outcome of this analysis graphically. The robustness of the results was to be discussed based on the magnitude of deviations from MAR required to change the results.

Analysis of other secondary endpoints

Absolute change from baseline to week 24 in percent predicted DLco was compared between the treatment arms using a rank ANCOVA. Change from baseline to week 24 was used as the outcome variable and the standardized rank baseline value was included as a covariate in the model.

The following secondary efficacy endpoints were analysed using a rank ANVOCA model with the week 24 score as the outcome variable and including the standardized rank baseline score as a covariate:

- 6MWD
- UCD-SOBQ
- Leicester Cough Questionnaire
- Cough visual analog scale
- SGRQ total score

The following secondary efficacy endpoints were analysed using Kaplan-Meier plots and log-rank tests; hazard ratios and corresponding 95% CI estimates were obtained from Cox proportional hazard models adjusted for the randomization stratification factors:

- Time from randomization to first occurrence of all-cause non-elective hospitalization
- Time from randomization to first occurrence of respiratory non-elective hospitalization
- Progression Free Survival (PFS), defined as the time from randomization to the first occurrence of a >10% absolute decline in percent predicted FVC, a >50 m decline of 6MWD, or death from any cause
- An alternative definition of PFS, defined as the time from randomziation to the first occurrence of a >10% relative decline in FVC, non-elective respiratory hospitalization, or death
- Time from randomization to death from any cause
- Time from randomization to death from respiratory diseases assessed by the SOC "Respiratory, thoracic, and mediastinal disorders"
- Time to first investigator-reported acute exacerbation

The incidence of investigator reported acute exacerbations in the two treatment arms was also compared using Fisher's exact test.

Subgroup analyses

Subgroup analyses of the decline in FVC in mL (home and site spirometry) and selected other secondary endpoints were conducted for the following subgroups:

- The four groups resulting from combinations of the two stratification factors:
    - Concomitant MMF treatment (yes/no)
    - Presence/absence of IPAF as defined by the MDT
- Gender: Male, Female
- Age (years): <65 years, ≥ 65 years
- Percent predicted FVC at Baseline: <65%, ≥65% to < 80%, ≥80%
- Percent predicted DLco at Baseline: <35%, ≥35%
- Body weight: <60 kg, ≥60 kg
- Previous Biopsy (yes/no)

Type I error control

No multiplicity adjustments were performed for testing secondary endpoints. p-values for all secondary endpoints were reported in a descriptive fashion.

Interim analyses

No formal interim analyses were planned or conducted.

CHMP comment

The results of the pre-specified primary endpoint based on daily home FVC measurements cannot be considered reliable and can at best be considered to provide supportive data. Re-analysis of the primary endpoint based on daily home FVC measurements with modified quality flagging can also only be considered to provide supportive data. The secondary endpoint based on FVC measurements collected during site visits could be considered to provide a stronger basis for decision-making, but this endpoint was not multiplicity controlled.

Furthermore, the primary analysis approach for these two endpoints relies on strong linearity and missing at random assumptions. It is not agreed with the applicant that no imputation method was applied in this analysis, as use of predicted 24-week FVC decline values for subjects without observed week 24 FVC values is a form of imputation. Therefore, the choice of analysis to be presented in section 5.1 should a positive benefit/risk be concluded remains under assessment.

Of the three approaches introduced to evaluate the robustness of the analysis of the secondary endpoint to the missing at random (MAR) assumption in SAP version 3.0, the tipping point analysis with shifts is considered to be of greatest relevance. The fixed missing imputation based on Placebo distribution and the fixed imputation between Q1 and Q3 of Placebo distribution, being single imputation approaches, are not considered to provide adequate estimates of the treatment effect standard error and are consequently of lower interest.

The following additional analyses are requested to assess the impact of the linearity assumption on the analyses of the primary and secondary FVC endpoints and of an alternative missing data assumption on the secondary FVC endpoint:

- The assumption of a linear rate of decline in FVC over 24 weeks at both the individual patient level and the treatment group level has not been sufficiently justified by the applicant. Extrapolation of a (comparable) linear rate of decline in FVC beyond 24 weeks has also not been justified by the applicant. The applicant should justify the validity of these linearity assumptions, e.g. by presenting plots of individual patient FVC (home/site) trajectories by treatment arm, and/or evaluating the need for higher order terms in the regression models used to predict individual patient FVC values. **(OC)**

- The applicant should present an analysis of the rate of decline in FVC in mL measured by spirometry during site visits over the 24-week double-blind treatment period using a mixed model repeated measures (MMRM) model with fixed effects for treatment, baseline FVC, visit, treatment-by-visit, baseline FVC-by-visit and stratification factors and using an unstructured covariance pattern for the within-subject repeated measures. Parameters should be estimated using REML and Kenward-Roger degrees of freedom. A missing data sensitivity analysis for this model using reference-based imputation under the jump-to-reference assumption should also be presented. Observed and least

squares means for each treatment group and the treatment group difference at each visit should be presented. It is understood that no FVC measurements were collected after discontinuation of assigned treatment. **(OC)**

Additionally, the following points for clarification are raised as other concerns:

- The applicant should clarify the date of database lock for the primary analysis of study MA38189. CSR Table 8 states this to be 03 MAR 2019 while CSR section 3.9.11.3 states it to be 28 FEB 2019 **(OC)**
- The clinical report stated that the Categorical changes of FVC > 5% and 10% of the clinic visits are deleted from SAP V2 to Sap V3. However, according to SAP version 3.0, the FVC of home visits are deleted. Please confirm that the analyses according to the home FVC were deleted.
- A number of ranked ANCOVA approaches have been presented in the statistical literature. The applicant should describe the ranked ANVOCA approach used for the analysis of secondary endpoints in this study in greater detail. **(OC)**

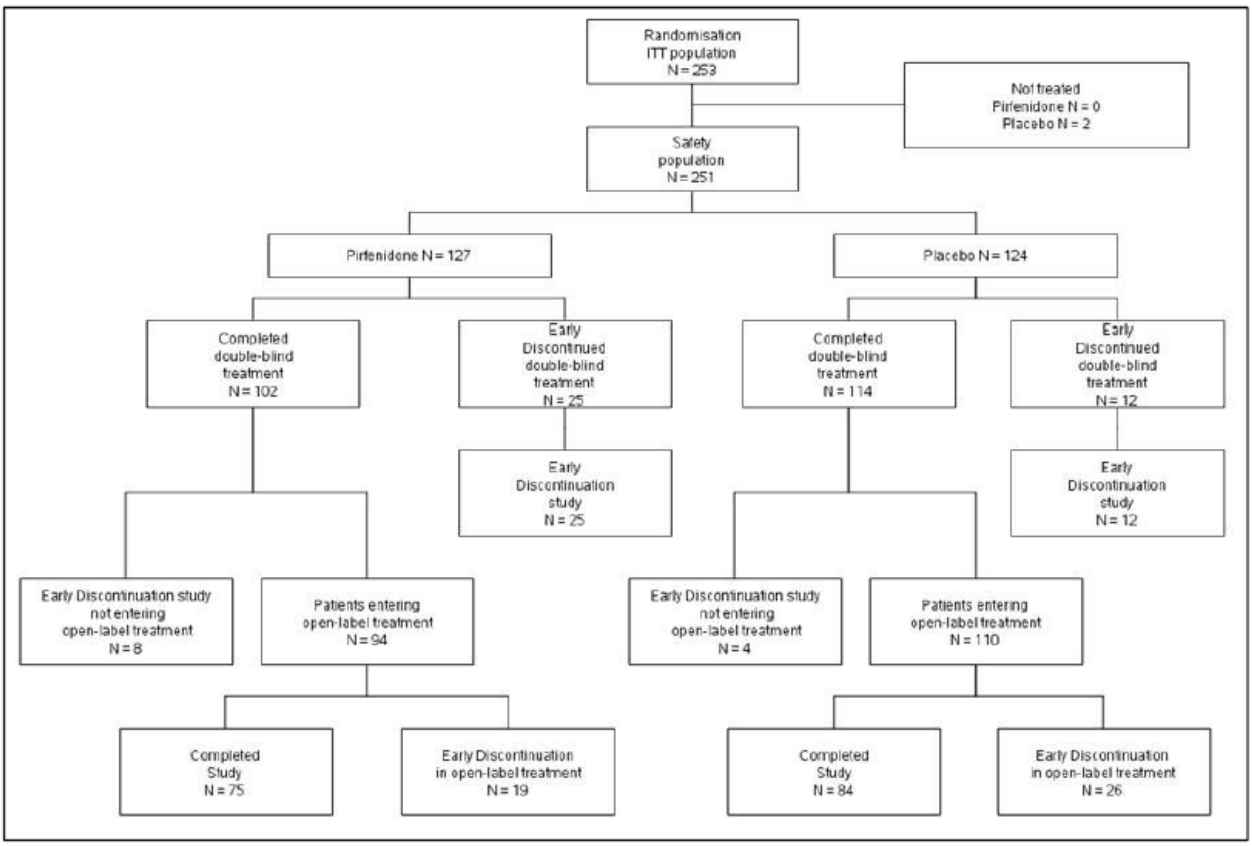
Results

Participant flow

A total of 253 patients were randomized and assigned to the pirfenidone group (127 patients) and to the placebo group (126 patients.)
Two patients in the placebo group were not treated. Therefore, the safety population included 251 patients (127 patients in the pirfenidone group and 124 patients in the placebo group).

Overall, a total of 48 patients were screen failures. A total of 102 patients (80.3%) in the pirfenidone group and 114 patients (90.5%) in the placebo group completed the double-blind treatment period of the study. A total of 94 patients (74.0%) in the pirfenidone group and 110 patients (87.3%) in the placebo group entered the additional 12-month safety follow-up period. Overall, 75 patients (59.1%) previously treated with pirfenidone and 84 patients (66.7%) previously treated with placebo, completed the study.

Figure 2 ***Patient Disposition (ITT Population)***



Patients withdrawn prematurely from treatment

Of the 253 randomized patients, 25 patients (19.7%) in the pirfenidone group and 12 patients (9.5%) in the placebo group discontinued early from the double-blind treatment period and did not enter the safety follow-up period. The known side effects of pirfenidone (GI disorders and investigations [LFT increased]) led to a higher discontinuation rate in the pirfenidone group than in the placebo group.

The most common primary reason for early discontinuation from the study was because of AEs, followed by withdrawal of consent. A total of 102 patients (80.3%) in the pirfenidone group and 114 patients (90.5%) in the placebo group completed the double-blind treatment period of the study; of those, 8 patients (6.3%) in the pirfenidone group and 4 patients (3.2%) in the placebo group did not enter the additional 12-month safety follow-up period. Of the patients who entered the additional 12-month safety follow-up period, 19 patients (15.0%) previously treated with pirfenidone and 26 patients (20.6%) previously treated with placebo discontinued from the study during the additional 12-month safety follow-up period. The most common primary reason for early discontinuation from the study during the additional 12-month safety follow-up period was death due to respiratory disorders.

Recruitment

The date of the first patient first visit was 15 May 2017; the date of the last patient last visit and the primary
efficacy and safety analysis of the double-blind period was 18 December 2018. A total of 253 patients were randomized at 65 study centers in the following countries:

Australia (8 centers), Belgium (3 centers), Canada (2 centers), Czech Republic (3 centers), Denmark (3 centers), Germany (5 centers), Greece (3 centers), Ireland (2 centers), Israel (7 centers), Italy (5 centers), Poland (3 centers), Portugal (4 centers), Spain (5 centers), and the United Kingdom (12 centers).

Conduct of the study

Amendments to the trial protocol

The original protocol dated 15 November 2016 was amended on 2 occasions (global amendments) after the first enrollment: on 03 March 2017 and 28 June 2018.

Protocol Version 2.0 (03 March 2017)

- Protocol v1.0 was amended mainly to provide additional guidance on trial-specific procedures. Major changes and clarifications to the protocol were as follows:

- Protocol v1.0 was amended to include additional safety monitoring during the 12-month safety follow-up period,

- Guidance text for sections on inclusion and exclusion criteria was amended to provide clearer guidance as to when patients must fulfil the eligibility criteria in order to participate in the trial, since results for screening assessments could not all be available at the time of screening.

- Section on "Trial Rationale and Benefit-Risk Assessment" was amended to provide further clarification that trial patients were allowed to be treated with MMF regardless of which treatment arm they were randomly assigned to during the 24-week, double-blind period and throughout the study.

- Section on "Method of Treatment Assignment and Unblinding" was amended to delete the sentence providing investigators with the option of unblinding patients for any other reason but safety. Unblinding could only occur for safety reasons.

- The "Cough Visual Analog Scale" was amended to replace the previous scale with the actual scale and guidance text that was provided to the patients.

Protocol Version 3.0 (28 June 2018)

- Protocol v2.0 was amended mainly to provide additional guidance on trial-specific procedures. Major changes and clarifications to the protocol were as follows:

- Protocol Section 4.5.5 (FVC) was amended to provide guidance on when to use a short-acting bronchodilator prior to on-site spirometry (clinic spirometry) for patients who were routinely treated with such medication.

    - The following text was added: If a patient is routinely treated with a short-acting bronchodilator (for example albuterol, salbutamol), the bronchodilator should be taken approximately 30 minutes prior to the on-site spirometry.

- Protocol Sections 4.5.9 (Electrocardiograms) and 5.1.1.8 (Management of Increases in QT Interval) were amended to provide clearer guidance for ECGs and the management of increases in QT intervals.

- Protocol Section 4.5.10 (Patient-Reported Outcomes) was amended as the timing for completion of the Patient-Reported Outcomes was independent of the administration time of the trial treatment.

- Protocol Section 4.6.1 (Patient Discontinuation) was amended to include lung transplantation during the trial as a reason for patient discontinuation.

- Schedule of Assessments was amended to reflect the changes made to the body of the protocol and also to provide further trial-specific guidance.

CHMP comment:

The following text was added as a part of a second amendment to the study protocol "If a patient is routinely treated with a short-acting bronchodilator (for example albuterol, salbutamol), the bronchodilator should be taken approximately 30 minutes prior to the on-site spirometry." The applicant should discuss on how this recommendation could influence the study results **(OC).**

Protocol deviation

Overall, 43 patients (33.9%) in the pirfenidone group and 52 patients (41.3%) in the placebo group had one or more major protocol deviations.

Table 5 ***Major Protocol Deviations (ITT Population)***

	Pirfenidone (N=127) n (%)	Placebo (N=126) n (%)
Patients with any major protocol deviation	43 (33.9)	52 (41.3)
Inclusion criteria	7 (5.5)	7 (5.6)
RBR ICF not signed but samples taken	2 (1.6)	5 (4.0)
6MWD <150 m or not done at screening	1 (0.8)	0
FEV_1/FVC <0.7	2 (1.6)	1 (0.8)
DLco <30% predicted value or not done at screening	3 (2.4)	1 (0.8)
Exclusion criteria	10 (7.9)	6 (4.8)
LFTs out of range or not done at screening	7 (5.5)	4 (3.2)
Dose of MMF not stable for at least 3 months prior to screening	0	1 (0.8)
Prednisone or non-MMF immunosuppressant within 4 weeks	1 (0.8)	0
Creatinine clearance out of range or not done at screening	2 (1.6)	1 (0.8)
Procedural	36 (28.3)	46 (36.5)
Dose titration schedule not adhered to	1 (0.8)	0
Re-screening if not performed as approved by SMT	0	1 (0.8)
Treatment with wrong IMP (not according to IxRS assignment)	1 (0.8)	1 (0.8)
AE requiring immediate report not reported as such	3 (2.4)	2 (1.6)
Failure to capture DLco recurrently	1 (0.8)	2 (1.6)
Failure to perform LFTs	3 (2.4)	3 (2.4)
Failure to reconsent or inadequate consent given	1 (0.8)	4 (3.2)
Treatment regimen not adhered to unless due to AE or intolerance	0	2 (1.6)
Use of prohibited concomitant therapy during the trial	4 (3.1)	1 (0.8)
Failure to not follow-up in case of increased QTc	3 (2.4)	2 (1.6)
Failure to capture FVC with a handheld spirometer on a regular basis	28 (22.0)	30 (23.8)

6MWD = 6-minute walk distance; AE = adverse event; DLco = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ICF = Informed Consent Form; IMP = investigational medicinal product; ITT = intent-to-treat; IxRS = interactive voice or web-based response system; LFTs (liver function tests) = AST (aspartate aminotransferase), ALT (alanine aminotransferase), bilirubin, and alkaline phosphatase; MMF = mycophenolate mofetil/sodium or mycophenolate acid; QTc = QT interval corrected using Fridericia's formula; RBR = research biosample repository; SMT = study management team.
Note: A patient may have multiple protocol deviations.
Source: Table 14.1.1.4 .

CHMP comment:

As per the CSR for study MA39189, the most commonly reported major protocol deviation (PD) was "failure to capture FVC handheld on a regular basis" (reported for 28 subjects [22.0%] in the pirfenidone group and 30 subjects [23.8%] in the placebo group). Clarify how "on a regular basis" was defined, and what actions were taken with subjects where this PD was reported. In addition, clarify if issues relating to the quality of home spirometry testing (e.g recording of biologically implausible values / data deemed non-acceptable quality) were considered as PDs. If it was considered a deviation, provide further details on the classification, incidence and any actions taken on identification of these issues. Alternatively, provide a justification if it was not considered a PD **(OC)**

Baseline data

Demographic and baseline characteristics were similar between the pirfenidone and placebo groups. The median age of patients was similar between the two groups (pirfenidone = 70.0 years and placebo = 69.0 years). The majority of patients were male (pirfenidone = 55.1% and placebo = 54.8%), White (pirfenidone = 94.5% and placebo = 97.6%), and not Hispanic or Latino (pirfenidone = 90.6% and placebo = 88.9%). The median height, weight, and body mass index at baseline were 166.0 cm, 80.8 kg, and 28.6 kg/m2 in the pirfenidone group and were similar to the placebo group.

Table 6 ***Demographic and Baseline Characteristics (ITT Population)***

	Pirfenidone (N=127)	Placebo (N=126)
Age (years) at screening		
n observed	127	126
Mean (SD)	68.0 (10.07)	67.7 (9.19)
Median	70.0	69.0
Q1 - Q3	61.0 - 76.0	63.0 - 74.0
Min - Max	38 - 85	26 - 85
Age categories [n (%)]		
<45 years	4 (3.1)	2 (1.6)
≥45 to <65 years	39 (30.7)	40 (31.7)
≥65 to <85 years	82 (64.6)	83 (65.9)
≥85 years	2 (1.6)	1 (0.8)
<65 years	43 (33.9)	42 (33.3)
≥65 years	84 (66.1)	84 (66.7)
Gender [n (%)]		
Male	70 (55.1)	69 (54.8)
Female	57 (44.9)	57 (45.2)
Race [n (%)]		
White	120 (94.5)	123 (97.6)
Black or African American	1 (0.8)	2 (1.6)
Asian	5 (3.9)	0
Native Hawaiian or other Pacific Islander	0	0
American Indian or Alaska Native	1 (0.8)	0
Unknown	0	1 (0.8)
Other	0	0
Ethnicity [n (%)]		
Hispanic or Latino	7 (5.5)	9 (7.1)
Not Hispanic or Latino	115 (90.6)	112 (88.9)
Not reported	5 (3.9)	5 (4.0)
Unknown	0	0
Weight (kg) at baseline		
n observed	127	126
Mean (SD)	82.5 (17.62)	81.4 (17.88)
Median	80.8	82.4
Q1 - Q3	71.0 - 94.0	69.1 - 94.4
Min - Max	40 - 150	43 - 120
Height (cm) at baseline		
n observed	127	126

	Pirfenidone (N=127)	Placebo (N=126)
Mean (SD)	165.5 (9.09)	166.1 (10.75)
Median	166.0	166.8
Q1 - Q3	158.0 - 172.5	159.0 - 173.0
Min - Max	145 - 185	132 - 189
BMI (kg/m²) at baseline		
n observed	127	126
Mean (SD)	30.1 (6.08)	29.4 (5.33)
Median	28.6	29.3
Q1 - Q3	26.5 - 32.9	26.2 - 32.7
Min - Max	16 - 64	16 - 46
Childbearing potential (female) [n (%)]		
Childbearing potential without contraceptive protection	0	1 (1.8)
Childbearing potential with contraceptive protection	2 (3.5)	2 (3.5)
Surgically sterilized	0	3 (5.3)
Postmenopausal	48 (84.2)	49 (86.0)
Premenarcheal	0	0
Non-childbearing potential	7 (12.3)	2 (3.5)

BMI = body mass index; ITT = intent-to-treat; Max = maximum; Min = minimum; Q = quartile; SD = standard deviation.
Percentages of females with childbearing potential were based on the total number of females included in the ITT population.
Source: Table 14.1.2.1

During Safety Follow-Up Period

The demographic and baseline characteristics were similar to the previously treated with pirfenidone and previously treated with placebo groups (ITT population), except for the percentage of female patients of non-childbearing potential (higher proportion in previously treated with pirfenidone group [15.0%] than in the previously treated with placebo group [3.9%]).

Tobacco Use History

A total of 64 patients (50.4%) in the pirfenidone group and 72 patients (57.1%) in the placebo group reported a history of tobacco use. The median pack years reported by smokers was 30.0 pack years in the pirfenidone group and 17.5 pack years in the placebo group.

Baseline Disease Characteristics

Overall, approximately 74% of patients in the study did not have a low-confidence diagnosis and were therefore assigned to the category of "UILD." The number of patients with UILD was similar between the pirfenidone and placebo groups (73.2% vs. 73.8%). The proportion of patients who fulfilled IPAF criteria was also similar between treatment groups (12.6% vs. 14.3%). The median time from ILD diagnosis to randomization was 11.0 months in the pirfenidone group and 12.8 months in the placebo group. All randomized patients had historical HRCT. Around one-third of patients included in the study had a historical surgical lung biopsy (pirfenidone group: 31.5%; placebo group: 38.1%). The median time from most recent surgical lung biopsy to randomization was lower in the pirfenidone group than in the placebo group (10.3 months vs. 16.3 months).

Table 7 ***UILD-Specific Baseline Characteristics – Time from ILD Diagnosis (ITT Population)***

	Pirfenidone (N=127)	Placebo (N=126)
Diagnosis of uILD (n [%])		
Low confidence RA-ILD	0	0
Low confidence SSc-ILD	0	1 (0.8)
Low confidence undifferentiated CTD-ILD	3 (2.4)	2 (1.6)
Low confidence cHP-ILD	10 (7.9)	9 (7.1)
Low confidence idiopathic NSIP-ILD	4 (3.1)	3 (2.4)
Low confidence sarcoidosis-ILD	0	0
Low confidence myositis-ILD	0	0
Low confidence other defined ILD	1 (0.8)	0
UILD	93 (73.2)	93 (73.8)
Fulfils criteria of IPAF	16 (12.6)	18 (14.3)
Time from ILD diagnosis to randomization (months)		
n observed	127	126
Mean (SD)	29.2 (39.27)	27.2 (35.22)
Median	11.0	12.8
Q1 - Q3	4.9 - 36.5	4.2 - 37.3
Min - Max	0 - 233	0 - 199
Number of patients with historical high-resolution computed tomography (n [%])	127 (100)	126 (100)
Time from most recent high-resolution computed tomography to randomization (months)		
n observed	127	126
Mean (SD)	5.3 (3.72)	5.3 (4.83)
Median	4.7	4.1
Q1 - Q3	2.0 - 8.0	1.8 - 7.6
Min - Max	0 - 14	0 - 36
Number of patients with historical surgical lung biopsy (n [%])	40 (31.5)	48 (38.1)
Time from most recent surgical lung biopsy to randomization (months)		
n observed	40	48
Mean (SD)	25.5 (43.69)	30.1 (36.58)
Median	10.3	16.3
Q1 - Q3	4.2 - 26.7	7.4 - 41.0
Min - Max	1 - 233	1 - 199

cHP = chronic hypersensitivity pneumonitis; CTD = connective tissue disease; ILD = interstitial lung disease; IPAF = interstitial pneumonia with autoimmune features; ITT = intent-to-treat; Max = maximum; Min = minimum; NSIP = non-specific interstitial pneumonia; Q = quartile; RA = rheumatoid arthritis; SD = standard deviation; SSc = systemic sclerosis; UILD = unclassifiable interstitial lung disease.
Source: Table 14.1.2.4

Table 8 ***Baseline Clinic Spirometry Test Results Measured at Site (ITT Population)***

	Pirfenidone (N=127)	Placebo (N=126)
FVC (L)		
n observed	127	126
Mean (SD)	2.36 (0.793)	2.38 (0.747)
Median	2.24	2.33
Q1 - Q3	1.77 - 2.85	1.91 - 2.81
FVC (% predicted)		
n observed	127	126
Mean (SD)	73.95 (18.815)	73.95 (19.974)
Median	71.00	71.50
Q1 - Q3	59.00 - 87.30	58.00 - 88.00
FEV_1 (L) / FVC (L) ratio		
n observed	127	126
Mean (SD)	0.821 (0.0663)	0.830 (0.0619)
Median	0.820	0.840
Q1 - Q3	0.780 - 0.860	0.780 - 0.870
DLco (% predicted)		
n observed	126	125
Mean (SD)	46.19 (12.403)	49.57 (13.931)
Median	44.55	48.00
Q1 - Q3	36.90 - 53.50	38.40 - 59.00
Hemoglobin-corrected DLco (mmol/min/kPa)		
n observed	126	125
Mean (SD)	3.56 (1.140)	4.01 (1.693)
Median	3.31	3.78
Q1 - Q3	2.74 - 4.28	3.05 - 4.58

DLco = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; ITT = intent-to-treat; Max = maximum; Min = minimum; Q = quartile; SD = standard deviation.
Source: Modified from Table 14.2.2.1 and Table 14.2.3.1.

The proportion of patients who stopped the test before 6 minutes was similar between treatment groups (7.9% vs. 6.3% for pirfenidone vs. placebo, respectively). The mean (SD) saturation at rest was higher than that of mean (SD) saturation after the test between both treatment groups. The proportion of patients who required oxygen after the test was low (19 patients in the pirfenidone group and 14 patients in the placebo group).

Table 9 ***Summary of 6-Minute Walking Test and Additional Oxygen Requirements at Baseline (ITT Population)***

	Pirfenidone (N=127)	Placebo (N=126)
Number of patients who performed the 6-minute walking test (n [%])	127 (100)	126 (100)
Number of patients who rested for at least 10 minutes before the test (n [%])	124 (97.6)	125 (99.2)
Number of patients who stopped the test before 6 minutes (n [%])	10 (7.9)	8 (6.3)
Number of patients needing O_2 during the test (n [%])	19 (15.0)	15 (11.9)
Oxyhemoglobin saturation at rest (%)		
n observed	127	126
Mean (SD)	95.8 (2.29)	96.0 (2.15)
Median	96.0	96.0
Q1 - Q3	95.0 - 97.0	95.0 - 97.0
Min - Max	89 - 100	90 - 100
Oxyhemoglobin saturation after the test (%)		
n observed	127	126
Mean (SD)	89.4 (6.03)	90.4 (5.51)
Median	90.0	92.0
Q1 - Q3	86.0 - 93.0	86.0 - 95.0
Min - Max	71 - 100	77 - 99

ITT = intent-to-treat; Max = maximum; Min = minimum; O_2 = oxygen; Q = quartile; SD = standard deviation.
Source: Modified from Table 14.1.2.8

Prior and Concomitant Medications

Overall, 125 patients (98.4%) in the pirfenidone group and 120 patients (96.8%) in the placebo group reported the use of at least one prior medication.

The most common classes of prior medications were ophthalmologicals (80 patients [63.0%] in the pirfenidone group and 61 patients [49.2%] in the placebo group), drugs for acid-related disorders (70 patients [55.1%] in the pirfenidone group and 78 patients [62.9%] in the placebo group), **corticosteroids for systemic use (65 patients [51.2%] in the pirfenidone group and 48 patients [38.7%] in the placebo group)**, antidiarrheals, intestinal anti-inflammatory/anti-infective agents (59 patients [46.5%] in the pirfenidone group and 49 patients [39.5%] in the placebo group), and stomatological preparations (53 patients [41.7%] in the pirfenidone group and 59 patients [47.6%] in the placebo group).

Almost all patients (126 patients [99.2%] in the pirfenidone group and 123 patients [99.2%] in the placebo group) reported the use of at least one concomitant medication. The most common top 5 classes of concomitant medications were ophthalmologicals (102 patients [80.3%] in the pirfenidone group and 87 patients [70.2%] in the placebo group), drugs for acid-related disorders (81 patients [63.8%] in the pirfenidone group and 89 patients [71.8%] in the placebo group), corticosteroids for systemic use (78 patients [61.4%] in the pirfenidone group and 65 patients [52.4%] in the placebo group), stomatological preparations (74 patients [58.3%] in the pirfenidone group and 73 patients [58.9%] in the placebo group), and antidiarrheals, intestinal anti-inflammatory/anti-infective agents (73 patients [57.5%] in the pirfenidone group and 66 patients [53.2%] in the placebo group)

CHMP comment

In general, demographic characteristics were balanced between the treatment groups. The median age was 70.0 years for the pirfenidone group and 69.0 years for the placebo group.

Overall, approximately 74% of patients in the study did not have a low-confidence diagnosis and were therefore assigned to the category of "UILD." The number of patients with UILD was similar between the pirfenidone and placebo groups (73.2% vs. 73.8%). The proportion of patients who fulfilled IPAF criteria was also similar between treatment groups (12.6% vs. 14.3%). All randomized patients had historical HRCT. Around one-third of patients included in the study had a historical surgical lung biopsy (pirfenidone group: 31.5%; placebo group: 38.1%).

The baseline clinic spirometry test results measured at site were balanced between the treatment groups with the mean FVC (% predicted) 73.95 recorded in both treatment groups.

In the trial, patients could use concomitant therapy with MMF. High dose systemic corticosteroids (15 mg/d of prednisolone or equivalent) for longer than 28 days, immunosuppressive therapies (e.g. azathioprine), treatment with NAC for fibrotic lung disease were not allowed. It is noted however that corticosteroids for systemic use were taken by 78 patients [61.4%] in the pirfenidone group and 65 patients [52.4%] in the placebo group. The applicant should provide further details in relation to the use of corticosteroid in the study and comment on their potential influence of the study results **(OC).**

Numbers analysed

Table 10 ***Overview of Analysis Population***

Population	Randomized Pirfenidone (N=127) n (%)	Randomized Placebo (N=126) n (%)
ITT	127 (100.0%)	126 (100.0%)
Safety	127 (100.0%)	124 (98.4%)
Safety follow-up[a]	94 (74.0%)	110 (87.3%)

ITT = intent-to-treat

[a] In safety follow-up period, all patients received open-label treatment with pirfenidone and safety follow-up population included the patients previously treated with either pirfenidone or placebo in the double-blind period.

Outcomes and estimation

The primary efficacy endpoint was to evaluate the rate of decline in FVC measured in millilitres with daily home spirometer over the 24-week, double-blind treatment period.

Analysis of the primary endpoint, as pre-specified in the SAP Version 2.0, was rendered invalid due to unforeseen issues with the recorded home spirometry values and biologically implausible data points.

Analysis of the primary endpoint was impacted by high variability in 1) predicted 24-week change and 2) home spirometry values. Firstly, patients with short observation periods (and few measurements) led to predicted 24-week changes in FVC that were physiologically implausible e.g., daily home FVC values of <500 mL or >6 L and predicted 24-week changes in FVC as extreme as +33 L.

Secondly, in some cases, the spirometer device recorded physiologically implausible individual values that affected the calculation of the predicted 24-week change. These outliers meant that the planned statistical model could not be applied to the primary endpoint data, because the statistical assumptions (requiring continuous data with independent observations in each sample that are normally distributed with equal variances) for applying a Student's t-test were not fulfilled. This resulted in a highly biased

estimate of the group means (-17.8 mL for the pirfenidone group and 116.6 mL for the placebo group) which did not provide a robust characterization of the data.

In the primary analysis, overall, 32166 (75.7%) acceptable quality measurements and 1899 (4.5%) non-acceptable quality measurements were recorded.

In the updated analysis, overall, 25693 (60.4%) acceptable quality measurements and 8372 (19.7%) non-acceptable quality measurements were recorded. Of the 32166 (75.7%) acceptable quality measurements, 25140 (59.1%) were still acceptable in the updated analysis and a total of 7026 (16.5%) acceptable quality measurements in the primary analysis were non-acceptable quality measurements in the updated analysis.

Of the 1899 (4.5%) non-acceptable quality measurements, 1346 (3.2%) were still non-acceptable in the updated analysis and a total of 553 (1.3%) non-acceptable quality measurements in the primary analysis were acceptable quality measurements in the updated analysis. By analyzing the flow curves manually, the wrong flow curves that were qualified as good blows and acceptable measurements during the primary analysis or correct flow curves that were qualified as non-acceptable blows, were detected during the updated analysis. The applicant contends that the re-read has increased the confidence of the data points and therefore the analysis of these data can be deemed more trustworthy.

Table 11 ***Quality of Daily Home Spirometry Measurements Included in the Analyses (ITT Population)***

	Updated Analysis (2020)[b]		
Primary Analysis (2019)[a]	**Acceptable Quality Measurements**	**Non-Acceptable Quality Measurements**	**Total Number of Blows for Primary Analysis**
Total no. of patients (N=253)			
Total number of expected home FVC measurements (n [%])			42504 (100.0)
Number of measurements with acceptable quality measurements (n [%])	25140 (59.1)	7026 (16.5)	32166 (75.7)
Number of measurements with non-acceptable quality measurements (n [%])	553 (1.3)	1346 (3.2)	1899 (4.5)
Total number of blows for updated analysis	25693 (60.4)	8372 (19.7)	34065 (80.1)

FVC = forced vital capacity; ITT = intent-to-treat.
[a] Acceptable quality measurements included in the primary analysis were selected with the quality device flag DPQLTFL=YES.
[b] Acceptable quality measurements included in the updated analysis were selected with the alternative quality flag QCgrade=130.
Source: Table 14.2.1.5

In the primary analysis, the pre-planned statistical model was not robustly applicable to the primary endpoint of this study. To provide a more robust parameter of central tendency, the median FVC decline estimate over 24 weeks was calculated and yielded declines of -87.7 mL in the pirfenidone group and -157.1 mL in the placebo group, which represented a treatment difference of 69.4 mL in favor of pirfenidone.

The updated analysis of the home spirometry measurements showed estimates of the group means (-90.3 mL for the pirfenidone group and 125.6 mL for the placebo group). The median FVC decline estimate over 24 weeks yielded declines of -85.6 mL in the pirfenidone group and -183.5 mL in the placebo group, which represented a treatment difference of 97.8 mL in favor of pirfenidone (p=0.0274).

Table 12 ***Summary of FVC Decline (mL) from Baseline to Week 24 Measured by Home Spirometry Including Median Comparison (ITT Population)***

	Pirfenidone (N=127)	Placebo (N=126)	Pirfenidone vs. Placebo
FVC decline (mL) at Week 24, primary analysis (2019)[a]			
n observed	124	123	
Mean	-17.8	116.6	-134.4
Median	-87.7	-157.1	69.4
Q1 - Q3	-338.1 - 148.6	-370.9 - 70.1	
Min - Max	-5799 - 16411	-7256 - 33794	
95% CI[a]	-311.6; 276.0	-451.9; 685.2	-772.2; 503.4
p-value[b]			0.6781
p-value[c]			0.2187
FVC decline (mL) at Week 24, updated analysis (2020)[a]			
n observed	116	116	
Mean	-90.3	125.6	-216.0
Median	-85.6	-183.5	97.8
Q1 - Q3	-312.8 - 122.8	-360.9 - 5.6	
Min - Max	-1467 - 674	-1204 - 33794	
95% CI[a]	-157.0; -23.7	-458.4; 709.6	-803.6; 371.7
p-value[b]			0.4682
p-value[c]			0.0274

CI = confidence interval; FVC = forced vital capacity; ITT = intent-to-treat; Max = maximum; Min = minimum; Q = quartile; vs. = versus.

[a] FVC decline (mL) at Week 24 measured with home spirometry and estimated from linear regression model. Two-sided CI for mean value was based on percentiles of the t-distribution.

[b] Comparison of mean FVC decline between treatment groups using a Student's t-test with a two-sided significance level of 0.05.

[c] A two-sample Wilcoxon test was used for treatment comparison.

Source: Table 14.2.1.1.

Different tests for normality of the underlying distribution function were applied and yielded constant p-values below 0.05, which indicated that the assumption for performing Student's t-test on the primary endpoint has not been fulfilled in the primary analysis.

Sensitivity Analysis of Primary Endpoint

A summary of FVC decline from baseline to Week 24 measured with home spirometry based on mixed models is provided in Table 13. During the primary analysis, FVC decline estimate (SE) at Week 24 in pirfenidone vs. placebo was 86.45 (47.14) mL and was nonsignificant (95% CI: -5.94; 178.84; p=0.0667). The updated analysis showed that FVC decline estimate (SE) at Week 24 in pirfenidone vs. placebo was 113.02 (39.87) mL and was significant (95% CI: 34.87; 191.17; p=0.0046). The updated analysis confirmed the results of the primary analysis.

Table 13 ***Summary of FVC Decline (mL) from Baseline to Week 24 Measured with Home Spirometry Based on Mixed Models (ITT Population)***

	Pirfenidone (N=127)	Placebo (N=126)	Pirfenidone vs. Placebo
FVC decline (mL) Week 24 primary analysis (2019)[a]			
n observed	126	126	
Estimate	-74.82	-161.27	86.45
95% CI	-140.87; -8.76	-225.95; -96.58	-5.94;178.84
SE	33.70	33.00	47.14
P-value			0.0667
FVC decline (mL) Week 24 with strata primary analysis[b]			
n observed	126	126	
Estimate	-74.78	-161.25	86.48
95% CI	-140.91; -8.64	-226.01; -96.49	-6.02; 178.97
SE	33.74	33.04	47.19
P-value			0.0669
FVC decline (mL) Week 24 updated analysis (2020)[a]			
n observed	118	120	
Estimate	-71.69	-184.71	113.02
95% CI	-127.31; -16.07	-239.67; -129.75	34.87; 191.17
SE	28.38	28.04	39.87
P-value			0.0046
FVC decline (mL) Week 24 with strata updated analysis[b]			
n observed	118	120	
Estimate	-71.64	-184.69	113.04
95% CI	-127.26; -16.02	-239.64; -129.73	34.90; 191.19
SE	28.38	28.04	39.87
P-value			0.0046

CHMP comment:

The primary efficacy endpoint in this study was the rate of decline in FVC measured in millilitres with daily home spirometer over the 24-week, double-blind treatment period. The original primary analysis performed in 2019 showed unreliable results with high intra-individual variability and extreme outliers in home spirometry values in both treatment groups. Physiologically implausible values were recorded.

In order to be confident that only truly acceptable blows were included in the analysis, an external organization (eResearchTechnology Inc.) was contracted by the applicant to perform a manual re-read of 32166 flow curves. The validity of the process of manual re-read of flow curves in spirometry and maintaining of the blind during this review is not clear and it should be discussed by the applicant **(OC).**

Based on this re-read almost 20 % of measurements with non-acceptable quality were removed from the dataset.

The updated analysis of the home spirometry measurements performed in 2020 showed the median FVC decline over 24 weeks of -85.6 mL in the pirfenidone group and -183.5 mL in the placebo group, which represented a treatment difference of 97.8 mL in favour of pirfenidone (p=0.0274). The applicant claims that these results of the updated analysis of the primary endpoint are more reliable, which is not supported.

There are still extreme outliers in home spirometry values and the conference intervals are very broad. Therefore, it is not agreed that the results of this post hoc analysis (therefore not controlled for type one error), is used by the applicant to claim treatment benefits of pirfenidone in patients with unclassifiable ILDs **(MO).**

In relation to the primary efficacy results, it is not clear from the information provided by the applicant why issues relating to the quality of data for home spirometry measurements were not identified during the trial (or if they were identified, why they were not corrected).
The applicant is requested to clarify the following:
- What oversight mechanisms were in place for both investigators/sites and for the sponsor to ensure that subjects were conducting daily spirometry assessments and to ensure the quality of the results being recorded. In addition, provide clarification on whether these measures were sufficient to identify issues with the conduct or quality of spirometry assessments during the trial, and what actions were taken to prevent reoccurrence of any issues that were identified.
- Provide details on how data that was collected through the daily spirometry assessment was handled throughout the study, including any data validation or reconciliation activities that were conducted. In particular, the applicant should clarify whether the investigators/sites and/or sponsor had oversight of the data as it was being collected, and if there were any checks or controls in place (whether automated/manual, systematic or otherwise) to identify either where data wasn't being collected, or where data was being collected that was not of sufficient quality (e.g. biologically implausible data). If no such checks or controls were in place during the study, but were implemented as part of data review/cleaning at the end of the study, please state and outline when such activities commenced **(MO).**

Secondary endpoints

FVC Decline (mL) from Baseline to Week 24 Measured by Clinic Spirometry (ITT Population).

Analyses of this endpoint were repeated due to additional data cleaning activities that were not conducted during the primary analysis. In addition, as per FDA recommendation, additional analyses were performed and included linear mixed effects modelling, a tipping point analysis of FVC measured by clinic spirometry to investigate the robustness of the data collected, and the statistical analyses performed for the corresponding endpoints.

During the primary analysis, at Week 24, mean FVC declines for pirfenidone and placebo were -17.8 mL and -113.0 mL, respectively, with an overall mean difference of 95.3 mL (Student's t-test p=0.0018; 95% CI: 35.9, 154.6). Over 24 weeks, >5% and >10% categorical declines in FVC (percent predicted) were higher in the placebo group than in the pirfenidone group (>5% decline, odds ratio: 0.42; 95% CI: 0.25, 0.69; p=0.0006; >10% decline, odds ratio: 0.44; 95% CI: 0.23, 0.84 p=0.0114).

The p-values were descriptive only. The pre-specified secondary endpoint, change of percent predicted FVC measured by clinic spirometry from baseline until end of treatment, analyzed by rank ANCOVA with change from baseline as outcome variable and standardized rank baseline value as covariate, resulted in a p-value of 0.0383.

Per updated analysis, at Week 24, mean FVC declines for pirfenidone and placebo were -24.8 mL and -109.1 mL, respectively, with an overall mean difference of 84.3 mL (Student's t-test p=0.0096; 95% CI: 20.7, 147.8). Over 24 weeks, >5% and >10% categorical declines in FVC (percent predicted) were higher in the placebo group than in the pirfenidone group (>5% decline, odds ratio: 0.43; 95% CI: 0.26, 0.71; p=0.0009; >10% decline, odds ratio: 0.46; 95% CI: 0.24, 0.88; p=0.0168). The p-values were descriptive only. The pre-specified secondary endpoint of change in percent predicted FVC measured by clinic spirometry from baseline until the end of treatment, analyzed by rank ANCOVA, with change from baseline as outcome variable and standardized rank baseline value as covariate, resulted in a p-value of 0.0239.

Table 14 ***Summary of FVC Decline (mL) from Baseline to Week 24 Measured by Clinic Spirometry (ITT Population)***

	Pirfenidone (N=127)	Placebo (N=126)	Pirfenidone vs. Placebo
Primary Analysis (2019)			
FVC decline (mL)[a]			
n observed	118	119	
Mean	-17.8	-113.0	95.3
95% CI[a]	-62.6; 27.0	-152.5; -73.6	35.9; 154.6
p-value[b]			0.0018
Change in FVC (% predicted) (rank ANCOVA)[c]			
p-value			0.0383
Categorical decline in FVC (% predicted)[d]			
>5%	47 (37.0)	74 (58.7)	
Odds ratio			0.42
95% CI			0.25; 0.69
p-value			0.0006
>10%	18 (14.2)	34 (27.0)	
Odds ratio			0.44
95% CI			0.23; 0.84
p-value			0.0114
Updated Analysis (2020)			
FVC decline (mL)[a]			
n observed	114	118	
Mean	-24.8	-109.1	84.3
95% CI[a]	-72.6; 22.9	-151.7; -66.5	20.7; 147.8
p-value[b]			0.0096
Change in FVC (% predicted) (rank ANCOVA)[c]			
p-value			0.0239
Categorical decline in FVC (% predicted)[d]			
>5%	47 (37.0)	73 (57.9)	
Odds ratio			0.43
95% CI			0.26; 0.71
p-value			0.0009
>10%	18 (14.2)	33 (26.2)	
Odds ratio			0.46
95% CI			0.24; 0.88
p-value			0.0168

ANCOVA = analysis of covariance; CI = confidence interval; FVC = forced vital capacity; ITT = intent-to-treat; vs. = versus.
Note: p-values were not adjusted for multiplicity and were provided for descriptive purpose only.
[a] FVC decline (mL) at Week 24 measured by clinic spirometry and estimated from linear regression model. Only patients with at least two post-baseline measurements were included in the analysis. Two-sided CI for mean value was based on percentiles of the t-distribution.
[b] Mean FVC decline comparison between treatment groups using a Student's t-test with a two-sided significance level of 0.05.
[c] Changes from baseline to Week 24 or early discontinuation visit were compared between the treatment arms using a rank ANCOVA with standardized rank change from baseline as outcome variable and standardized rank baseline value as covariate.
[d] Treatment comparison was analyzed using a Cochran-Mantel-Haenszel test stratified by randomization stratification factors.
Source: Modified from Table 14.2.2.2

Table 15 ***Summary of FVC Decline (mL) from Baseline to Week 24 Measured by Clinic Spirometry Based on Mixed Models (ITT Population)***

	Pirfenidone (N=127)	Placebo (N=126)	Pirfenidone vs. Placebo
FVC decline (mL) Week 24[a]			
n observed	127	125	
Estimate	-14.14	-105.66	91.52
95% CI	-55.81; 27.52	-145.81; -65.52	33.66; 149.38
SE	21.23	20.46	29.49
p-value			0.0020
FVC decline (mL) Week 24 with strata[b]			
n observed	127	125	
Estimate	-14.13	-105.66	91.53
95% CI	-55.80; 27.53	-145.81; -65.52	33.67; 149.39
SE	21.23	20.46	29.49
p-value			0.0020

CI = confidence interval; FVC = forced vital capacity; ITT = intent-to-treat; SE = standard error; vs. = versus.

[a] The time-adjusted mean FVC decline was estimated by a repeated measures mixed model with patient effects fitted as random and day of measurement and randomized treatment fitted as fixed effects.
p-values were not adjusted for multiplicity and were provided for descriptive purpose only.

[b] The time-adjusted mean FVC decline were estimated by a repeated measures mixed model with patient effects fitted as random and day of measurement and randomized treatment plus the stratification factors fitted as fixed effects.
p-values were not adjusted for multiplicity and were provided for descriptive purpose only.

Missing data sensitivity analysis

A summary of the tipping point analysis for the FVC decline from baseline to Week 24 measured by clinic spirometry based on mixed models with shifts for pirfenidone and placebo (ITT population) is provided in the table below. The header rows show the shifts applied to dropouts in the placebo group, with "20" meaning a 20 mL/24 week rate of increase in FVC imposed on the assumed background MAR rate of decline in placebo (penalty); similarly, the header columns show a range of shifts applied to dropouts in the pirfenidone arm, with "-80" meaning an additional 80 mL/year rate of decline imposed on the assumed background MAR rate of decline in pirfenidone. The cells provide p-values for the comparisons between the pirfenidone and placebo groups for the corresponding shifts in placebo pirfenidone.

The results indicate that a shift from a positive outcome, i.e., a p-value $\leqslant$0.05, and a negative outcome, i.e., p-value >0.05, occurs at approximately a difference in estimated semi-annual slopes between pirfenidone and placebo of 60 mL. Assuming the same linear decline in the pirfenidone and placebo groups from week 24 to week 48, this difference represents an annual difference in decline of FVC of approximately 120 mL and could be considered a clinically meaningful treatment effect size in this indication. The results of this sensitivity analysis thus support the primary analysis.

Table 16 ***Summary of Tipping Point Analysis for FVC Decline (mL) from Baseline to Week 24 Measured by Clinic Spirometry Based on Shifts for Pirfenidone and Placebo (ITT Population)***

Shift S1 (Change in mL/24 weeks)		Shift S2 (Change in mL/24 weeks) Placebo						
Pirfenidone	Estimate	-40	-20	0	20	40	60	80
-80	Treatment difference	66.63	61.72	56.81	51.89	46.98	42.07	37.15
	p-value	0.0298	0.0435	0.0628	0.0894	0.1252	0.1719	0.2309
-60	Treatment difference	75.76	70.85	65.94	61.03	56.12	51.21	46.29
	p-value	0.0122	0.0187	0.0285	0.0428	0.0632	0.0917	0.13
-40	Treatment difference	84.89	79.98	75.07	70.16	65.25	60.34	55.42
	p-value	0.0046	0.0073	0.0117	0.0185	0.029	0.0445	0.0668
-20	Treatment difference	94.02	89.11	84.2	79.28	74.37	69.46	64.55
	p-value	0.0016	0.0026	0.0044	0.0073	0.0121	0.0198	0.0315
0	Treatment difference	103.14	98.23	93.32	88.4	83.49	78.58	73.67
	p-value	0.0005	0.0009	0.0015	0.0027	0.0047	0.0081	0.0137

Treatment differences and p-values were calculated from random slope models with effects for strata and time x treatment, based on 100 imputed datasets using sequential regression with shift parameters S1 applied to the pirfenidone arm and S2 applied to the placebo arm.
Source: Table 14.2.2.8

Descriptive Analysis

Mean (SD) FVC values at baseline and Week 24 in the pirfenidone group were 2.36 (0.793) L and 2.37 (0.863) L, respectively, whereas the values in the placebo group were 2.38 (0.747) L and 2.34 (0.773) L, respectively. Among patients who completed 24 weeks of treatment, the mean FVC decreased from baseline by -0.02 (0.239) L in the pirfenidone group and by -0.08 (0.240) L in the placebo group.

Mean (SD) FVC (percent predicted) values at baseline and Week 24 in the pirfenidone group were 73.95 (18.815)% and 72.95 (20.819)%, respectively, whereas the values in the placebo group were 73.95 (19.974)% and 73.55 (22.383)%, respectively. Among the patients who completed 24 weeks of treatment, the mean FVC (percent predicted) decreased from baseline by -0.39 (6.938)% in the pirfenidone group and by -2.47 (9.213)% in the placebo group.

Table 17 ***Site spirometry test results measured at site and changes from baseline over time (ITT Population). Roche-MA39189-uILD Final Analysis (Database Snapshot Date:06-Apr-2020)***

Parameter/ Visit	Pirfenidone (N=127) Value	Pirfenidone (N=127) Change from Baseline	Placebo (N=126) Value	Placebo (N=126) Change from Baseline
FVC (L)				
Baseline				
n observed	127		126	
Mean (std)	2.36 (0.793)		2.38 (0.747)	
Median	2.24		2.33	
Q1 - Q3	1.77 - 2.85		1.91 - 2.81	
Min - Max	1.0 - 5.2		0.9 - 5.5	
Missing	0		0	
Week 4				
n observed	120	120	121	121
Mean (std)	2.37 (0.818)	0 (0.205)	2.37 (0.786)	0 (0.242)
Median	2.24	0	2.31	-0.02
Q1 - Q3	1.79 - 2.89	-0.10 - 0.10	1.88 - 2.82	-0.09 - 0.06
Min - Max	1.1 - 5.2	-0.7 - 0.9	0.7 - 5.8	-1.3 - 1.0
Missing	0	0	0	0
Week 8				
n observed	115	115	117	117
Mean (std)	2.37 (0.822)	0.01 (0.261)	2.36 (0.816)	-0.03 (0.207)
Median	2.24	0.01	2.32	-0.06
Q1 - Q3	1.80 - 2.88	-0.09 - 0.13	1.83 - 2.74	-0.13 - 0.04
Min - Max	1.1 - 4.9	-1.6 - 0.9	0.8 - 6.7	-0.7 - 1.2
Missing	1	1	0	0
Week 12				
n observed	110	110	114	114
Mean (std)	2.37 (0.820)	0.01 (0.246)	2.35 (0.773)	-0.04 (0.189)
Median	2.24	0	2.25	-0.05
Q1 - Q3	1.83 - 2.86	-0.10 - 0.13	1.82 - 2.82	-0.13 - 0.04
Min - Max	1.0 - 5.1	-1.4 - 0.9	0.8 - 5.5	-0.7 - 0.8
Missing	1	1	1	1
Week 16				
n observed	103	103	113	113
Mean (std)	2.41 (0.860)	0.02 (0.227)	2.31 (0.782)	-0.08 (0.199)
Median	2.28	0	2.30	-0.08
Q1 - Q3	1.75 - 2.90	-0.12 - 0.15	1.75 - 2.72	-0.19 - 0.02
Min - Max	1.1 - 5.2	-0.7 - 0.9	0.6 - 5.6	-0.8 - 0.5
Missing	1	1	2	2
Week 20				
n observed	102	102	115	115
Mean (std)	2.40 (0.866)	0.01 (0.257)	2.30 (0.796)	-0.10 (0.224)
Median	2.28	0.02	2.29	-0.11
Q1 - Q3	1.78 - 2.87	-0.18 - 0.16	1.79 - 2.66	-0.24 - 0.03
Min - Max	0.9 - 4.9	-0.6 - 0.9	0.6 - 5.9	-0.8 - 0.6
Missing	1	1	0	0
Week 24				
n observed	101	101	112	112
Mean (std)	2.37 (0.863)	-0.02 (0.239)	2.34 (0.773)	-0.08 (0.240)
Median	2.25	0	2.36	-0.09
Q1 - Q3	1.76 - 2.83	-0.16 - 0.12	1.80 - 2.79	-0.21 - 0.03
Min - Max	1.0 - 5.1	-0.6 - 0.6	0.6 - 5.1	-0.8 - 0.7
Missing	0	0	2	2
Early discontinuation				
n observed	18	18	5	5
Mean (std)	2.08 (0.708)	-0.07 (0.196)	2.01 (0.106)	-0.37 (0.439)
Median	1.97	-0.06	1.99	-0.14
Q1 - Q3	1.44 - 2.67	-0.13 - 0.09	1.97 - 2.04	-0.60 - -0.08
Min - Max	1.0 - 3.3	-0.5 - 0.2	1.9 - 2.2	-1.0 - 0
Missing	3	3	3	3

Mean (SD) FVC (percent predicted) values at baseline and Week 24 in the pirfenidone group were 73.95 (18.815)% and 72.95 (20.819)%, respectively, whereas the values in the placebo group were 73.95 (19.974)% and 73.55 (22.383)%, respectively. Among the patients who completed 24 weeks of

treatment, the mean FVC (percent predicted) decreased from baseline by -0.39 (6.938)% in the pirfenidone group and by -2.47 (9.213)% in the placebo group.

Change from Baseline in Percent Predicted DLco

Mean (SD) DLco (percent predicted) values at baseline and Week 24 in the pirfenidone group were 46.19 (12.403)% and 45.45 (13.983)%, respectively, whereas the values in the placebo group were 49.57 (13.931)% and 48.57 (15.366)%, respectively. Among the patients who completed 24 weeks of treatment, the mean (SD) DLco (percent predicted) decreased from baseline by -0.65 (7.113)% in the pirfenidone group and by -2.48 (8.893)% in the placebo group.

Mean (SD) hemoglobin corrected DLco values at baseline and Week 24 in the pirfenidone group were 3.56 (1.140) mmol/min/kPa and 3.55 (1.159) mmol/min/kPa, respectively, whereas the values in the placebo group were 4.01 (1.693) mmol/min/kPa and 3.85 (1.757) mmol/min/kPa, respectively. Among the patients who completed 24 weeks of treatment, the mean (SD) hemoglobin corrected DLco decreased from baseline by -0.09 (0.605) mmol/min/kPa in the pirfenidone group and by -0.29 (1.856) mmol/min/kPa in the placebo group.

Table 18 ***DLco (Percent Predicted) Results and Changes from Baseline to Week 24 (ITT Population)***

	Pirfenidone (N=127)	Placebo (N=126)
Mean (SD)	-0.09 (0.605)	-0.29 (1.856)
Median	-0.06	-0.17
Q1 - Q3	-0.37 - 0.23	-0.49 - 0.10
Min - Max	-2.3 - 2.7	-8.7 - 9.6

DLco = diffusing capacity of the lung for carbon monoxide; ITT = intent-to-treat; Max = maximum; Min = minimum; Q = quartile; SD = standard deviation.
Source: Modified from Table 14.2.3.1.

Change from baseline in categorical decline in DLco (percent predicted) analyzed by logistic regression resulted in a p-value of 0.0150. Change from baseline DLco (percent predicted) analyzed by rank ANCOVA resulted in a p-value of 0.1191 (p-values were descriptive only). A categorical decline with >15% absolute decrease in DLco (percent predicted) was higher for the placebo group than for the pirfenidone group (odds ratio: 0.15; 95% CI: 0.03, 0.69).

Change in 6MWD in Meters

Mean (SD) 6MWD at baseline and Week 24 in the pirfenidone group were 391.6 (114.93) m and 397.1 (131.08) m, respectively, whereas the values in the placebo group were 394.0 (108.09) m and 369.8 (125.25) m, respectively. Among the patients who completed 24 weeks of treatment, the mean 6MWD showed reduced declines in the pirfenidone group (-2.0 [68.11] m) compared with the placebo group (-26.7 [79.32] m).

Table 19 ***6-Minute Walking Distance Test Results and Changes from Baseline***

Over Time(ITT Population)

	Pirfenidone (N=127)	Placebo (N=126)
Distance walked (m)		
Baseline		
n observed	127	126
Mean (SD)	391.6 (114.93)	394.0 (108.09)
Median	372.0	395.0
Q1 - Q3	303.0 - 487.0	325.0 - 472.0
Min - Max	150 - 669	160 - 635
Week 24		
n observed	99	108
Mean (SD)	397.1 (131.08)	369.8 (125.25)
Median	400.0	380.0
Q1 - Q3	305.0 - 513.0	290.0 - 464.5
Min - Max	60 - 679	60 - 663
Change from baseline		
n observed	99	108
Mean (SD)	-2.0 (68.11)	-26.7 (79.32)
Median	0	-12.0
Q1 - Q3	-39.0 - 40.0	-53.5 - 10.5
Min - Max	-274 - 189	-293 - 249

6MWD = 6-minute walk distance; ITT = intent-to-treat; Max = maximum; Min = minimum; Q = quartile; SD = standard deviation.
Source: Modified from Table 14.2.4.1.

Change from baseline in categorical decline in 6MWD analyzed by logistic regression resulted in a p-value of 0.8574. Change from baseline in 6MWD (m) analyzed by rank ANCOVA resulted in a p-value of 0.0299. Categorical decline with >50 m absolute decrease in 6MWD was similar between treatment groups (odds ratio: 0.95; 95% CI: 0.55, 1.65)

Incidence of and Time to First Investigator-Reported Acute Exacerbations

Overall, **5 patients (3.9%)** in the pirfenidone group and **7 patients (5.6%)** in the placebo group had at least one acute exacerbation. The risk of experiencing acute exacerbations was numerically lower in the pirfenidone group than in the placebo group (HR, 0.85; 95% CI: 0.26, 2.78; p=0.7871). The median time to the event was not calculable.

Non-Elective Hospitalization

Overall, the incidences of all-cause hospitalizations were similar between treatment groups (**12.6% in thepirfenidone group vs. 10.3% in the placebo group).**

A summary of time from randomization to the first occurrence of all-cause non-elective hospitalization and respiratory-related non-elective hospitalization (ITT population) is provided in incidences of respiratory-related non-elective hospitalizations were similar between the pirfenidone group and the placebo group (3.9% and 4.0%, respectively).
The risk of occurrence of respiratory-related non-elective hospitalization was numerically lower in the pirfenidone group compared with the placebo group (HR: 1.04; 95% CI: 0.30, 3.59)

PFS, Alternatively Defined as Time to First Occurrence of >10% Relative Decline in FVC (Measured by Clinic Spirometry), Non-Elective Respiratory Hospitalization, or Death

Overall, 40 patients (31.5%) in the pirfenidone group and 49 patients (38.9%) in the placebo group were reported to have experienced events. The median time to an event was not calculable. The risk of

time to the first occurrence of >10% relative decline in FVC, non-elective respiratory hospitalization, or death was numerically lower in the pirfenidone group compared with the placebo group (HR: 0.82; 95% CI: 0.54, 1.24; p=0.3386).

Time to Death from any Cause and Time to Death from Respiratory Diseases

Overall, 1 patient each in the pirfenidone group and the placebo group were reported to have experienced events that led to death.

Patient-reported outcomes

George's respiratory questionnaire scores

Among the patients who completed 24 weeks of treatment, there was a slight increase in mean (SD) SGRQ total score from baseline to Week 24 (0.05 [12.549] in the pirfenidone group and 0.85 [13.383] in the placebo group). Overall, the difference in mean change in SGRQ total score from baseline to Week 24 (-4.13) was numerically in favor of the pirfenidone group compared with the placebo group (p=0.1851).

UNIVERSITY OF CALIFORNIA, SAN DIEGO–SHORTNESS OF BREATH QUESTIONNAIRE SCORES

Among the patients who completed 24 weeks of treatment, there was an increase in mean (SD) UCSD-SOBQ total score from baseline to Week 24 (5.21 [18.701] in the pirfenidone group and 5.30 [22.078] in the placebo group). Overall, the mean change in UCSD-SOBQ total score from baseline to Week 24 (-3.45) was numerically in favor of the pirfenidone group compared with the placebo group (p=0.8289).

LEICESTER COUGH QUESTIONNAIRE SCORES

Among the patients who completed 24 weeks of treatment, there was an increase in mean (SD) Leicester Cough Questionnaire total score from baseline to Week 24 (0.35 [2.884] in the pirfenidone group and 0.04 [3.702] in the placebo group). Overall, the difference in mean change in Leicester Cough Questionnaire total score from baseline to Week 24 (1.00) was numerically in favour of the pirfenidone group compared with the placebo group (p=0.2019).

Cough visual analog scale scores

Among the patients who completed 24 weeks of treatment, there was a decrease in mean (SD) cough VAS score from baseline to Week 24 in the pirfenidone group (-2.52 [26.720]) and an increase in the placebo group (0.78 [30.121]). Overall, the difference in mean change in cough VAS scores from baseline to Week 24 (-3.03) was numerically in favor of the pirfenidone group compared with the placebo group (p=0.3372).

CHMP comment

FVC Decline (mL) from baseline to week 24 measured by clinic spirometry was a secondary endpoint in this study. The results of the spirometry measurements recorded during sites visits seemed to be more reliable although the analyses of this endpoint were also repeated "due to additional data cleaning activities that were not conducted during the primary analysis". The applicant should clarify why these cleaning activities needed to be performed for this endpoint **(MO)**

The results of the primary analysis as well as updated analysis of this secondary endpoint showed a smaller magnitude of decline in FVC in the pirfenidone as compared to the placebo group.

During the primary analysis, at Week 24, mean FVC declines for pirfenidone and placebo were -17.8 mL and -113.0 mL, respectively, with an overall mean difference of 95.3 mL (Student's t-test p=0.0018; 95% CI: 35.9, 154.6). Over 24 weeks, >5% and >10% categorical declines in FVC (percent predicted) were higher in the placebo group than in the pirfenidone group (>5% decline, odds ratio: 0.42; 95% CI: 0.25, 0.69; p=0.0006; >10% decline, odds ratio: 0.44; 95% CI: 0.23, 0.84 p=0.0114). Per updated analysis, at Week 24, mean FVC declines for pirfenidone and placebo were -24.8 mL and -109.1 mL, respectively, with an overall mean difference of 84.3 mL (Student's t-test p=0.0096; 95% CI: 20.7, 147.8).

It needs to be highlighted however, as this endpoint was not included in the multiplicity control strategy, these results cannot be considered as pivotal. In addition, the duration of the observation period was too short, as at least 52 weeks double-blind treatment period would be expected.

DLco and change in 6-minute walk distance were also investigated as secondary endpoints. However, these endpoints were not included in the multiplicity control strategy and robustness of results with respect to missing data assumptions has not been examined.

In relation to the mean changes in DLco (percent predicted) from baseline at Week 24 endpoint there was no difference between the treatment groups. A categorical decline with >15% absolute decrease in DLco (percent predicted) was higher in the placebo group than the pirfenidone group (odds ratio: 0.15; 95% CI: 0.03, 0.69; p=0.0150).

In relation to the Mean (SD) changes in 6MWD from baseline at Week 24 analysed by rank ANCOVA resulted in a p-value of 0.0299 (showing improvements in patients receiving pirfenidone) however, categorical decline with >50 m absolute decrease in 6MWD was similar between treatment groups (odds ratio: 0.95; 95% CI: 0.55, 1.65; p=0.8574).

As discussed, the rate of decline in forced vital capacity (FVC), DLco and change in 6-minute walk distance are only surrogate endpoints and therefore it is considered that a positive trend in other endpoints investigating direct clinical effects needs to be shown in the study. However, the results of endpoints investigating direct clinical effects were inconclusive.

The results of patients reported outcomes, i.e. George's respiratory questionnaire scores, University of California, San Diego–shortness of breath questionnaire scores, Leicester cough questionnaire scores, cough visual analog scale scores have not showed significant differences between the treatment groups.

Events such as acute exacerbations, non-elective hospitalization, deaths were recorded in the study; however, the number of these events was too small to make any meaningful conclusion.

Overall, 1 patient each in the pirfenidone group and the placebo group were reported to have experienced events that led to death.

Acute Exacerbations were reported infrequently in both treatment groups (5 patients in the pirfenidone group and 7 patients in the placebo group) and therefore the median time to First Investigator-Reported Acute Exacerbations was not calculable.
The incidences of all-cause hospitalizations and respiratory-related non-elective hospitalizations were similar between the treatment groups during the double-blind treatment period.

Ancillary analyses

Subgroup analyses of the decline in FVC in mL (home and site spirometry) and selected other secondary endpoints were conducted for the following subgroups:

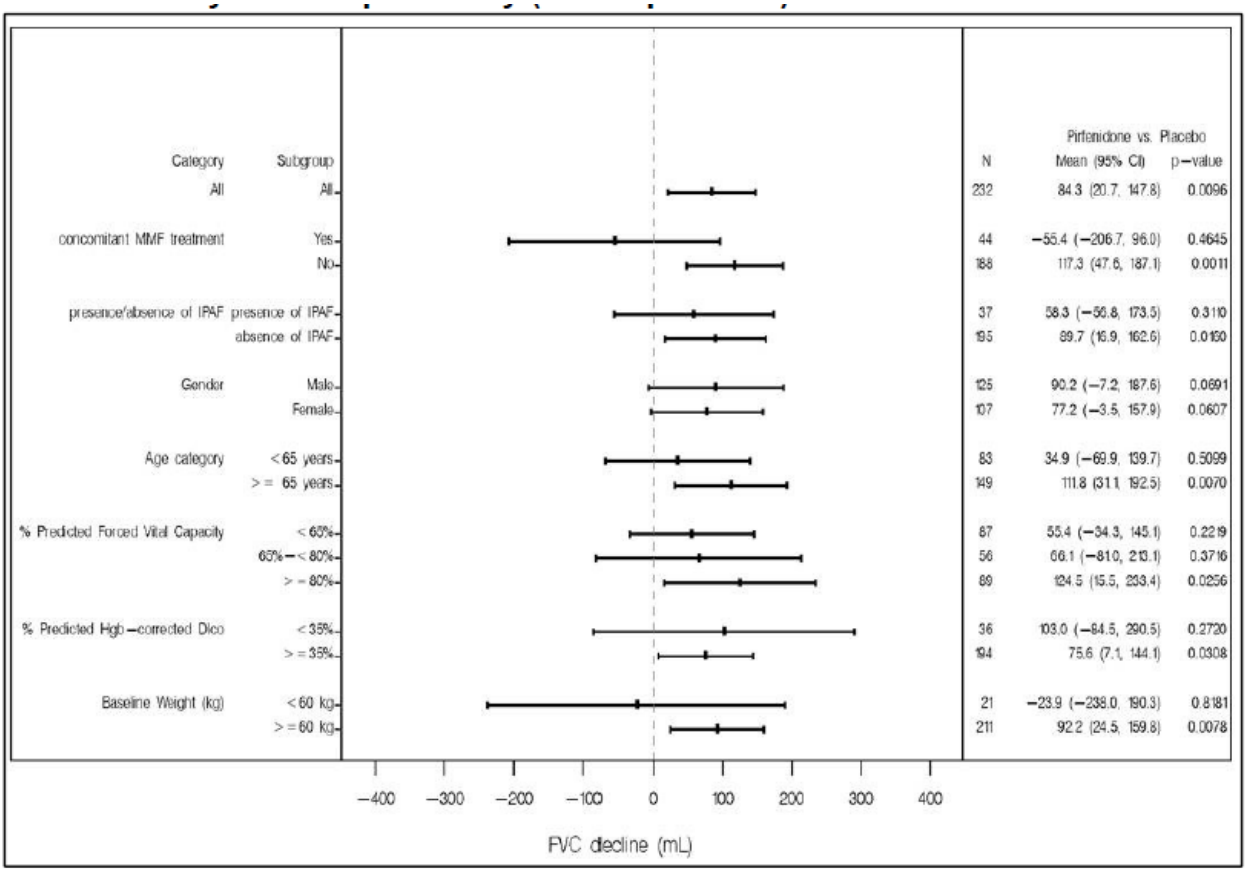
- The four groups resulting from combinations of the two stratification factors:
  - Concomitant MMF treatment (yes/no)
  - Presence/absence of IPAF as defined by the MDT
- Gender: Male, Female
- Age (years): <65 years, ≥ 65 years
- Percent predicted FVC at Baseline: <65%, ≥65% to < 80%, ≥80%
- Percent predicted DLco at Baseline: <35%, ≥35%
- Body weight: <60 kg, ≥60 kg
- Previous Biopsy (yes/no)

Table 20 ***Overview of Subgroups (ITT Population)***

	Pirfenidone (N=127) n (%)	Placebo (N=126) n (%)
Surgical lung biopsy in past		
Yes	40 (31.5)	48 (38.1)
No	87 (68.5)	78 (61.9)
MMF treatment		
Yes	23 (18.1)	22 (17.5)
No	104 (81.9)	104 (82.5)
IPAF subgroup		
Presence of IPAF	20 (15.7)	21 (16.7)
Absence of IPAF	107 (84.3)	105 (83.3)
Gender		
Male	70 (55.1)	69 (54.8)
Female	57 (44.9)	57 (45.2)
Age category		
<65 years	43 (33.9)	42 (33.3)
≥65 years	84 (66.1)	84 (66.7)
% Predicted forced vital capacity		
<65%	45 (35.4)	52 (41.3)
65%-<80%	31 (24.4)	28 (22.2)
≥80%	51 (40.2)	46 (36.5)
% Predicted Hgb-corrected DLco		
<35%	22 (17.3)	16 (12.7)
≥35%	104 (81.9)	109 (86.5)
Missing	1 (0.8)	1 (0.8)
Baseline Weight (kg)		
<60	8 (6.3)	16 (12.7)
≥60	119 (93.7)	110 (87.3)

DLco = diffusing capacity of the lung for carbon monoxide; hgb = hemoglobin; IPAF = interstitial pneumonia with autoimmune features; ITT = intent-to-treat; MMF = mycophenolate mofetil.
Source: Table 14.1.3.4

Figure 3 ***Forest Plot of FVC Decline (mL) from Baseline to Week 24 Measured by Clinic Spirometry (ITT Population)***



Source: Figure 14.2.2.3

Table 21 ***Site spirometry test results measured at site and changes from baseline over time by patients with/without lung biopsy (ITT Population)***

- The results for patients with lung biopsy

Parameter/ Visit	Pirfenidone (N=127) Value	Pirfenidone (N=127) Change from Baseline	Placebo (N=126) Value	Placebo (N=126) Change from Baseline
Week 24				
n observed	33	33	42	42
Mean (std)	2.57 (0.721)	-0.06 (0.246)	2.46 (0.856)	-0.10 (0.241)
Median	2.50	-0.05	2.38	-0.09
Q1 - Q3	1.95 - 3.05	-0.25 - 0.10	1.74 - 2.89	-0.18 - 0.01
Min - Max	1.4 - 4.1	-0.6 - 0.5	1.2 - 5.1	-0.8 - 0.5
Missing	0	0	1	1

- The results for patients without lung biopsy

Parameter/ Visit	Pirfenidone (N=127) Value	Pirfenidone (N=127) Change from Baseline	Placebo (N=126) Value	Placebo (N=126) Change from Baseline
Week 24				
n observed	68	68	70	70
Mean (std)	2.28 (0.915)	0 (0.235)	2.28 (0.716)	-0.06 (0.240)
Median	2.13	0	2.34	-0.08
Q1 - Q3	1.62 - 2.68	-0.15 - 0.13	1.84 - 2.77	-0.21 - 0.03
Min - Max	1.0 - 5.1	-0.5 - 0.6	0.6 - 3.9	-0.6 - 0.7
Missing	0	0	1	1

CHMP comment:

In the study, patients were stratified by the concomitant use of MMF treatment (yes/no) and presence/absence of IPAF diagnosis as defined by the MDT at enrolment. It is noted that the efficacy was lower in patients receiving MMF treatment. The applicant is requested to discuss and justify the use of pirfenidone in this population of patients **(OC).**

The applicant is requested to further discuss the efficacy results separately in patients with and without lung biopsy. It seems that patients with lung biopsy had higher FVC decline as compared to those without biopsy and the efficacy of pirfenidone seem to be lower in this subgroup. The relevant discussion and forest plot needs to be provided **(OC).**

Summary of main study(ies)

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

Table 22 Summary of Efficacy for trial MA39189

Title: MA39189 - Multicenter, International, Double-Blind, Two-Arm, Randomized, Placebo-Controlled, Phase II Trial of Pirfenidone in Patients with Unclassifiable Progressive Fibrosing ILD.			
Study identifier	MA39189; NCT03099187; EudraCT 2016-002744-17		
Design	This was a multicenter, international, double-blind, two-arm, randomized, placebo-controlled, Phase II study with an open-label extension in patients with fibrosing ILD who cannot be classified with moderate or high confidence into any other category of fibrosing ILD by multidisciplinary teams (MDT) review to evaluate the efficacy and safety of pirfenidone.		
	Duration of Main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks + 28 days for safety reporting not applicable 52 weeks + 28 days for safety reporting
Hypothesis	Superiority		
Treatments groups	Pirfenidone group (PFN)		Pirfenidone, 24 weeks, n=127 patients randomised
	Placebo group (PLO)		Placebo, 24 weeks, n=126 patients
Endpoints and definitions	Primary endpoint	FVCh	Rate of decline in forced vital capacity (FVC) measured in millilitres (mL) by daily handheld spirometer (daily home spirometry) over the 24-week double-blind treatment period
	Secondary endpoint	FVCc	Change in percent predicted FVC and in mL measured by spirometry during clinic visits (clinic spirometry)
	Secondary endpoint	CatDec5%	Categorical change in FVC of >5% (absolute change in percent predicted and relative change in mL), measured both by daily home spirometry as well as by clinic spirometry
	Secondary endpoint	CatDec10%	Categorical change in FVC of >10% (absolute change in percent predicted and relative change in mL), measured both by daily home spirometry as well as by clinic spirometry
	Secondary endpoint	DLco	Change in percent predicted diffusing capacity of the lung for carbon monoxide (DLco) from baseline to Week 24
	Secondary endpoint	6MWD	Change in 6 minute walking distance (6MWD) in meters from baseline to Week 24
Database lock	Primary analysis: 3 March 2019; Final analysis: 6 April 2020		
Results and Analysis			
Analysis description	**Primary Analysis (2019) – FVCh; Mean analyses pre-specified, median analyses not pre-specified**		
Analysis population and time point description	Intent to treat; 3 March 2019 All Patients Randomized		
Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=124	n=123
	FVCh mean	-17.8 mL	116.6 mL
	95% confidence interval	-311.6, 276.0	-451.9, 685.2

	FVCh median	-87.7 mL	-157.1 mL
Effect estimate per comparison	FVCh	Comparison groups	PFN vs PLO
		Mean difference between	-134.4 mL
		95% confidence interval	-772.2, 503.4
		P-value Student's t-test P-value Wilcoxon test (not pre-planned)	0.6781 0.2187
		Median difference between groups (not pre-planned)	69.4 mL
Notes	Patients with less than 3 observations were excluded from analysis because no regression analysis could be performed. The primary analysis of the primary efficacy endpoint (daily home spirometry) was affected by high intra-individual variability and extreme outliers in home spirometry values in both treatment groups. The updated analysis of the primary endpoint was performed in 2020, based on the re-read of home spirometry data that was used for the primary analysis in March 2019, to adjudicate and eliminate single readings if they were deemed to be of non-acceptable quality. The corrected dataset did not include physiologically implausible values obtained for FVC decline by home spirometry. As a sensitivity analysis for the primary endpoint of daily home spirometry, time-adjusted mean FVC decline was estimated by a repeated measures mixed model for both the data collected for the primary analysis in 2019 and re-read data from 2020.		
Analysis description	**Updated Analysis (2020) - FVCh**		
Analysis population and time point description	Intent to treat; 6 April 2020 All Patients Randomized		
Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=116	n=116
	FVCh mean	-90.3 mL	125.6 mL
	95% confidence interval	-157.0, -23.7	-458.4, 709.6
	FVCh median	-85.6 mL	-183.5 mL
Effect estimate per comparison	FVCh	Comparison groups	PFN vs PLO
		Mean difference between groups	-216.0 mL
		95% confidence interval	-803.6, 371.7
		P-value Student's t-test P-value Wilcoxon test	0.4682 0.0274
		Median difference between	97.8 mL

Notes	Patients with less than 3 observations were excluded from analysis because no regression analysis could be performed. The primary analysis of the primary efficacy endpoint (daily home spirometry) was affected by high intra-individual variability and extreme outliers in home spirometry values in both treatment groups. The updated analysis of the primary endpoint was performed in 2020, based on the re-read of home spirometry data that was used for the primary analysis in March 2019, to adjudicate and eliminate single readings if they were deemed to be of non-acceptable quality. The corrected dataset did not include physiologically implausible values obtained for FVC decline by home spirometry. As a sensitivity analysis for the primary endpoint of daily home spirometry, time-adjusted mean FVC decline was estimated by a repeated measures mixed model for both the data collected for the primary analysis in 2019 and re-read data from 2020.		
Analysis description	**Analysis by Mixed Models (2019 Primary Analysis) - FVCh**		
Analysis population and time point description	Intent to treat; 3 March 2019 All Patients Randomized		
Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=126	n=126
	FVCh estimate	-74.82 mL	-161.27 mL
	95% confidence interval	-140.87, -8.76	-225.95, -96.58
	Standard error	33.70 mL	33.00 mL

Effect estimate per comparison	FVCh	Comparison groups	PFN vs PLO
		Difference between groups	86.45 mL
		95% confidence interval	-5.94, 178.84
		P-value	0.0667
		Standard error	47.14 mL

Notes	Patients with less than 3 observations were excluded from analysis because no regression analysis could be performed. The primary analysis of the primary efficacy endpoint (daily home spirometry) was affected by high intra-individual variability and extreme outliers in home spirometry values in both treatment groups. The updated analysis of the primary endpoint was performed in 2020, based on the re-read of home spirometry data that was used for the primary analysis in March 2019, to adjudicate and eliminate single readings if they were deemed to be of non-acceptable quality. The corrected dataset did not include physiologically implausible values obtained for FVC decline by home spirometry. As a sensitivity analysis for the primary endpoint of daily home spirometry, time-adjusted mean FVC decline was estimated by a repeated measures mixed model for both the data collected for the primary analysis in 2019 and re-read data from 2020.		
Analysis description	**Analysis by Mixed Models (2020 Updated Analysis) - FVCh**		
Analysis population and time point description	Intent to treat; 6 April 2020 All Patients Randomized		
Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=118	n=120
	FVCh estimate	-71.69 mL	-184.71 mL

	95% confidence interval		-127.31; -16.07	-239.67; -129.75
	Standard error		28.38 mL	28.04 mL
Effect estimate per comparison	FVCh	Comparison groups	PFN vs PLO	
		Difference between groups	113.02 mL	
		95% confidence interval	34.87; 191.17	
		P-value	0.0046	
		Standard error	39.87 mL	
Notes	Patients with no observations were excluded from analysis. The primary analysis of the primary efficacy endpoint (daily home spirometry) was affected by high intra-individual variability and extreme outliers in home spirometry values in both treatment groups. The updated analysis of the primary endpoint was performed in 2020, based on the re-read of home spirometry data that was used for the primary analysis in March 2019, to adjudicate and eliminate single readings if they were deemed to be of non-acceptable quality. The corrected dataset did not include physiologically implausible values obtained for FVC decline by home spirometry. As a sensitivity analysis for the primary endpoint of daily home spirometry, time-adjusted mean FVC decline was estimated by a repeated measures mixed model for both the data collected for the primary analysis in 2019 and re-read data from 2020.			
Analysis description	**Secondary Analysis (2019 Primary Analysis) – FVCc; Pre-specified**			
Analysis population and time point description	Intent to treat; 3 March 2019 All Patients Randomized			
Descriptive statistics and estimate variability	Treatment group		PFN	PLO
	Number of subjects		n=118	n=119
	FVCc mean		-17.8 mL	-113.0 mL
	95% confidence interval		-62.6, -27.0	-152.5, -73.6
Effect estimate per comparison	FVCc	Comparison groups	PFN vs PLO	
		Mean difference between groups	95.3 mL	
		95% confidence interval	35.9, 154.6	
		P-value Student's t-test	0.0018	
Notes	Patients with less than 3 observations were excluded from analysis because no regression analysis could be performed.			
Analysis description	**Secondary Analysis (2020 Updated Analysis) – FVCc; Not pre-specified**			
Analysis population and time point description	Intent to treat; 6 April 2020 All Patients Randomized			
Descriptive statistics and estimate variability	Treatment group		PFN	PLO
	Number of subjects		n=114	n=118
	FVCc mean		-24.8 mL	-109.1 mL
	95% confidence interval		-72.6, 22.9	-151.7, -66.5
	FVCc	Comparison groups	PFN vs PLO	

Effect estimate per comparison		Mean difference between groups	84.3 mL
		95% confidence interval	20.7, 147.8
		P-value Student's t-test	0.0096
Notes	Patients with less than 3 observations were excluded from analysis because no regression analysis could be performed. Secondary endpoint parameters have been updated during the final analysis due to data cleaning activities.		
Analysis description	**Secondary Analysis (Analysis by Mixed Models [2020 Analysis]) – FVCc; Not pre-specified**		
Analysis population and time point description	Intent to treat; 6 April 2020 All Patients Randomized		
Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=127	n=125
	FVCc estimate	-14.14 mL	-105.66 mL
	95% confidence interval	-55.81, 27.52	-145.81, -65.52
Effect estimate per comparison	FVCc	Comparison groups	PFN vs PLO
		Estimated difference between groups	91.52 mL
		95% confidence interval	33.66, 149.38
		P-value	0.0020
		Standard error	29.49
Notes	Patients with no observations were excluded from analysis.		
Analysis description	**Secondary Analysis (2019 Primary Analysis) - CatDec5%; Pre-specified**		
Analysis population and time point description	Intent to treat; 3 March 2019 All Patients Randomized		
Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=127	n=126
	CatDec5% (percent)	47 (37.0%)	74 (58.7%)
Effect estimate per comparison	CatDec5%	Comparison groups	PFN vs PLO
		Odds ratio	0.42
		95% confidence interval	0.25, 0.69
		P-value	0.0006
Notes	-		
Analysis description	**Secondary Analysis (2020 Updated Analysis) – CatDec5%; Not pre-specified**		
Analysis population and time point description	Intent to treat; 6 April 2020 All Patients Randomized		
	Treatment group	PFN	PLO

Descriptive statistics and estimate variability	Number of subjects	n=127	n=126
	CatDec5% (percent)	47 (37.0%)	73 (57.9%)

Effect estimate per comparison	CatDec5%	Comparison groups	PFN vs PLO
		Odds ratio	0.43
		95% confidence interval	0.26, 0.71
		P-value	0.0009

Notes	-
Analysis description	**Secondary Analysis (2019 Primary Analysis) – CatDec10%; Pre-specified**
Analysis population and time point description	Intent to treat, 3 March 2019 All Patients Randomized

Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=127	n=126
	CatDec10% (percent)	18 (14.2%)	34 (27.0%)

Effect estimate per comparison	CatDec10%	Comparison groups	PFN vs PLO
		Odds ratio	0.44
		95% confidence interval	0.23, 0.84
		P-value	0.0114

Notes	-
Analysis description	**Secondary Analysis (2020 Updated Analysis) – CatDec10%; Not pre-specified**
Analysis population and time point description	Intent to treat; 6 April 2020 All Patients Randomized

Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=127	n=126
	CatDec10% (percent)	18 (14.2%)	33 (26.2%)

Effect estimate per comparison	CatDec10%	Comparison groups	PFN vs PLO
		Odds ratio	0.46
		95% confidence interval	0.24, 0.88
		P-value	0.0168

Notes	-
Analysis description	**Secondary Analysis – DLco (% predicted) changes from baseline to Week 24; Pre-specified**
Analysis population and time point description	Intent to treat; 3 March 2019 All Patients Randomized

Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=97	n=110

	DLco (% predicted) changes from baseline to Week 24 Mean	-0.65	-2.48
	Standard deviation	7.113	8.893

Effect estimate per comparison	DLco (% predicted) changes from baseline to Week 24	Comparison groups	PFN vs PLO
		P-value Rank ANCOVA	0.1191
Notes	Patients without week 24 data excluded from descriptive analysis.		

Analysis description	**Secondary Analysis – Categorical decline with >15% absolute decrease in DLco (% predicted); Pre-specified**		
Analysis population and time point description	Intent to treat; 3 March 2019 All Patients Randomized		
Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=127	n=126
	Categorical decline with >15% absolute decrease in DLco (% predicted)	2 (1.6%)	12 (9.5%)

Effect estimate per comparison	Categorical decline with >15% absolute decrease in DLco (% predicted)	Comparison groups	PFN vs PLO
		Odds ratio	0.15
		95% confidence interval	0.03; 0.69
		P-value	0.0150
Notes	-		
Analysis description	**Secondary Analysis – 6MWD (changes from baseline to Week 24); Pre-specified**		
Analysis population and time point description	Intent to treat; 3 March 2019 All Patients Randomized		
Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=99	n=108
	6MWD (changes from baseline to Week 24) Mean	-2.0 m	-26.7 m
	Standard deviation	68.11 m	79.32 m

Effect estimate per comparison	6MWD (changes from baseline to Week 24)	Comparison groups	PFN vs PLO
		P-value Rank ANCOVA	0.0299
Notes	Patients without week 24 data excluded from descriptive analysis.		
Analysis description	**Secondary Analysis – Categorical decline with > 50 m absolute decrease in 6MWD; Pre-specified**		
Analysis population and time point description	Intent to treat; 3 March 2019 All Patients Randomized		

Descriptive statistics and estimate variability	Treatment group	PFN	PLO
	Number of subjects	n=127	n=126
	Categorical decline with > 50 m absolute decrease in 6MWD	34 (26.8%)	35 (27.8%)

Effect estimate per comparison	Categorical decline with > 50 m absolute decrease in 6MWD	Comparison groups	PFN vs PLO
		Odds ratio	0.95
		95% confidence interval	0.55; 1.65
		P-value	0.8574
Notes	-		

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

N/A

Clinical studies in special populations

N/A

Supportive study(ies)

The applicant supported the application with reference with a comparison of the FVC decline with the previous IPF application and with literature. The literature was provided to show the durability of the response.

- **Comparison with clinical studies in IPF**

Study MA 39189: Using clinical trial site spirometry to monitor FVC, the predicted 24-week decline (estimated by linear regression) in FVC was 84.3 mL (95% CI: 20.7; 147.8 and p-value: 0.01) lower in patients given pirfenidone compared with placebo.

Although not directly comparable due to differences in the handling of missing data, a similar treatment benefit for mean decline in FVC was observed in a pre-specified pooled analysis of the Phase 3 trials of pirfenidone in IPF. After 24 weeks, an absolute treatment difference of 104 mL (Rank ANCOVA p-value: <0.001) was observed for pirfenidone versus placebo, which increased to 148 mL (Rank ANCOVA p-value: <0.001) after 12 months of treatment (Noble et al. 2016). The sponsor therefore determined, that a 24-week treatment period would be sufficient to observe any statistically significant differences in the FVC assessment.

- **Durability of response**

To assess the durability of response in clinical trial site FVC for the chronic therapy of Unclassifiable ILD, the Sponsor performed a post-hoc analysis in three confirmatory clinical trials of pirfenidone in IPF.

In the estimated slopes for semi-annual and annual decline are presented together with a predicted 12 months FVC decline calculated from the six months estimate. The correlation of the predicted and estimated annual decline for all treatment arms in the three studies appeared to be reasonably high, between 0.6 and 0.7 (Table 23)

The results show that a decline in FVC in the first 6 months of observation time is higher compared to that of the second half year.

This indicates that a clinically meaningful decline in FVC was established already in the first six months of these analysed studies. (Table 23).

Table 23 Estimated declines in FVC (mL) by study and correlation of individual slopes estimated from mixed models (ITT) – pirfenidone trials

Roche-MA39189-uILD Final Analysis (Database Snapshot Date: 06-Apr-2020)

Estimated declines in FVC (mL) by study and correlations of individual slopes estimated from mixed models (ITT population)

Treatment	Study	Estimated decline (SE) at 6 months (estimated from 6 months data) Model 1	Estimated decline (SE) at 12 months (predicted from 6 months data) Model 2	Estimated decline (SE) at 12 months (estimated from 12 months data) Model 3	Correlation of slopes from Model 2 with slopes from Model 3 [1]
Capacity 1 [2] (PIPF-006)	Pirfenidone	-61.1 (52.80)	-122.2 (105.61)	-98.4 (24.90)	0.57
	Placebo	-210.6 (53.49)	-421.3 (106.98)	-157.4 (25.03)	0.68
	Difference between treatments	149.5 (53.79)	299.1 (107.57)	59.0 (32.69)	
Capacity 2 [2] (PIPF-004)	Pirfenidone	-17.0 (49.87)	-34.0 (99.73)	-115.5 (23.63)	0.63
	Placebo	-110.0 (50.37)	-220.1 (100.73)	-197.9 (23.93)	0.61
	Difference between treatments	93.0 (52.87)	186.1 (105.74)	82.4 (31.19)	
Ascend [2] (PIPF-016)	Pirfenidone	-110.6 (30.47)	-221.1 (60.94)	-163.6 (17.79)	0.66
	Placebo	-286.6 (30.11)	-573.3 (60.23)	-279.6 (17.76)	0.69
	Difference between treatments	176.1 (34.16)	352.1 (68.32)	116.0 (23.66)	

–

Note: For missing values no imputation was made. SE=Standard Error. Months 3, 6, 9, 12 correspond to Weeks 12, 24, 36, 48 for study PIPF-004.
[1] Pearson correlation coefficient
[2] Calculated from the Mixed Linear Model comparing Pirfenidone 2403 mg/d to Placebo, with change as the outcome variable; sex by height, sex by age, and assessment time by treatment as fixed effects and subject and subject by assessment time as random effects with variance components covariance structure.
Clinipace: 05OCT2020 / adapted from FDA_slope_fvc_ph_rise.lst / FDA_slope_fvc_ph_rise.sas
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CHMP comment

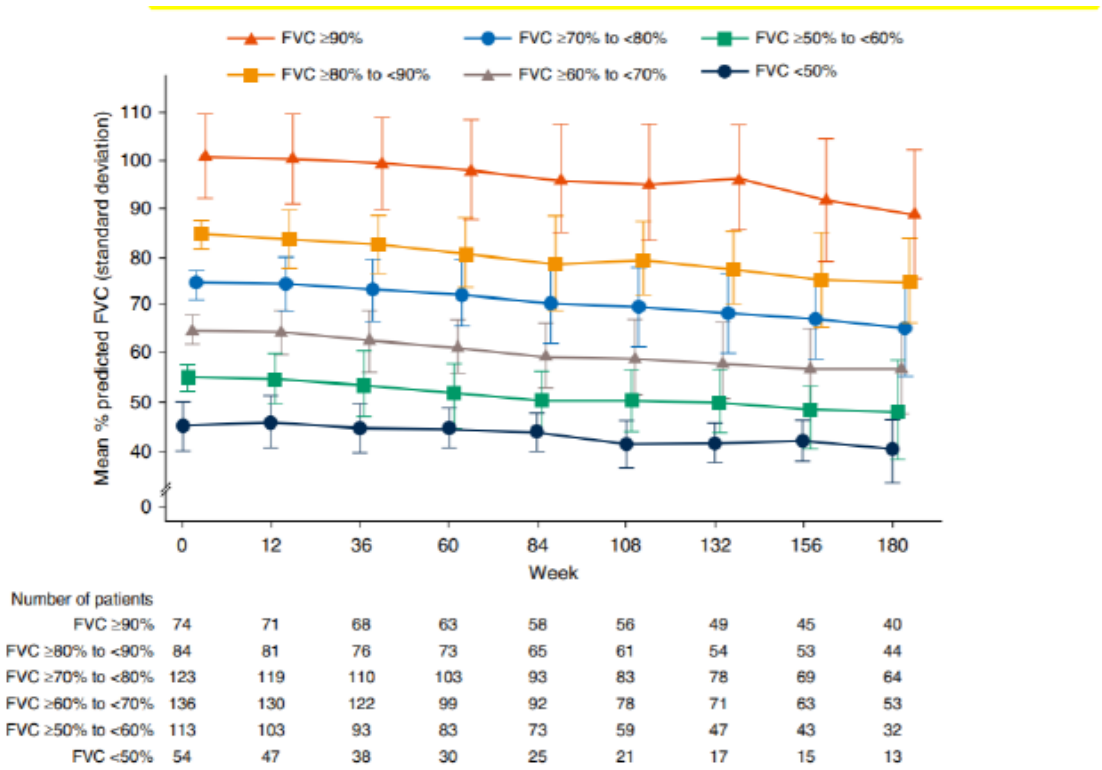
It appears that in this table, a post hoc analyses are made of the FVC decline in IPF. Various models are used, that are not further specified. This makes it hard to interpret the data.

The durability of the response is also supported by 4 literature references:

- **Maher et all presented a post hoc analyses of CAPACITY and RECAP at the ERS:**

RECAP (PIPF-012; NCT00662038) was an open-label, long-term extension study in patients with IPF who had completed ASCEND [NCT01366209]]or CAPACITY [NCT00287716/NCT00287729]]. The post hoc analyses found that long-term pirfenidone in reducing FVC decline was maintained for over 4 years, with little change in annual rate of FVC decline after more than 1 year of treatment in individuals who received pirfenidone during CAPACITY.

Figure 4 Rate of lung function decline over 180 weeks by baseline (%) predicted forced vital capacity (FVC) in RECAP



Number of patients									
FVC ≥90%	74	71	68	63	58	56	49	45	40
FVC ≥80% to <90%	84	81	76	73	65	61	54	53	44
FVC ≥70% to <80%	123	119	110	103	93	83	78	69	64
FVC ≥60% to <70%	136	130	122	99	92	78	71	63	53
FVC ≥50% to <60%	113	103	93	83	73	59	47	43	32
FVC <50%	54	47	38	30	25	21	17	15	13

Source Maher et al 2019

- **Jouneau et all presented the result of the French Ancillery study**

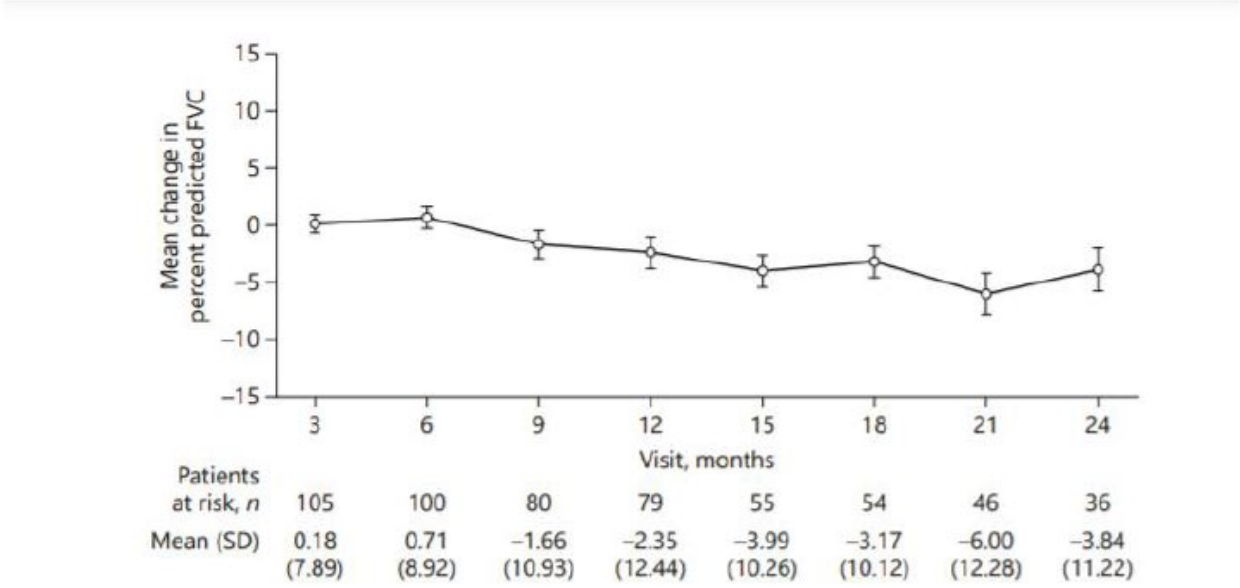
The PASSPORT registry (NCT02699879) was an observational, multicentre, prospective, post-authorization safety study of IPF patients treated with pirfenidone, monitored for up to 2 years. The study was conducted in 10 EU countries, including France.

The mean absolute change in the percentage of predicted FVC was −2.4% and −3.8% at months 12 and 24 (Figure 5). The efficacy data of FAS are consistent with the efficacy results of the Phase III clinical trials of pirfenidone in IPF. Approximately one-third of IPF patients treated with pirfenidone in real-life settings were still under treatment 2 years after initiation, and there were no signs of any loss of efficacy over this period.

CHMP comment

The assessment of efficacy was performed in patients who remained on pirfenidone in the study, and attribution of the study population observed over the 2-year follow- up may lead to overestimation of the stability of FVC

Figure 5 Changes of percent predicted FVC in patients at risk in PASSPORT



Source: Jouneau et al. 2019

- **Vanchieri et all described the IRENE study**.

The IRENE was an observational, retrospective, multicentre study of patients with IPF treated with pirfenidone in clinical practice in Italy. The study population comprised 379 patients with IPF. The mean absolute change from baseline in FVC at Month 6 and Month 12 was -98.6 mL (standard deviation [SD], 484.3 mL) and -81.8 mL (SD, 419.6 mL), respectively.

- **Zurkova et al. 2019 presented data from Czech IPF patients included in the EMPIRE registry.**

The EMPIRE registry included a total of 841 patients were included in this analysis: 383 patients (45.5%) received pirfenidone, 218 patients (25.9%) received no-antifibrotic treatment and 240 patients (28.5%) were excluded (missing data, nintedanib treatment).
During a 2-year follow-up, less than a quarter of the patients progressed on pirfenidone as assessed by the decline of >10% FVC (17.0%) and >15% DLCO (14.3%). Pirfenidone increased the 5-year overall survival (OS) over no-antifibrotic treatment (55.9% vs 31.5% alive, P=0.002).

References

- Maher T et al. Correlation between home and clinic spirometry in subjects with IPF: results from the INMARK trial. ERJ 2019 54: PA1318; DOI: 10.1183/13993003.congress-2019.PA1318
- Jouneau S et al. A 2-Year Observational Study in Patients Suffering from Idiopathic Pulmonary Fibrosis and Treated with Pirfenidone: A French Ancillary Study of PASSPORT. Respiration DOI: 10.1159/000496735
- Vanchieri C et al. Pirfenidone in real life: A retrospective observational multicentre study in Italian patients with idiopathic pulmonary fibrosis. Respiratory Medicine 156 (2019) 78 Https://doi.org/10.1016/j.rmed.2019.08.006

4.4.3. Discussion on clinical efficacy

Pirfenidone (ESBRIET®) is a small molecule that has been shown to exert both antifibrotic and anti-inflammatory activity in a variety of animal models and in vitro systems.

In 2011, pirfenidone gained approval for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF) in adults. The application was based on two pivotal studies of 72-week duration. Both studies showed numerical improvements in lung function and a functional patient-derived outcome: one study showed a statistically significant improvement in lung function (FVC), while the other showed a statistically significant benefit in a patient-derived outcome i.e. 6 MWD.

Given these beneficial effects in IPF, it was hypothesised that antifibrotic therapy may be beneficial in patients with unclassifiable ILD, particularly in cases characterised by progressive disease, because of the overlap between clinical, radiological, and histopathological features of IPF and unclassifiable ILD. Therefore, study MA39189 was initiated in unclassifiable ILD. The current variation applies for a new indication *"Esbriet is indicated in adults for the treatment of unclassifiable interstitial lung disease (UILD)"* and is based on a single pivotal trial, study MA 39189.

Design and conduct of clinical studies

The applicant submitted one study (MA39189) investigating the use of pirfenidone in patients with fibrosing ILD that, following MDT review, could not be classified with either high or moderate confidence as a specific idiopathic interstitial pneumonia or other defined ILD. The study was originally designed as a phase II trial but will now be used as a confirmative phase III trial to support the applied extension of the indication.

MA39189 study had a 24-week double-blind treatment period and 12-month safety follow-up in which patients were receiving open-label pirfenidone. No spirometry or other efficacy assessments were conducted during the 12-month safety follow-up.

There are no EU guidelines on the clinical investigation of medicinal products for the treatment of ILD. Nevertheless, taking into consideration previous regulatory decisions it is considered that the duration of the double-blind treatment period was too short **(MO).** It is noted that PIPF-004 and PIPF-006 studies supporting the idiopathic pulmonary fibrosis indication had 72 weeks double-blind treatment periods. Studies INPULSIS-1, INPULSIS-2, INBUILD and SENSCIS investigating nintedanib in various ILD indications each had 52 week double-blind treatment periods.

Inclusion criteria

The 2002 ATS/ERS classification proposed an "unclassifiable" category of IIP, acknowledging that a final diagnosis may not be achieved in all cases.

MA39189 study enrolled patients with confirmed fibrosing ILD that, following MDT review, could not be classified with either high or moderate confidence as a specific idiopathic interstitial pneumonia or other defined ILD. The inclusion criteria to the study were very broad as not only patients with "UILD" diagnosis or who fulfilled research classification criteria for IPAF could be enrolled, but also those with low confidence diagnosis of specific ILDs including NSIP, cHP, CTD-ILD.

The applicant should further justify these inclusion criteria and present the efficacy data after exclusion of patients with any diagnosis of specific ILDs **(OC)**. It is noted that in this study, the MDT discussion was mandatory before the qualifying diagnosis of uILD can be made. This is supported. On the other hand, a surgical lung biopsy was not required to be performed. This is considered as a limitation, although it is acknowledged that some patients are unable or unwilling to undergo lung biopsy.

As postulated by Guler and colleagues, there are likely important differences in patients with interstitial lung disease who are unclassifiable despite a surgical lung biopsy and patients who are unclassifiable in the absence of a surgical biopsy. Therefore, the applicant is requested to further discuss the efficacy results separately in patients with and without lung biopsy **(OC).** The reasons why lung biopsy was not performed should be presented and discussed by the applicant **(OC).**

All enrolled patients had to have extent of fibrosis >10% on HRCT and progressive disease as considered by the investigator. Progressive disease was defined based on the presence of a decline in FVC % (>5%) within the last 6 months or significant symptomatic worsening not due to cardiac, pulmonary, vascular, or other causes. The study is, however, not stratified according to baseline FVC decline > 5% yes/no, and clarification is needed if this baseline characteristic is evenly divided among the two treatments (OC), particularly as one of the outcome measures is the comparison of the proportion of patients showing an FVC decline > 5% or 10%. In addition, clarification is needed if the baseline FVC decline > 5% is defined as absolute % predicted or as relative % from baseline. **(OC)**

The applicant is proposing the following indication: *Esbriet is indicated in adults for the treatment of unclassifiable interstitial lung disease (UILD).* This indication is not supported as the pivotal study was only enrolling patients with progressive disease and this need to be reflected in the text of the indication **(MO).**

Further, the study population was limited to patients with baseline DLCO ≥30% and FVC ≥45% indicating that the inclusion was limited to mild to moderate disease. The applicant should discuss whether these criteria should be reflected in the text of the indication. It is noted that currently Esbriet is indicated the treatment of **mild to moderate** IPF only **(MO).**

Study treatment

In the study patients were randomised in a 1:1 ratio to pirfenidone and matching placebo administered at a daily dose of 2403 mg. The study did not include an active comparator. The comparison with placebo is justified, as no product was approved in the treatment of unclassifiable ILD.

Patients had to remain on a stable maintenance dose for the duration of the treatment period unless the dose was reduced, or dosing was interrupted to manage an AE. In the trial, patients could use concomitant therapy with MMF (MMF treatment includes mycophenolate mofetil/sodium or mycophenolic acid). As MMF may have an effect on the disease course of unclassifiable ILD, patients were stratified according to whether they received concomitant MMF treatment during the trial.

High dose systemic corticosteroids (15 mg/d of prednisolone or equivalent) for longer than 28 days, immunosuppressive therapies (e.g. azathioprine), treatment with NAC for fibrotic lung disease, CYP1A2 inhibitors and inducers were not allowed in the study.

Study endpoints

The primary endpoint of this study was the rate of decline in FVC measured in millilitres by daily handheld spirometer (daily home spirometry) over the 24-week double-blind treatment period.

The applicant decided to use handheld daily home spirometry as opposed to spirometry performed during clinic visits as in previous studies (Russell et al. 2016; Johannson et al. 2017) home spirometry showed a good correlation with hospital-obtained readings. In addition it was believed that home spirometry had the potential to detect functional decline earlier. However, taking into consideration previous regulatory decisions and unproven advantages of home spirometry, it is considered that that the annual rate of decline in forced vital capacity (FVC) measured at clinic spirometry visits should have been selected as a primary endpoint in the study **(MO).**

The rate of FVC decline from baseline to week 24 and categorical change in FVC of >5% and 10% measured by clinic spirometry visits was investigated as secondary endpoints. However, these endpoints and also all other secondary endpoints were not under type I error control. This is considered another significant limitation of this study.

In addition, the rate of the FVC decline was measured in mL rather than % predicted. The FVC as absolute percent predicted standardises the absolute measurements and eliminates the variability due to demographic features such as age, gender and body size (EPAR nintedanib). As such, it is more reliable outcome than the FVC measured in mL. The applicant is requested to provide the outcomes in % predicted as well **(OC).**

Further, it is important to highlight that the rate of decline in forced vital capacity (FVC) is only a surrogate endpoint and therefore it is considered that a positive trend in other endpoints investigating direct clinical effects (for example patients reported outcomes or survival) needs to be shown in the study.

In the study patient-reported outcomes and survival were investigated; however, as stated these endpoints were not under type 1 error control.

Other secondary outcome measurements

Other secondary outcome measures referred to lung function outcomes (change in FVC in mL or % predicted, categorical FVC decline (FVC > 5% or FVC > 10%), DLco; functional improvements (6MWD), patient-derived outcome measures (exacerbations, death, PFS) and patients reported outcomes by means of various questionnaires.
The choice of these secondary outcome measures is generally understood:

- The change in FVC (mL or percentage predicted) can be used to support the primary outcome/key secondary outcome. A categorical decline of FVC > 10% of predicted value is associated with an increased mortality risk and as such most indicative of a patient benefit
- the DLco is an important lung function measurement in ILD. Its decline is strongly associated with the progressive interstitial lung disease. However, the outcome measurement is associated with a high variability, making it hard to show a statistical improvement.
- The 6 MWD is an important secondary outcome measure, as it can determine the functional improvement by therapy. In IPF, the minimal reported clinically relevant distance (MCID) is reported to be about 24-45 m [Du Bois 2012], while a decrease of 50 m is associated with increased mortality [Du Bois, 2013]. However, the minimal clinically important difference in unclassifiable ILD is not established but given the usual better prognosis of unclassifiable ILD than IPF, a higher lower limit of the MCID would be expected.
- Other secondary outcomes included patient-derived outcomes like the hospitalisations, exacerbations, death rates and the composite endpoints of PFS. These outcomes indicate improvement or deterioration, but differences between treatments are unlikely to occur considering the limited treatment duration.
- During the study, patient-reported outcomes were measured by at least 4 questionnaires. This number is high but for a study with an exploratory design acceptable. None of these questionnaires was specifically designed for UILD, although the UCSD-SOBQ is developed for measuring disease burden longitudinally in IPF.

- **Additional concern: statistical analyses lack of multiplicity correction**

During the trial, various secondary outcome measures were conducted. However, the results are not corrected for multiplicity.

- **Additional concern: statistical analyses of secondary outcomes without taking into account the missing values**

In addition, the analyses of the secondary outcome measures are based on patients who completed the 24-week treatment and conducted the assessment. This will result in completer analyses. It is not clear which effect this analysis estimates. It may give a biased estimate of the ITT (treatment policy) treatment effect, as this would need the assumption that in both groups the non-completers are comparable to the completers (i.e. not selective drop-out). Also, as an estimate of the effect in who can tolerate the treatment, it is likely biased because different selection in both groups may have occurred.

More patients in the pirfenidone group than in the placebo group discontinued treatment i.e. n= 25 (19.7%) vs n=12 (9.7%). The most common primary reason for early discontinuation from the study was because of AEs (n=19 pirfenidone, vs n=3 placebo). The number of patients who have stopped because of ineffective treatment is missing. (**OC**)

- **Additional concern conducts of the trial: possible lack of standardisation of procedures.**

During the study, various efficacy parameters were measured based on Spirometry, lung diffusion tests and the 6 minutes walking test. However, the study procedures for determining efficacy were not standardised in this multicentre trial as no references is made to ATS/ERS guidelines for spirometry 6 Minute Walking distance, DL_{Co}. The lack of standardisation may increase the risk of a type I error, i.e. falsely conclude that a treatment effect exists.

Efficacy data and additional analyses

A total of 253 patients were randomized and assigned to the pirfenidone group (127 patients) and to the placebo group (126 patients).
The discontinuation rate was higher in the group of patients receiving pirfenidone. 25 patients (19.7%) in the pirfenidone group and 12 patients (9.5%) in the placebo group discontinued early from the 24-week double-blind treatment period and did not enter the 12-month safety follow-up period. The most common reasons for discontinuation were adverse events and withdrawal of consent.

A total of 94 patients (74.0%) in the pirfenidone group and 110 patients (87.3%) in the placebo group entered the additional 12-month safety follow-up period. Overall, 75 patients (59.1%) previously treated with pirfenidone and 84 patients (66.7%) previously treated with placebo, completed the study.

Baseline data

In general, demographic characteristics were balanced between the treatment groups. The median age was 70.0 years for the pirfenidone group and 69.0 years for the placebo group.

Overall, approximately 74% of patients in the study did not have a low-confidence diagnosis and were therefore assigned to the category of "UILD." The number of patients with UILD was similar between the pirfenidone and placebo groups (73.2% vs. 73.8%). The proportion of patients who fulfilled IPAF criteria was also similar between treatment groups (12.6% vs. 14.3%). All randomized patients had historical HRCT. Around one-third of patients included in the study had a historical surgical lung biopsy (pirfenidone group: 31.5%; placebo group: 38.1%). However, some imbalances were observed which need clarification as they may affect the efficacy parameters e.g. i.e. number of pack-years (pirfenidone 30 vs 17.5 placebo), time of recent lung biopsy to treatment pirfenidone 10.3 months, placebo 16 months) **(OC)**

The baseline clinic spirometry test results measured at site were balanced between the treatment groups with the mean FVC (% predicted) 73.95 recorded in both treatment groups.

In the trial, patients could use concomitant therapy with MMF. High dose systemic corticosteroids (15 mg/d of prednisolone or equivalent) for longer than 28 days, immunosuppressive therapies (e.g. azathioprine), treatment with NAC for fibrotic lung disease were not allowed. It is noted however that corticosteroids for systemic use were taken by 78 patients [61.4%] in the pirfenidone group and 65 patients [52.4%] in the placebo group. The applicant should provide further details in relation to the use of corticosteroid in the study and comment on their potential influence on the study results **(OC).**

Primary endpoint results

The primary efficacy endpoint in this study was the rate of decline in FVC measured in millilitres with daily home spirometer over the 24-week, double-blind treatment period. The original primary analysis performed in 2019 showed unreliable results with high intra-individual variability and extreme outliers in home spirometry values in both treatment groups. Physiologically implausible values were recorded.

In order to increase confidence that only truly acceptable blows were included in the analysis, an external organization (eResearchTechnology Inc.) was contracted by the applicant to perform a manual re-read of 32166 flow curves.

Based on this re-read almost 20 % of measurements with non-acceptable quality were removed from the dataset.

Both the initial databases of 2019 and 2020 showed a numerical improvement for placebo compared to pirfenidone in the **mean** FVC: (e.g. data set 2019: pirfenidone mean (95% CI) -17.8 (-311, 276) , placebo 116.6 (-451.9, 685.2) (p=0.67) (table page 49 source table 14.2.1.1)

The updated analysis of the home spirometry measurements performed in 2020 showed the **median** FVC decline over 24 weeks of -85.6 mL in the pirfenidone group and -183.5 mL in the placebo group, which represented a treatment difference of 97.8 mL in favour of pirfenidone (p=0.0274). The applicant claims that these results of the updated analysis of the primary endpoint are more reliable, which is not supported.

There are still extreme outliers in home spirometry values and the confidence intervals are very broad. Therefore, it is not agreed that the results of this post hoc analysis (therefore not controlled for type one error), is used by the applicant to claim treatment benefits of pirfenidone in patients with unclassifiable ILDs **(MO).**

The key secondary endpoint-rate of FVC decline measured by clinic spirometry

The rate of FVC decline from baseline to week 24 and categorical change in FVC of >5% and 10% measured by clinic spirometry visits was investigated as key secondary endpoints. The results of the spirometry measurements recorded during sites visits seemed to be more reliable although the analyses of this endpoint were also repeated "due to additional data cleaning activities that were not conducted during the primary analysis".

The results of the primary analysis as well as updated analysis of this secondary endpoint showed a smaller magnitude of decline in FVC in the pirfenidone as compared to the placebo group.

During the primary analysis, at Week 24, mean predicted FVC declines by the clinical spirometry for pirfenidone and placebo were -17.8 mL and -113.0 mL, respectively, with an overall mean difference of 95.3 mL (Student's t-test p=0.0018; 95% CI: 35.9, 154.6). Per updated analysis, at Week 24, mean predicted FVC declines for pirfenidone and placebo were -24.8 mL and -109.1 mL, respectively, with an overall mean difference of 84.3 mL (Student's t-test p=0.0096; 95% CI: 20.7, 147.8).
These results were supported by the additional sensitivity analyses (mixed models, tipping point analyses) based on the data set of 2020. The sensitivity analyses for the primary dataset of 3 Mar 2019 are missing.

It needs to be highlighted however, as this endpoint was not included in the multiplicity control strategy, these results cannot be considered as pivotal. In addition, the duration of the observation period was too short, as at least 52 weeks double-blind treatment period would be expected.

Categorical FVC decline

The FVC decline by clinic spirometry is supported with a significantly lower proportion of patients showing an FVC deterioration of >5% (37% vs 59% HR 0.42 (95% CI 0.0.25-0.69, p=0.001) or > 10% from baseline (14% vs 27% HR 0.44 (95% CI 0.23-0.84) p=0.01, respectively. Clarification is required if for this specific outcome measure the decline was measured as a change in percent predicted FVC (i.e. absolute change in FVC % predicted baseline minus end of treatment), or as rate of decline from baseline measured by linear regression and/or repeated measures mixed models. (**OC**)
In literature, an annual FVC decline > 10% is associated with increased mortality, when this outcome measure is based on the actual change in absolute FVC % predicted (baseline minus follow up) and is not based on linear regression. Therefore, the results should be presented as FVC % predicted change from baseline in order to be able to contextualise the results. (**OC**)

In order to contextualise the data, we made a cross-study comparison with nintedanib in a comparable target population. Nintedanib showed a difference with placebo in the presented decline in FVC in clinic spirometry of mean (95% CI) 68.3 (-31.4-168.1) mL. (Wells2020[3]), which aligns with the currently reported difference between pirfenidone and placebo (84.3 (95% CI 20.7-147.8) mL. However, cross-study comparisons must be interpreted with caution, e.g. as different inclusion criteria and methods of analyses can be applied.

Notwithstanding these reported beneficial effects, there appears to be a difference in the decrease in FVC by spirometry in mL by means the descriptive analyses and the linear regression, which needs discussion. The reported point estimate of the difference with placebo was in the descriptive analyse about 60 mL while the difference was point estimate 95.3 mL or 84.3 mL when the FVC was measured by linear regression. (**OC**)

Other secondary endpoints

Change in percent predicted DLco and change in 6MWD in meters were investigated as secondary endpoints. However, these endpoints were not included in the multiplicity control strategy and robustness of results with respect to missing data assumptions has not been examined. Therefore, the randomization might be lost for the analysed patient population and additional sensitivity analyses are needed like the mixed models and applied sensitivity analyses with imputations for missing values such as conducted for the key secondary outcome measures. **(OC)**

In relation to the mean changes in DLco (percent predicted) from baseline at Week 24 endpoint there was no difference between the treatment groups. A categorical decline with >15% absolute decrease in DLco (percent predicted) was higher in the placebo group than the pirfenidone group (odds ratio: 0.15; 95% CI: 0.03, 0.69; p=0.0150).

The Mean change in 6MWD from baseline at Week 24 analysed by rank ANCOVA resulted in a p-value of 0.0299 (showing improvements in patients receiving pirfenidone) however, categorical decline with >50 m absolute decrease in 6MWD was similar between treatment groups (odds ratio: 0.95; 95% CI: 0.55, 1.65; p=0.8574).

The results of endpoints investigating direct clinical effects were inconclusive.

The results of patients reported outcomes, i.e. George's respiratory questionnaire scores, University of California, San Diego–shortness of breath questionnaire scores, Leicester cough questionnaire scores, cough visual analog scale scores have not showed significant differences between the treatment groups. The trial was of short duration, which may have contributed to this observation.

Events such as acute exacerbations, non-elective hospitalization, deaths were recorded in the study; however, the number of these events was too small to make any meaningful conclusion:

[3] www.thelancet.com/respiratory **Published online March 5, 2020 https://doi.org/10.1016/S2213-2600(20)30036-9**

- Overall, 1 patient each in the pirfenidone group and the placebo group were reported to have experienced events that led to death.
- Acute Exacerbations were reported infrequently in both treatment groups (5 patients in the pirfenidone group and 7 patients in the placebo group) and therefore the median time to First Investigator-Reported Acute Exacerbations was not calculable.
- The incidences of all-cause hospitalizations and respiratory-related non-elective hospitalizations were similar between the treatment groups during the double-blind treatment period.

Conduct of the trial

The conduct of the study raises concerns about the validity of the generated database and whether the obtained efficacy results could be used to support the application **(MO).**

Previous studies showed that the home FVC could be used as primary outcome in clinical trials. However, it is currently insufficiently clarified why study population currently included was unable to generate home spirometry data of sufficient quality. The applicant is invited to explain why the generated home FVC data was of insufficient quality to support the application.

In addition, there are concerns regarding the apparent insufficient internal quality control of the generated data as the poor quality of the home FVC was not recognised during the trial. Therefore, the applicant is requested to clarify the following:

a. What oversight mechanisms were in place for both investigators/sites and for the sponsor to ensure that subjects were conducting daily spirometry assessments and to ensure the quality of the results being recorded. In addition, provide clarification on whether these measures were sufficient to identify issues with the conduct or quality of spirometry assessments during the trial, and what actions were taken to prevent reoccurrence of any issues that were identified.

b. Provide details on how data that was collected through the daily spirometry assessment was handled throughout the study, including any data validation or reconciliation activities that were conducted. In particular, the applicant should clarify whether the investigators/sites and/or sponsor had oversight of the data as it was being collected, and if there were any checks or controls in place (whether automated/manual, systematic or otherwise) to identify either where data wasn't being collected, or where data was being collected that was not of sufficient quality (e.g. biologically implausible data).

Furthermore, the database set of 3 Mar 2019 has been subject to additional cleaning activities not only in relation to the primary endpoint but also secondary endpoints.

The cleaning activities of the primary research dataset need to be further clarified and the applicant is requested to provide all details (Who, What, When, Where and Why) about all cleaning activities after database lock 3 Mar 2019. This applies to both the home FVC as well as the secondary outcome measures. For example, it needs to be clarified on which criteria the independent third party accepted or rejected the FVC data. The validity of the process of manual re-read of flow curves in spirometry should be discussed by the applicant. The maintaining of the blind during this review is not clear and should be discussed by the applicant.

Subgroup according to MMF use

The results were also analysed according to predefined subgroups. The provided subgroup analyses data do not indicate a benefit for patients who use MMF concomitantly. This subgroup using concomitant MMF showed a higher rate of lung function decline when MMF was co-administered with pirfenidone compared to placebo (-55.4 vs. 117.3 mL), while also a higher rate of hospitalisations was reported (22% vs 9%. Although the included number of MMF patients is low (n=22 each), the current data do not support the concomitant use of pirfenidone with MMF. The use in this subpopulation needs to be further discussed and the relevant information included in section 5.1 of the SmPC **(OC).**

Additional supportive literature

The applicant also provided additional supportive literature, showing the long-term efficacy in patients with IPF. Most studies were observational studies and the long term follow up might have introduced selection bias to individuals with more preserved lung function over time, because they will be less likely to discontinue treatment. The applicant as requested to discuss how the long-term results obtained in IPF can be extrapolated to the current application (**OC**).

In summary, it is considered that the available single pivotal study results are not compelling (CPMP/EWP/2330/99) and do not meet regulatory expectations for the clinical investigation of medicinal products for treatment of interstitial lung disease.

This is based on the following issues:

- Taking into consideration previous regulatory decisions, it is considered that the duration of the double-blind treatment period was too short
- The results of the primary efficacy endpoint, i.e. the rate of decline in FVC measured in millilitres with daily home spirometer over the 24-week treatment period, are not reliable
- Some improvements were seen in other secondary endpoints (the rate of FVC decline from baseline to week 24 and categorical change in FVC of >5% and 10% measured by clinic spirometry, a categorical decline with >15% absolute decrease in DLco and changes in 6MWD) however, due to the fact that these endpoints were not included in the multiplicity control strategy these results cannot be considered as pivotal and can be used for descriptive purposes only. In addition, for DLco and 6MWD endpoints robustness of results with respect to missing data assumptions has not been examined.
- The pivotal study does not provide consistent and robust evidence of a clinically meaningful improvement, neither in terms of the prevention of exacerbations/hospitalisation/death nor the control of symptoms associated with interstitial lung disease.

The conduct of the study raises concerns about the validity of the generated database and whether the obtained efficacy results could be used to support the application.

Additional expert consultation

N/A

Assessment of paediatric data on clinical efficacy

N/A

4.4.4. Conclusions on the clinical efficacy

Major objections were identified in relation to efficacy. It is considered that the available single pivotal study results are not compelling (CPMP/EWP/2330/99) and do not fulfil regulatory expectations for the clinical investigation of medicinal products for treatment of interstitial lung disease. In addition, the wording of the indication is not agreed.

Finally, there are also a number of other concerns which need to be addressed by the applicant.

4.5. Clinical safety

Introduction

The clinical safety data described is primarily based on the pivotal Phase II study MA39189, a double-blind (DB), multicentre, international, randomized, two-arm, placebo-controlled study with an open-label extension (OLE) in patients with fibrosing interstitial lung disease (ILD) who could not be classified with moderate or high confidence into any other category of fibrosing ILD by multidisciplinary team (MDT) review (UILD).

In addition, pooled safety data from pirfenidone Phase III studies in patients with idiopathic pulmonary fibrosis (IPF) are also presented in a quantitative side-by-side comparison with safety results from Study MA39189, in order to provide context for the safety assessment of pirfenidone treatment in UILD.

Ancillary safety information from four additional studies with pirfenidone in other ILDs (ML29875, ML30171 [TRAIL1], ML29864 [RELIEF] and PSSc-001 [LOTUSS]) are also presented, as requested by the Food and Drug Administration (FDA). Due to the limited data deriving from these trials, i.e. small trial or ongoing, direct comparisons with the available safety data from Study MA39189 are not applicable. Instead, a qualitative safety assessment is provided.

Table 24 **Summary of Studies Contributing to Safety Evaluation**

Study No.	Study Design	Company Sponsored or Supported	Indication	Population	Status	No. of Patients Evaluable for Safety	Study Duration
Pivotal Study in UILD							
MA39189	Phase II, multicenter, international, double-blind, two-arm, randomized, placebo-controlled	Sponsored	UILD	Patients with UILD	Complete	DB period: N=253: Pirfenidone: 127 Placebo: 126 Safety follow-up period: N=204*	First patient visit: 15 May 2017; Last patient last visit in study: 10 Jan 2020 (32 months)
Phase III Studies in IPF							
PIPF-004	Randomized, double-blind, placebo-controlled	Sponsored (InterMune)	IPF	Patients with IPF	Complete	N=435; Pirfenidone (2403 mg/day): 174 Pirfenidone (1197 mg/day): 87 Placebo: 174	First patient visit: 14 Jul 2006; Last patient completed study: 07 Nov 2008 (27 Months)
PIPF-006	Randomized, double-blind, placebo-controlled	Sponsored (InterMune)	IPF	Patients with IPF	Complete	N=344; Pirfenidone: 171 Placebo: 173	First patient visit: 27 Apr 2006; Last patient completed study: 31 Oct 2008 (30 Months)
PIPF-016	Randomized, double-blind, placebo-controlled	Sponsored (InterMune)	IPF	Patients with IPF	Complete	N=555; Pirfenidone: 278 Placebo: 277	First patient visit: 13 Jun 2011; Last patient completed study: 06 Feb 2014 (31 Months)

Studies with Pirfenidone in other ILDs							
PSSc-001 (LOTUSS)	Phase II, open-label, randomized (NCT01933334)	Sponsored	Scleroderma-associated ILD	Patients with SSc-ILD	Complete	N = 63 enrolled	First patient enrolled: 31 Oct 2013; Last patient completed study: 16 Sep 2014 (10.5 Months)
ML29864 (RELIEF)	Phase II, randomized, double-blind, placebo-controlled, parallel group, multicenter (EUdraCT #2014-000861-32)	Supported (IIS)	Progressive, non-IPF lung fibrosis	Patients with fNSIP, CVDLF, ALF and chronic HP	Terminated	N = 127 enrolled	First patient enrolled: 05 Apr 2016; Last patient completed study: 04 Oct. 2018 (30 Months)
ML29875	Phase II/III, single-center, randomized, double–blind, placebo-controlled (NCT02958917)	Supported (IIS)	CHP	Patients with Fibrotic Hypersensitivity Pneumonitis	Ongoing	N = 40 planned	Ongoing
ML30171 (TRAIL1)	Phase II, randomized, double-blind, placebo-controlled (NCT02808871)	Supported (IIS)	RA–ILD	Patients with RA–ILD	Ongoing	N = 270 planned	Ongoing

ALF = Asbestos induced lung fibrosis; CVDLF = Lung Fibrosis associated with Collagen / Vascular Disease; DB= Double-blind; fNSIP = fibrotic Non-Specific Interstitial Pneumonia; Hypersensitivity Pneumonitis = HP; IIS = Investigator-Initiated Study; ILD = Interstitial Lung Disease; IPF = Idiopathic Pulmonary Fibrosis; RA-ILD = Rheumatoid Arthritis Interstitial Lung Disease; SSc-ILD = systemic sclerosis–related ILD UILD = Unclassifiable Interstitial Lung Disease

*A total of 94 patients in the pirfenidone group and 110 patients in the placebo group entered the additional 12-month safety follow-up period.

Note: In the clinical trials listed above, the administered dose of pirfenidone was 2403 mg/day (3 × 267 mg capsules [801 mg], orally, three times daily). For PIPF-004, an additional dosing regimen 1197 mg/day (3 × 133 mg, orally, three times daily) was studied.

Sources: Khanna et al. 2016, Behr et al. 2017, Solomon et al. 2019

MA39189 (UILD)

Key features of the completed Study MA39189 are presented in **Error! Reference source not found.**. Enrolled patients were randomized to the pirfenidone or the placebo arm in a 1:1 ratio.

The MA39189 Primary CSR (data cut-off 18 December 2018) reported the results of the primary efficacy and safety analysis of the 24-week double-blind period.

The MA39189 Final CSR (last patient last visit [LPLV] 10 January 2020) reported the results from the final analysis after all subjects completed the additional open-label 12-month safety follow-up period (during which all patients received pirfenidone) and final follow-up visit, 28 days after the last open-label dose.

CHMP comment

The data cut-off of MA39189 Primary CSR for the analyses of safety data (data cut-off 18 December 2018) is different compared to the statement in the item 'under conduct of the study (see efficacy section): Collection of efficacy and safety data based on the 24 week double-blind treatment (database lock 3 Mar 2019)'. The applicant is requested to explain the differences and discuss the consequences of the difference. This also applies to MA39189 Final CSR. (**OC**)

Studies with Pirfenidone in IPF

The safety analyses from the IPF monotherapy studies included in this safety section are based on the pooled safety population (N = 623) treated with pirfenidone from studies PIPF-004 (N = 174), PIPF-006 (N = 171) and PIPF-016 (N = 278). Key study design features from these three IPF studies are presented in the table above.

CHMP comment

The 2010 Marketing Authorisation Application (MAA) was based on a development program that included two double-blind placebo-controlled randomized Phase 3 studies, Study PIPF-004 and Study PIPF-006. At the request of US FDA, Study PIPF-016, a Phase 3 randomized, double-blind, placebo-controlled study of pirfenidone in the treatment of mild to moderate IPF has been submitted with a type II variation. In that variation, the safety consisted form the pooling of these three studies. Therefore, the current comparison with these three studies is appropriate.

Studies with Pirfenidone in other ILDs

The characteristics of studies PSSc-001 (LOTUSS), ML29864 (RELIEF), ML29875 and ML30171 (TRAIL1) are described in the table above.

CHMP comment

The main safety analyses are the analyses of safety data from the pivotal Phase II study MA39189 and the comparisons with the pooled safety data from pirfenidone Phase III studies in patients with idiopathic pulmonary fibrosis (IPF).

Patient exposure

- **During double-blind treatment period**

The mean (SD) dose interruptions were short and were 5.6 (12.37) days in the pirfenidone group and 1.9 (10.35) days in the placebo group. The median daily doses of pirfenidone (2281.62 mg/day) and placebo (2299.80 mg/day) were comparable. The median dose intensity (%) of pirfenidone (94.94%) and placebo (95.27%) were comparable.

The proportion of patients with at least one dose modification was higher in the pirfenidone group (51 patients [40.2%]) than in the placebo group (34 patients [27.4%]). Similarly, the proportion of patients with at least one dose interruption was higher in the pirfenidone group (40 patients [31.5%]) than in the placebo group (12 patients [9.7%]). AEs known to be associated with pirfenidone such as nausea, LFT
increased, and photosensitivity reaction were the most commonly reported reason for dose modification and dose interruption (109 [64.5%] and 49 [90.7%], respectively, in the pirfenidone group and 32 [44.4%] and 9 [69.2%], respectively, in the placebo group).

Table 25 ***Extent of Exposure to Study Treatment***

	Pirfenidone (N=127) n (%)	Placebo (N=124) n (%)
Overall treatment duration, including dose interruptions (weeks)[a]		
n observed	127	124
Mean (SD)	21.47 (6.359)	23.04 (4.492)
Median	24.00	24.07
Q1 - Q3	23.43 - 24.29	23.86 - 24.43
Min - Max	0.1 - 28.3	0.9 - 28.0
Overall dose interruptions (days)[b]		
n observed	127	124
Mean (SD)	5.6 (12.37)	1.9 (10.35)
Median	0	0
Q1 - Q3	0 - 5.0	0 - 0
Min - Max	0 - 56	0 - 104
Average daily dose (mg/day)[c]		
n observed	126	124
Mean (SD)	2010.75 (446.077)	2167.30 (321.405)
Median	2281.62	2299.80
Q1 - Q3	1886.08 - 2301.67	2268.41 - 2302.88
Min - Max	165.7 - 2313.5	658.8 - 2317.2
Dose intensity (%)[d]		
n observed	126	124
Mean (SD)	83.41 (18.505)	89.86 (13.629)
Median	94.94	95.27
Q1 - Q3	78.49 - 95.34	93.85 - 95.54
Min - Max	6.9 - 96.1	27.4 - 96.4

Max = maximum; Min = minimum; Q = quartile; SD = standard deviation.
[a] Overall treatment duration, including dose interruptions = (Date of last positive dose of randomized treatment received [pirfenidone/placebo] - date of first intake of randomized treatment + 1) / 7.
[b] Overall number of days treatment interrupted.
[c] Average daily dose was calculated by summing up the number of capsules taken, divided by the number of days on treatment, including treatment interruptions.
[d] Dose intensity = (total dose received / total dose planned) *100.

Extent of Exposure to Study Treatment – safety follow up

The mean [SD] treatment duration, including dose interruptions, was similar between treatment groups (44.81 [12.566] weeks in the previously treated with pirfenidone group and 43.33 [14.489] weeks in the previously treated with placebo group). The mean (SD) duration of dose interruptions was higher in the previously treated with placebo group than in the previously treated with pirfenidone group (9.6 [22.68] vs 3.3 [8.85] days, respectively).
The median daily dose in the previously treated with pirfenidone group was higher than in the previously treated with placebo group (2341.90 mg/day vs 2258.14 mg/day).
The median dose intensity (%) was similar between those previously treated with pirfenidone (89.75%) and those previously treated with placebo (87.91%) The proportion of patients with at least one dose modification was higher in the previously treated with placebo group (60 patients [54.5%]) than in the previously treated with pirfenidone group (41 patients [43.6%]). Similarly, the proportion of patients with at least one dose interruption was higher in the previously treated with placebo group (34 patients [30.9%]) than in the previously treated with pirfenidone group (24 patients [25.5%]). AEs were the most commonly reported reason for dose modification and dose interruption (99 [55.9%] and 26 [89.7%], respectively, in the previously treated with pirfenidone group and 170 [68.3%] and 46 [90.2%], respectively, in the previously treated with placebo group).

Table 26 ***Overall summary of treatment duration and interruptions during the 12-month safety follow-up period (Safety Follow-up Population)***

	Randomized Pirfenidone (N=94)	Randomized Placebo (N=110)	All treated with Pirfenidone (N=204)
Overall treatment duration including dose interruptions (weeks) [a]			
n observed	94	110	204
Mean (std)	44.81 (12.566)	43.33 (14.489)	44.01 (13.624)
Median	49.14	49.36	49.14
Q1 - Q3	47.71 - 51.43	47.57 - 51.14	47.71 - 51.14
Min - Max	2.3 - 52.9	2.0 - 58.0	2.0 - 58.0
Overall treatment duration excluding dose interruptions (weeks) [b]			
n observed	94	110	204
Mean (std)	44.34 (12.519)	41.96 (14.827)	43.06 (13.830)
Median	48.79	48.86	48.86
Q1 - Q3	47.29 - 51.00	39.29 - 50.71	45.07 - 50.86
Min - Max	2.3 - 52.9	2.0 - 58.0	2.0 - 58.0
Overall dose interruptions (days) [c]			
n observed	94	110	204
Mean (std)	3.3 (8.85)	9.6 (22.68)	6.7 (17.94)
Median	0	0	0
Q1 - Q3	0 - 1.0	0 - 7.0	0 - 2.0
Min - Max	0 - 56	0 - 139	0 - 139

CHMP comment

The safety data on pirfenidone in patients with unclassifiable interstitial lung disease (UILD) is derived from one study (MA39189) which enrolled 253 patients (127 in the pirfenidone group and 126 in the placebo group).

Exposure

The study consisted of the double – blind period (24 weeks) and the safety follow-up (12 months). A total of 102 patients (80.3%) in the pirfenidone group and 114 patients (90.5%) in the placebo group completed the double-blind treatment period of the study, whereas 159 (59.1% previously treated with pirfenidone and 66.7% previously treated with placebo) completed the whole study period. See patients flow in the efficacy section.

During the double–blind period, the mean (SD) treatment duration, including dose interruptions, was 21.47 [6.359] weeks in the pirfenidone group vs. 23.04 [4.492] weeks in the placebo group. During the safety follow-up the mean [SD] treatment duration, including dose interruptions, was 44.01 weeks. A significant proportion of patients on pirfenidone had at least one dose interruption (31.5% in double – blind period and 28.4% in safety follow up) and at least one dose modification (40.2% in double – blind period and 49.5% in safety follow up). Of note, AEs were the most commonly reported reason for dose modification and dose interruption.

Adverse events

- **Double-blind treatment period**

General overview of TEAEs

Overall, 120 patients (94.5%) in the pirfenidone group and 101 patients (81.5%) in the placebo group reported at least 1 TEAE; 90 patients (70.9%) in the pirfenidone group and 57 patients (46.0%) in the placebo group reported at least 1 TEAE that was considered by the investigator to be related to study treatment.

The majority of patients had at least 1 TEAE of severity Grade 1 (102 patients [80.3%] in the pirfenidone group and 89 patients [71.8%] in the placebo group) or Grade 2 (85 patients [66.9%] in the pirfenidone group and 57 patients [46.0%] in the placebo group). There were 29 patients (22.8%) in the pirfenidone group and 26 patients (21.0%) in the placebo group with TEAEs of severity Grade ≥3. TEAEs with fatal outcomes (Grade 5) were reported in 1 patient (0.8%) in each treatment group. These deaths were

assessed by the Investigator as not related to the study treatment. After the double-blind treatment period but before the open-label treatment period, 2 patients (1.6%) in the placebo group died more than 28 days after last positive dose of randomized treatment, without receiving open-label treatment.

Overall, 18 patients (14.2%) in the pirfenidone group and 19 patients (15.3%) in the placebo group reported 31 and 22 SAEs, respectively, of which 1 patient in each treatment group had drug-related SAEs according to the investigator.

A total of 19 patients (15.0%) in the pirfenidone group and 5 patients (4.0%) in the placebo group discontinued study treatment due to a total of 33 and 6 TEAEs, respectively. Overall, 27 patients (21.3%) in the pirfenidone group and 15 patients (12.1%) in the placebo group had TEAEs that led to dose reduction, and 32 patients (25.2%) in the pirfenidone group and 9 patients (7.3%) in the placebo group had TEAEs that led to dose interruption.

Unsurprisingly, the proportion of patients experiencing AEs known to be associated with pirfenidone such as GI disorders, photosensitivity reaction, rash, and weight decreased were higher in the pirfenidone group (72 [56.7%], 10 [7.9%], 19 [15.0%], and 11 [8.7%], respectively) compared with the placebo group (50 [40.3%], 2 [1.6%], 13 [10.5%], and 6 [4.8%], respectively).
There were no clinically meaningful differences in the safety profile in different subgroups (split by age, gender, weight, concomitant MMF, presence/absence of IPAF, baseline FVC or DLco).
The only clinically meaningful difference in vital signs was found for weight (increased weight loss in the pirfenidone group), which is in line with the known safety profile for pirfenidone.

Table 27 ***Summary of Safety Profile (Safety Population) During Double-Blind Treatment Period***

	Pirfenidone (N=127) n (%)	Placebo (N=124) n (%)
Number of patients experiencing any TEAEs	120 (94.5)	101 (81.5)
Number of patients experiencing any related TEAEs	90 (70.9)	57 (46.0)
Number of patients experiencing any serious TEAEs	18 (14.2)	19 (15.3)
Number of patients experiencing any related serious TEAEs	1 (0.8)	1 (0.8)
Number of patients experiencing any severe TEAEs	29 (22.8)	26 (21.0)
Number of patients experiencing any related severe TEAEs	6 (4.7)	2 (1.6)
Number of patients experiencing any TEAEs of special interest[a]	0	0
Number of patients experiencing any related TEAEs of special interest[a]	0	0
Number of patients experiencing any GI disorder[b]	72 (56.7)	50 (40.3)
Number of patients experiencing any related GI disorder[b]	60 (47.2)	32 (25.8)
Number of patients experiencing any hepatic side effects[c]	1 (0.8)	0
Number of patients experiencing any photosensitivity[d]	10 (7.9)	2 (1.6)
Number of patients experiencing any related photosensitivity[d]	10 (7.9)	2 (1.6)
Number of patients experiencing any rash[e]	19 (15.0)	13 (10.5)
Number of patients experiencing any related rash[e]	13 (10.2)	9 (7.3)
Number of patients experiencing any increase in QT interval[f]	1 (0.8)	1 (0.8)
Number of patients experiencing any angioedema	0	0
Number of patients experiencing any related angioedema	0	0
Number of patients experiencing any dizziness	11 (8.7)	13 (10.5)
Number of patients experiencing any related dizziness	10 (7.9)	4 (3.2)
Number of patients experiencing any weight decreased	11 (8.7)	6 (4.8)
Number of patients experiencing any related weight decreased	10 (7.9)	2 (1.6)
Number of patients experiencing any fatigue	21 (16.5)	19 (15.3)
Number of patients experiencing any related fatigue	16 (12.6)	12 (9.7)
Number of patients experiencing TEAEs leading to death	1 (0.8)	2 (1.6)
Number of patients experiencing related TEAEs leading to death	0	0
Number of patients experiencing TEAEs leading to treatment discontinuation	19 (15.0)	5 (4.0)
Number of patients experiencing related TEAEs leading to treatment discontinuation	16 (12.6)	1 (0.8)
Number of patients with Grade 3-4 laboratory liver test results	2 (1.6)	1 (0.8)
AST (SGOT)	1 (0.8)	0
ALT (SGPT)	1 (0.8)	1 (0.8)
Alkaline phosphatase	0	0
Total bilirubin	0	0

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ECG = electrocardiogram; GI = gastrointestinal; PT = preferred term; QTcF = QT interval corrected using Fridericia's formula; SGOT = glutamic-oxalacetic transaminase; SGPT = glutamic-pyruvic transaminase; SOC = system organ class; TEAE = treatment-emergent adverse event; ULN = upper limit of normal.
Medical Dictionary for Regulatory Activities (MedDRA) version 22.1 was used.
[a] Cases of potential drug-induced liver injury that included an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law: (ALT or AST >3 × ULN + total bilirubin >2 × ULN).
[b] GI Disorders (SOC).

The SOCs with the highest incidence of TEAEs were GI disorders (72 patients [56.7%] in the pirfenidone group and 50 patients [40.3%] in the placebo group), followed by infections and infestations (58 patients [45.7%] in the pirfenidone group and 53 patients [42.7%] in the placebo group), and respiratory, thoracic and mediastinal disorders (36 patients [28.3%] in the pirfenidone group and 43 patients [34.7%] in the placebo group). At the PT level, the TEAEs with the highest incidence were nausea (41 patients [32.3%] in the pirfenidone group and 9 patients [7.3%] in the placebo group), followed by diarrhea (23 patients [18.1%] in the pirfenidone group and 23 patients [18.5%] in the placebo group), and fatigue (21 patients [16.5%] in the pirfenidone group and 19 patients [15.3%] in the placebo group).

Table 28 ***Treatment-Emergent Adverse Events (≥5% in Either Treatment Group) by System Organ Class and Preferred Term (Safety Population)***

	Pirfenidone (N=127) n (%)	Placebo (N=124) n (%)
Patients with at least 1 TEAE	120 (94.5)	101 (81.5)
Total number of TEAEs	652	483
Gastrointestinal disorders		
Patients with at least one TEAE	72 (56.7)	50 (40.3)
Nausea	41 (32.3)	9 (7.3)
Diarrhea	23 (18.1)	23 (18.5)
Dyspepsia	17 (13.4)	7 (5.6)
Vomiting	14 (11.0)	6 (4.8)
Gastroesophageal reflux disease	10 (7.9)	6 (4.8)
Constipation	8 (6.3)	4 (3.2)
Infections and infestations		
Patients with at least one TEAE	58 (45.7)	53 (42.7)
Upper respiratory tract infection	12 (9.4)	9 (7.3)
Respiratory tract infection	11 (8.7)	5 (4.0)
Bronchitis	10 (7.9)	3 (2.4)
Lower respiratory tract infection	8 (6.3)	13 (10.5)
Nasopharyngitis	7 (5.5)	7 (5.6)
Respiratory, thoracic and mediastinal disorders		
Patients with at least one TEAE	36 (28.3)	43 (34.7)
Cough	20 (15.7)	16 (12.9)
Dyspnea	15 (11.8)	22 (17.7)
General disorders and administration site conditions		
Patients with at least one TEAE	34 (26.8)	29 (23.4)
Fatigue	21 (16.5)	19 (15.3)
Skin and subcutaneous tissue disorders		
Patients with at least one TEAE	34 (26.8)	22 (17.7)
Rash	9 (7.1)	8 (6.5)
Photosensitivity reaction	8 (6.3)	0
Metabolism and nutrition disorders		
Patients with at least one TEAE	33 (26.0)	20 (16.1)
Decreased appetite	20 (15.7)	11 (8.9)
Nervous system disorders		
Patients with at least one TEAE	31 (24.4)	27 (21.8)
Headache	13 (10.2)	4 (3.2)
Dizziness	11 (8.7)	13 (10.5)
Investigations		
Patients with at least one TEAE	27 (21.3)	13 (10.5)
Weight decreased	11 (8.7)	6 (4.8)
Musculoskeletal and connective tissue disorders		
Patients with at least one TEAE	20 (15.7)	26 (21.0)
Back pain	8 (6.3)	3 (2.4)
Psychiatric disorders		
Patients with at least one TEAE	17 (13.4)	6 (4.8)
Depression	7 (5.5)	0
Injury, poisoning and procedural complications		
Patients with at least one TEAE	11 (8.7)	9 (7.3)
Cardiac disorders		
Patients with at least one TEAE	10 (7.9)	9 (7.3)
Eye disorders		
Patients with at least one TEAE	10 (7.9)	2 (1.6)
Vascular disorders		
Patients with at least one TEAE	9 (7.1)	10 (8.1)

- **12-month safety follow-up**

General overview of TEAEs

Overall, 80 patients (85.1%) previously treated with pirfenidone and 99 patients (90.0%) previously treated with placebo reported at least 1 AE; 43 patients (45.7%) previously treated with pirfenidone and 74 patients (67.3%) previously treated with placebo reported at least 1 AE that was considered by the investigator to be related to study treatment. Overall, 34 patients (36.2%) previously treated with pirfenidone and 31 patients (28.2%) previously treated with placebo reported at least 1 severe AE.

Overall, 26 patients (27.7%) previously treated with pirfenidone and 27 patients (24.5%) previously treated with placebo reported SAEs, of which 1 patient in each treatment group had drug-related SAEs according to the investigator. The AEs with fatal outcomes were reported in 6 patients (6.4%) previously treated with pirfenidone and 9 patients (8.2%) previously treated with placebo.

Table 29 ***Summary of Safety Profile during 12-Month Safety Follow-Up Period***

(Safety Follow-Up Population)

	Randomized Pirfenidone (N=94) n (%)	Randomized Placebo (N=110) n (%)	All treated with Pirfenidone (N=204) n (%)
Number of patients experiencing any AEs	80 (85.1)	99 (90.0)	179 (87.7)
Number of patients experiencing any related AEs	43 (45.7)	74 (67.3)	117 (57.4)
Number of patients experiencing any serious AEs	26 (27.7)	27 (24.5)	53 (26.0)
Number of patients experiencing any related serious AEs	1 (1.1)	1 (0.9)	2 (1.0)
Number of patients experiencing any severe AEs	34 (36.2)	31 (28.2)	65 (31.9)
Number of patients experiencing any related severe AEs	6 (6.4)	3 (2.7)	9 (4.4)
Number of patients experiencing any AEs of special interest[a]	0	1 (0.9)	1 (0.5)
Number of patients experiencing any related AEs of special interest[a]	0	1 (0.9)	1 (0.5)
Number of patients experiencing any GI disorder[b]	43 (45.7)	67 (60.9)	110 (53.9)
Number of patients experiencing any related GI disorder[b]	28 (29.8)	55 (50.0)	83 (40.7)
Number of patients experiencing any hepatic side effects[c]	0	1 (0.9)	1 (0.5)
Number of patients experiencing any photosensitivity[d]	6 (6.4)	11 (10.0)	17 (8.3)
Number of patients experiencing any related photosensitivity[d]	5 (5.3)	11 (10.0)	16 (7.8)
Number of patients experiencing any rash[e]	13 (13.8)	21 (19.1)	34 (16.7)
Number of patients experiencing any related rash[e]	11 (11.7)	18 (16.4)	29 (14.2)
Number of patients experiencing any angioedema	0	0	0
Number of patients experiencing any related angioedema	0	0	0
Number of patients experiencing any dizziness	4 (4.3)	8 (7.3)	12 (5.9)
Number of patients experiencing any related dizziness	4 (4.3)	3 (2.7)	7 (3.4)
Number of patients experiencing any weight decreased	2 (2.1)	7 (6.4)	9 (4.4)
Number of patients experiencing any related weight decreased	1 (1.1)	5 (4.5)	6 (2.9)
Number of patients experiencing any fatigue	5 (5.3)	12 (10.9)	17 (8.3)
Number of patients experiencing any related fatigue	3 (3.2)	8 (7.3)	11 (5.4)
Number of patients experiencing AEs leading to death	6 (6.4)	9 (8.2)	15 (7.4)
Number of patients experiencing related AEs leading to death	0	0	0
Number of patients experiencing AEs leading to treatment discontinuation	7 (7.4)	14 (12.7)	21 (10.3)
Number of patients experiencing related AEs leading to treatment discontinuation	4 (4.3)	10 (9.1)	14 (6.9)
Number of patients with Grade 3-4 laboratory liver test results	0	1 (0.9)	1 (0.5)
AST (SGOT)	0	1 (0.9)	1 (0.5)

The SOCs with the highest incidence of AEs were infections and infestations (55 patients [58.5%] previously treated with pirfenidone and 58 patients [52.7%] previously treated with placebo), followed by GI disorders (43 patients [45.7%] previously treated with pirfenidone and 67 patients [60.9%] previously treated with placebo), and respiratory, thoracic and mediastinal disorders (33 patients [35.1%] previously treated with pirfenidone and 31 patients [28.2%] previously treated with placebo). At the PT level, the AEs with the highest incidence were nausea (15 patients [16.0%] previously treated with pirfenidone and 30 patients [27.3%] previously treated with placebo), followed by lower respiratory tract infection (10 patients
[10.6%] previously treated with pirfenidone and 16 patients [14.5%] previously treated with placebo), and nasopharyngitis (10 patients [10.6%] previously treated with pirfenidone and 11 patients [10.0%] previously treated with placebo).

Table 30 ***Adverse Events (≥5% in All Treated with Pirfenidone) by System Organ Class and Preferred Term During the 12-Month Safety Follow-Up***

Period (Safety Follow-Up Population)

	Randomized Pirfenidone (N=94) n (%)	Randomized Placebo (N=110) n (%)	All treated with Pirfenidone (N=204)
Patients with at least one AE	80 (85.1)	99 (90.0)	179 (87.7)
Total number of AEs	410	559	969
Infections and infestations			
Patients with at least one AE	55 (58.5)	58 (52.7)	113 (55.4)
Lower respiratory tract infection	10 (10.6)	16 (14.5)	26 (12.7)
Nasopharyngitis	10 (10.6)	11 (10.0)	21 (10.3)
Upper respiratory tract infection	10 (10.6)	4 (3.6)	14 (6.9)
Respiratory tract infection	9 (9.6)	9 (8.2)	18 (8.8)
Pneumonia	5 (5.3)	10 (9.1)	15 (7.4)
Gastrointestinal disorders			
Patients with at least one AE	43 (45.7)	67 (60.9)	110 (53.9)
Nausea	15 (16.0)	30 (27.3)	45 (22.1)
Diarrhea	9 (9.6)	15 (13.6)	24 (11.8)
Gastroesophageal reflux disease	7 (7.4)	7 (6.4)	14 (6.9)
Dyspepsia	5 (5.3)	8 (7.3)	13 (6.4)
Vomiting	4 (4.3)	18 (16.4)	22 (10.8)
Abdominal pain upper	1 (1.1)	10 (9.1)	11 (5.4)
Respiratory, thoracic and mediastinal disorders			
Patients with at least one AE	33 (35.1)	31 (28.2)	64 (31.4)
Cough	10 (10.6)	9 (8.2)	19 (9.3)
Dyspnea	9 (9.6)	11 (10.0)	20 (9.8)
Skin and subcutaneous tissue disorders			
Patients with at least one AE	22 (23.4)	35 (31.8)	57 (27.9)
Rash	8 (8.5)	16 (14.5)	24 (11.8)
Photosensitivity reaction	2 (2.1)	9 (8.2)	11 (5.4)

	Randomized Pirfenidone (N=94) n (%)	Randomized Placebo (N=110) n (%)	All treated with Pirfenidone (N=204)
General disorders and administration site conditions			
Patients with at least one AE	15 (16.0)	27 (24.5)	42 (20.6)
Fatigue	5 (5.3)	12 (10.9)	17 (8.3)
Nervous system disorders			
Patients with at least one AE	14 (14.9)	30 (27.3)	44 (21.6)
Dizziness	4 (4.3)	8 (7.3)	12 (5.9)
Headache	3 (3.2)	12 (10.9)	15 (7.4)
Metabolism and nutrition disorders			
Patients with at least one AE	13 (13.8)	18 (16.4)	31 (15.2)
Decreased appetite	7 (7.4)	13 (11.8)	20 (9.8)
Cardiac disorders			
Patients with at least one AE	12 (12.8)	9 (8.2)	21 (10.3)
Musculoskeletal and connective tissue disorders			
Patients with at least one AE	10 (10.6)	19 (17.3)	29 (14.2)
Vascular disorders			
Patients with at least one AE	10 (10.6)	10 (9.1)	20 (9.8)
Injury, poisoning and procedural complications			
Patients with at least one AE	8 (8.5)	7 (6.4)	15 (7.4)
Investigations			
Patients with at least one AE	6 (6.4)	16 (14.5)	22 (10.8)
Psychiatric disorders			
Patients with at least one AE	6 (6.4)	5 (4.5)	11 (5.4)

AE = adverse event.
Medical Dictionary for Regulatory Activities version 22.1 was used.
Source: Modified from Table 14.3.7.2.1

CHMP comment

In study MA39189, during the double-blind treatment period, more patients treated with pirfenidone experienced at least 1 TEAE than placebo patients (94.5% vs. 81.5%). In addition, there was higher rates of AEs leading to discontinuation (15% vs. 5.2%), treatment-related TEAEs (70.9% vs. 46.0%) in the pirfenidone group as compared to the placebo group.

There were no significant differences between the treatment groups in the percentage of patients experiencing serious (14.2% versus 15.3%) and severe TEAEs (22.8% versus 21.0%).

During the 12 month safety – follow up 88% of patients experienced at least 1 TEAE, 57% treatment-related TEAEs, 26% serious and 32% severe TEAEs.

During the double-blind treatment period the SOCs with the highest incidence of TEAEs were GI disorders (72 patients [56.7%] in the pirfenidone group and 50 patients [40.3%] in the placebo group), followed by infections and infestations (58 patients [45.7%] in the pirfenidone group and 53 patients [42.7%] in the placebo group), and respiratory, thoracic and mediastinal disorders (36 patients [28.3%] in the pirfenidone group and 43 patients [34.7%] in the placebo group). The same SOCs had the highest incidence of TEAEs also during the 12 month safety – follow up.

The most common AEs observed in the pirfenidone group and occurring with a higher incidence compared with placebo were nausea (32.3% vs. placebo 7.3%), fatigue (16.5 % vs. 15.3%), decreased appetite (15.7 % vs. placebo 8.9%), cough (15.7% vs. placebo 12.9%), dyspepsia (13.4% vs. placebo 5.6%) vomiting (11% vs. placebo 4.8), headache (10.2% vs. placebo 3.2%), upper respiratory tract infection (9.4% vs. placebo 7.3%), gastrooesophageal reflux disease (7.9% vs. placebo 4.8%), weight decreased (8.7% vs. placebo 4.8%), bronchitis (7.9 % vs. placebo 2.4%), rash (7.1% vs. placebo 6.5%), back pain (6.3% vs. placebo 2.4%), photosensitivity reaction(6.3 % vs. placebo 0%), constipation(6.3% vs.

placebo 3.2%) Of note, nausea, fatigue, decreased appetite were also the most frequently reported TEAEs leading to the treatment discontinuation.

All these TEAEs, with an exception of back pain and bronchitis are already included in section 4.8 of the SmPC.

Back pain is proposed to be added to the list of ADRs as a part of this procedure, which is supported. In relation to bronchitis, the applicant should discuss whether this AE should be included in the table of ADRs or provide the relevant justification, if otherwise **(OC).**

The applicant should also discuss imbalances which were observed in relation to the frequency of depression reported in the study i.e 5.5% of patients in the pirfenidone group and 0 patients receiving placebo. It is noted that one case of depression was considered related to the study drug by investigator **(OC).**

Further discussion is also required in relation to the long term safety of pirfenidone. There was no comparator arm during the 12 month safety follow up. Therefore, the applicant is requested to compare the exposure-adjusted incidence rates (EAIRs) for TEAEs reported during the safety follow up with the exposure-adjusted incidence rates (EAIRs) for TEAEs reported in the placebo group in the double-blind period. Any imbalances need to be commented by the applicant. This comparison should be also done for SAEs **(OC).**

In addition, the applicant should investigate whether there was any increase in the rate of TEAEs over time. Therefore, the exposure-adjusted incidence rates (EAIRs) for TEAEs reported in the double- blind period should be compared to the exposure-adjusted incidence rates (EAIRs) for TEAEs reported during the safety follow up **(OC).**

Adverse Events by Causality – double blind period

The SOCs with the highest incidence of related TEAEs were GI disorders (60 patients [47.2%] in the pirfenidone group and 32 patients [25.8%] in the placebo group), followed by skin and subcutaneous tissue disorders (25 patients [19.7%] in the pirfenidone group and 13 patients [10.5%] in the placebo group), and metabolism and nutrition disorders (22 patients [17.3%] in the pirfenidone group and 9 patients [7.3%] in the placebo group).

At the PT level, the related TEAEs with the highest incidence were nausea (38 patients [29.9%] in the pirfenidone group and 6 patients [4.8%] in the placebo group), followed by decreased appetite (19 patients [15.0%] in the pirfenidone group and 9 patients [7.3%] in the placebo group), diarrhea (16 patients [12.6%] in the pirfenidone group and 14 patients [11.3%] in the placebo group), and fatigue (16 patients [12.6%] in the pirfenidone group and 12 patients [9.7%] in the placebo group).

Table 31 ***Treatment-Emergent Related Adverse Events (≥5% in Either Treatment Group) by System Organ Class and Preferred Term (Safety Population)***

	Pirfenidone (N=127) n (%)	Placebo (N=124) n (%)
Patients with at least 1 TEAE	90 (70.9)	57 (46.0)
Total number of TEAEs	256	102
Gastrointestinal disorders		
Patients with at least one TEAE	60 (47.2)	32 (25.8)
Nausea	38 (29.9)	6 (4.8)
Diarrhea	16 (12.6)	14 (11.3)
Dyspepsia	11 (8.7)	4 (3.2)
Vomiting	8 (6.3)	3 (2.4)
Skin and subcutaneous tissue disorders		
Patients with at least one TEAE	25 (19.7)	13 (10.5)
Photosensitivity reaction	8 (6.3)	0
Rash	7 (5.5)	6 (4.8)
Metabolism and nutrition disorders		
Patients with at least one TEAE	22 (17.3)	9 (7.3)
Decreased appetite	19 (15.0)	9 (7.3)
General disorders and administration site conditions		
Patients with at least one TEAE	21 (16.5)	12 (9.7)
Fatigue	16 (12.6)	12 (9.7)
Investigations		
Patients with at least one TEAE	21 (16.5)	5 (4.0)
Weight decreased	10 (7.9)	2 (1.6)
Nervous system disorders		
Patients with at least one TEAE	16 (12.6)	7 (5.6)
Dizziness	10 (7.9)	4 (3.2)

TEAE = treatment-emergent adverse event.
Multiple occurrences of the same adverse event in one individual were only counted once.
System organ classes (SOCs) and preferred terms (PTs) within SOCs were presented by pirfenidone decreasing frequencies.
Medical Dictionary for Regulatory Activities version 22.1 was used.
Source: Modified from Table 14.3.2.3.1

Adverse Events by Causality- safety follow –up

Overall, 43 patients (45.7%) previously treated with pirfenidone and 74 patients (67.3%) previously treated with placebo reported 100 and 210 drug-related AEs, respectively. The SOCs with the highest incidence of patients who reported drug-related AEs were GI disorders (28 patients [29.8%] previously treated with pirfenidone and 55 patients [50.0%] previously treated with placebo) followed by skin and subcutaneous tissue disorders (14 patients [14.9%] previously treated with pirfenidone and 28 patients [25.5%] previously treated with placebo). At the PT level, the drug-related AEs with the highest incidence of patients were rash (7 patients [7.4%] previously treated with pirfenidone and 14 patients [12.7%] previously treated with placebo), followed by vomiting (3 patients [3.2%] previously treated with pirfenidone and 14 patients [12.7%] previously treated with placebo), and nausea (13 patients [13.8%] previously treated with pirfenidone and 28 patients [25.5%] previously treated with placebo).

Adverse Events by Intensity

The majority of patients had at least 1 TEAE of severity Grade 1 (102 patients [80.3%] in the pirfenidone group and 89 patients [71.8%] in the placebo group) or Grade 2 (85 patients [66.9%] in the pirfenidone group and 57 patients [46.0%] in the placebo group). There were 26 patients (20.5%) in the pirfenidone group and 20 patients (16.1%) in the placebo group with TEAEs of severity Grade 3; and 5 patients (3.9%) in the pirfenidone group and 7 patients (5.6%) in the placebo group with TEAEs of severity Grade 4. One patient (0.8%) in the pirfenidone group and 1 patient in the placebo group had a TEAE of severity Grade 5.

The SOCs with the highest incidence of TEAEs with a severity Grade ≥3 were metabolism and nutrition disorders, followed by infections and infestations, and respiratory, thoracic and mediastinal disorders. At the PT level, the TEAEs with the highest incidence with a severity of Grade ≥3 were dyspnoea, followed by exacerbation or progression of ILD, and pneumonia.

Table 32 **Treatment-emergent grade 3-5 adverse events by System Organ Class (SOC) i.e. Respiratory, thoracic and mediastinal disorders, Infections and infestations, and Metabolism and nutrition disorders, and Preferred Term (PT) (Safety Population)**

Primary System Organ Class Preferred Term	Pirfenidone (N=127) n (%)	Placebo (N=124) n (%)
Respiratory, thoracic and mediastinal disorders		
Pts with at least one TEAE	4 (3.1)	10 (8.1)
Total number of TEAEs	6	11
Cough	1 (0.8)	1 (0.8)
Dyspnoea	1 (0.8)	4 (3.2)
Interstitial lung disease	1 (0.8)	3 (2.4)
Pulmonary embolism	1 (0.8)	0
Pulmonary fibrosis	1 (0.8)	1 (0.8)
Respiratory disorder	1 (0.8)	0
Productive cough	0	1 (0.8)
Pulmonary hypertension	0	1 (0.8)
Infections and infestations		
Pts with at least one TEAE	6 (4.7)	5 (4.0)
Total number of TEAEs	8	5
Campylobacter gastroenteritis	1 (0.8)	0
Gastroenteritis	1 (0.8)	0
Influenza	1 (0.8)	0
Lower respiratory tract infection	1 (0.8)	1 (0.8)
Pneumonia	1 (0.8)	3 (2.4)
Respiratory tract infection bacterial	1 (0.8)	0
Urinary tract infection	1 (0.8)	0
Urosepsis	1 (0.8)	0
Parainfluenzae virus infection	0	1 (0.8)
Metabolism and nutrition disorders		
Pts with at least one TEAE	7 (5.5)	3 (2.4)
Total number of TEAEs	8	3
Hyponatraemia	2 (1.6)	1 (0.8)
Hypophosphataemia	2 (1.6)	0
Diabetic metabolic decompensation	1 (0.8)	0
Gout	1 (0.8)	0
Hyperglycaemia	1 (0.8)	0
Hyperkalaemia	1 (0.8)	0
Diabetes mellitus inadequate control	0	1 (0.8)
Hypoglycaemia	0	1 (0.8)

CHMP comment

In general, most AEs grade 3-5 occurred just once, especially in the pirfenidone group. Hyponatriaemia and hypophosphataemia occurred each twice in the pirfenidone group, while dyspnoea , interstitial lung disease, pneumonia occurred more than once in the placebo group. The numbers are too low for conclusions. The nature of the most severe TEAEs (grade 4 and 5) is not clearly presented and needs to be provided. (**OC**)

Serious adverse event/deaths/other significant events

- **Deaths - during double-blind treatment period**

Overall, 1 patient (0.8%) in each treatment group died during the double-blind treatment period; these deaths were assessed by the Investigator as not related to the study treatment.

Table 33 ***Deaths during Double-Blind Treatment Period (Safety Population)***

	Pirfenidone (N=127) n (%)	Placebo (N=124) n (%)
During double-blind treatment period[a]		
Death		
Yes	1 (0.8)	1 (0.8)
No	126 (99.2)	123 (99.2)
Death related to respiratory disease[b]		
Yes	1 (0.8)	0
No	0	1 (0.8)
Primary cause of death[c]		
Adverse event	1 (0.8)	1 (0.8)
Progression of disease	0	0
Other	0	0
Autopsy performed		
Yes	0	0
No	1 (0.8)	1 (0.8)
Unknown	0	0
After double-blind treatment period[d]		
Death		
Yes	0	2 (1.6)
No	127(100.0)	122 (98.4)
Death related to respiratory disease[b]		
Yes	0	1 (0.8)
No	0	1 (0.8)
Primary cause of death[c]		
Adverse event	0	2 (1.6)
Progression of disease	0	0
Other	0	0
Autopsy performed		
Yes	0	1 (0.8)
No	0	1 (0.8)
Unknown	0	0

eCRF = electronic case report form; SOC = system organ class
[a] Deaths reported from randomized treatment start date up to 28 days after last positive dose of randomized treatment.
[b] Deaths related to the SOC "Respiratory, thoracic and mediastinal disorders".
[c] Cause of death as reported in the study discontinuation eCRF page.
[d] Deaths reported more than 28 days after last positive dose of randomized treatment.
Source: Table 14.3.5.1.1

Patient 1 received the most recent dose of pirfenidone on Study Day 17 before the serious event of pulmonary fibrosis. On Study Day 25, the patient died due to unclassifiable lung fibrosis exacerbation and cardiac decompensation. The Investigator considered pulmonary fibrosis to be unrelated to study drug.

Patient 2 received the most recent dose of placebo on Study Day 97 before the fatal events of acute myocardial infarction and cardio-respiratory arrest. On the same day (Study Day 97), the patient died due to acute myocardial infarction and cardio-respiratory arrest during cardiac catheterization. The Investigator considered acute myocardial infarction and cardio-respiratory arrest to be unrelated to study drug. The local ethics committee has demanded that the patient is unblinded after the death, as a precaution measure towards the safety of the other patients of the study in the country. The unblinding has been granted by the study team and has been performed on 12 Jul 2018.

More Than 28 days after last positive dose of randomized treatment:

Patient 3 received the most recent dose of placebo on Study Day 171 before the fatal event of subarachnoid hemorrhage. On Study Day 202, the patient died due to subarachnoid hemorrhage.
The Investigator considered subarachnoid hemorrhage to be unrelated to study drug.

Patient 4 received the most recent dose of placebo on Study Day 84 before the fatal progression of pulmonary fibrosis when the patient also discontinued treatment.
On the same day, the patient was transferred to another hospital. When the 28-day follow-up visit was scheduled, the investigator has learned that the patient died on Study Day 113 due to pulmonary fibrosis in the other hospital. Therefore, study discontinuation date was set for Study Day 113 due to death but not as AE leading

Deaths - 12-month safety follow-up period

During the 12-month safety follow-up period, a total of **7 patients (7.4%) previously treated with pirfenidone and 10 patients (9.1%) previously treated with placebo died**; among these patients, 5 (5.3%) previously treated with pirfenidone and 4 (3.6%) previously treated with placebo had deaths related to the underlying respiratory disease. Of the 17 deaths during the safety follow-up period, all deaths were considered as not related to study drug by the investigator.

Patient 5 was hospitalized on suspicion of cerebrovascular accident and was diagnosed with Grade 4 cerebrovascular accident (life-threatening). On Study Day 406, the patient withdrew consent from the study as a result of continued hospitalization due to cerebrovascular accident which was reported as ongoing at study discontinuation. On Study Day 434, the patient died peacefully while in coma. It was reported that the patient's death was as a result of complications due to cerebrovascular accident (details not reported).

This death should not have been reported in the clinical database as the patient withdrew consent beforehand and has discontinued from the study before the event.

Patient 6 died 14 days after the last official dose of the open-label period (Study Day 564); therefore, there was no safety follow-up visit where an AE leading to death.

Table 34 ***Deaths During 12-Month Safety Follow-Up Period (Safety Follow-Up Population)***

	Randomized Pirfenidone (N=94) n (%)	Randomized Placebo (N=110) n (%)	All treated with Pirfenidone (N=204)
Death			
Yes	7 (7.4)	10 (9.1)	17 (8.3)
No	87 (92.6)	100 (90.9)	187 (91.7)
Death related to respiratory disease[a]			
Yes	5 (5.3)	4 (3.6)	9 (4.4)
No	2 (2.1)	6 (5.5)	8 (3.9)
Primary cause of death[b]			
Adverse event	5 (5.3)	8 (7.3)	13 (6.4)
Progression of disease	2 (2.1)	1 (0.9)	3 (1.5)
Other	0	0	0
Missing	0	1 (0.9)	1 (0.5)
Autopsy performed			
Yes	0	1 (0.9)	1 (0.5)
No	6 (6.4)	8 (7.3)	14 (6.9)
Missing	1 (1.1)	1 (0.9)	2 (1.0)

eCRF = electronic case report form; SOC = system organ class.
[a] Deaths related to the SOC Respiratory, thoracic and mediastinal disorders.
[b] Cause of death as reported in the study discontinuation eCRF page.
Source: Table 14.3.7.7.1

CHMP comment:

During the double blind period, 2 subjects died: 1 in the pirfenidone group and 1 in the placebo group. During the 12-month safety follow-up period, 17 patients died. None of these deaths were considered related to pirfenidone by investigators. However, further clarifications from the Applicant are requested. The table in the study report states that an adverse event was a primary cause of death in 13 patients. The applicant should provide the list of these events and discussion on their potential relationship to the study drug **(OC).**

Serious Adverse Events

During double-blind treatment period

Overall, 18 patients (14.2%) in the pirfenidone group and 19 patients (15.3%) in the placebo group reported a total of 31 and 22 serious TEAEs, respectively. The SOCs with the highest incidence of patients who reported SAEs were infections and infestations (7 patients [5.5%] in the pirfenidone group and 5 patients [4.0%] in the placebo group), followed by respiratory, thoracic and mediastinal disorders (5 patients [3.9%] in the pirfenidone group and 7 patients [5.6%] in the placebo group). At the PT level, the TEAEs with the highest incidence of patients who reported SAEs were exacerbation of ILD, pneumonia, and dyspnea (each PT occurred in 1 patient [0.8%] in the pirfenidone group and 3 patients [2.4%] in the placebo group) followed by cardiac failure congestive (2 patients [1.6%] in the pirfenidone group and 0 patients in the placebo group).

Overall, 1 patient (0.8%) each in the pirfenidone group and the placebo group reported a drug-related SAE. One patient (Patient) in the pirfenidone group had **decreased appetite** (Grade 2; from Study Day 13 to Study Day 53), and 1 patient (Patient) in the placebo group had ALT increased (Grade 3; from Study Day 50 to ongoing).

Table 35 ***Treatment-emergent serious adverse events by System Organ Class (SOC) and Preferred Term (PT) (Safety Population)***

Primary System Organ Class Preferred Term	Pirfenidone (N=127) n (%)	Placebo (N=124) n (%)
Patients with at least one TEAE	18 (14.2)	19 (15.3)
Total number of TEAEs	31	22
Infections and infestations		
Pts with at least one TEAE	7 (5.5)	5 (4.0)
Total number of TEAEs	9	5
Campylobacter gastroenteritis	1 (0.8)	0
Gastroenteritis	1 (0.8)	0
Influenza	1 (0.8)	0
Lower respiratory tract infection	1 (0.8)	1 (0.8)
Pneumonia	1 (0.8)	3 (2.4)
Respiratory tract infection	1 (0.8)	0
Respiratory tract infection bacterial	1 (0.8)	0
Urinary tract infection	1 (0.8)	0
Urosepsis	1 (0.8)	0
Parainfluenzae virus infection	0	1 (0.8)
Respiratory, thoracic and mediastinal disorders		
Pts with at least one TEAE	5 (3.9)	7 (5.6)
Total number of TEAEs	8	7
Chronic obstructive pulmonary disease	1 (0.8)	0
Cough	1 (0.8)	0
Dyspnoea	1 (0.8)	3 (2.4)
Interstitial lung disease	1 (0.8)	3 (2.4)
Pulmonary embolism	1 (0.8)	0
Pulmonary fibrosis	1 (0.8)	1 (0.8)
Respiratory disorder	1 (0.8)	0
Cardiac disorders		
Pts with at least one TEAE	3 (2.4)	3 (2.4)
Total number of TEAEs	3	4
Cardiac failure congestive	2 (1.6)	0
Cardiac failure	1 (0.8)	0
Acute myocardial infarction	0	1 (0.8)
Atrial fibrillation	0	1 (0.8)
Cardio-respiratory arrest	0	1 (0.8)
Pericarditis	0	1 (0.8)
Injury, poisoning and procedural complications		
Pts with at least one TEAE	3 (2.4)	1 (0.8)
Total number of TEAEs	3	1
Procedural pain	1 (0.8)	0
Spinal fracture	1 (0.8)	0
Wrist fracture	1 (0.8)	0
Spinal compression fracture	0	1 (0.8)
Metabolism and nutrition disorders		
Pts with at least one TEAE	3 (2.4)	0
Total number of TEAEs	3	0
Decreased appetite	1 (0.8)	0
Gout	1 (0.8)	0
Hyponatraemia	1 (0.8)	0
Nervous system disorders		
Pts with at least one TEAE	2 (1.6)	1 (0.8)
Total number of TEAEs	2	1
Cerebrovascular accident	1 (0.8)	1 (0.8)
Loss of consciousness	1 (0.8)	0
Eye disorders		
Pts with at least one TEAE	1 (0.8)	0
Total number of TEAEs	1	0
Retinal detachment	1 (0.8)	0
Musculoskeletal and connective tissue disorders		
Pts with at least one TEAE	1 (0.8)	0
Total number of TEAEs	1	0
Musculoskeletal pain	1 (0.8)	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)		
Pts with at least one TEAE	1 (0.8)	0
Total number of TEAEs	1	0

TEAEs: Treatment-emergent adverse events.
Multiple occurrences of the same adverse event in one individual counted only once

Primary System Organ Class Preferred Term	Pirfenidone (N=127) n (%)	Placebo (N=124) n (%)
Prostate cancer	1 (0.8)	0
General disorders and administration site conditions		
Pts with at least one TEAE	0	1 (0.8)
Total number of TEAEs	0	1
General physical health deterioration	0	1 (0.8)
Immune system disorders		
Pts with at least one TEAE	0	1 (0.8)
Total number of TEAEs	0	1
Lung transplant rejection	0	1 (0.8)
Investigations		
Pts with at least one TEAE	0	1 (0.8)
Total number of TEAEs	0	1
Alanine aminotransferase increased	0	1 (0.8)
Renal and urinary disorders		
Pts with at least one TEAE	0	1 (0.8)
Total number of TEAEs	0	1
Renal failure	0	1 (0.8)

12-month safety follow-up period

Overall, 26 patients (27.7%) previously treated with pirfenidone and 27 patients (24.5%) previously treated with placebo reported a total of 51 and 52 SAEs, respectively. The SOCs with the highest incidence of patients who reported SAEs were infections and infestations (11 patients [11.7%] previously treated with pirfenidone and 13 patients [11.8%] previously treated with placebo), followed by respiratory, thoracic and mediastinal disorders (11 patients [11.7%] previously treated with pirfenidone and 10 patients
[9.1%] previously treated with placebo). At the PT level, the SAEs with the highest incidence of patients were pneumonia (2 patients [2.1%] previously treated with pirfenidone and 6 patients [5.5%] previously treated with placebo), followed by exacerbation or progression of ILD (5 patients [5.3%] previously treated with pirfenidone and 3 patients [2.7%] previously treated with placebo), and atrial fibrillation (3 patients [3.2%] previously treated with pirfenidone and 0 patients previously treated with placebo).

CHMP comment:

During the double–blinded period, the incidence of SAEs was 14.2% in the pirfenidone group and 15.3% in the placebo group. Exacerbation of ILD, pneumonia, dyspnea and cardiac failure congestive were among the most frequent SAEs. Only one case of decreased appetite was considered to be related to pirfenidone and this ADR is already listed in the SmPC.

During the safety follow–up 53 patients (26.0%) experienced SAEs. For two patients SAEs were considered related the study drug i.e one patient had Grade 2 decreased appetite and 1 patient had Grade 3 ALT increased. Again these ADRs are already listed in the SmPC.

Pneumonia and exacerbation of ILD was the most frequently reported SAEs (8 patients each) followed by dyspnoea and lower respiratory tract infection (5 patients). A total 10 SAEs within the SOP of cardiac disorders were reported in the study.

Other Significant Adverse Events

Adverse events of special interest (AESI) for this trial include the following:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's law
- Suspected transmission of an infectious agent by the trial treatment.

No cases of AESI were reported.

Some other TEAE were subject to specific attention (selected AEs), i.e. nausea, diarrhoea, weight decreased, fatigue, decreased appetite, photosensitivity, rash, and SOC GI disorders.

Table 36 **Frequency of specific Treatment Emergent Adverse Events (Safety Population) During Double-Blind Treatment** *Period*

	Pirfenidone (N=127) n (%)	Placebo (N=124) n (%)
Number of patients experiencing any GI disorder[b]	72 (56.7)	50 (40.3)
Number of patients experiencing any related GI disorder[b]	60 (47.2)	32 (25.8)
Number of patients experiencing any hepatic side effects[c]	1 (0.8)	0
Number of patients experiencing any photosensitivity[d]	10 (7.9)	2 (1.6)
Number of patients experiencing any related photosensitivity[d]	10 (7.9)	2 (1.6)
Number of patients experiencing any rash[e]	19 (15.0)	13 (10.5)
Number of patients experiencing any related rash[e]	13 (10.2)	9 (7.3)
Number of patients experiencing any increase in QT interval[f]	1 (0.8)	1 (0.8)
Number of patients experiencing any angioedema	0	0
Number of patients experiencing any related angioedema	0	0
Number of patients experiencing any dizziness	11 (8.7)	13 (10.5)
Number of patients experiencing any related dizziness	10 (7.9)	4 (3.2)
Number of patients experiencing any weight decreased	11 (8.7)	6 (4.8)
Number of patients experiencing any related weight decreased	10 (7.9)	2 (1.6)
Number of patients experiencing any fatigue	21 (16.5)	19 (15.3)
Number of patients experiencing any related fatigue	16 (12.6)	12 (9.7)

b GI Disorders (SOC).
c Elevations in ALT and AST >3 × ULN at the same timepoint.
d PTs of photodermatosis, photosensitivity reaction, pruritus, pruritus allergic, and pruritus generalized.
e PTs of nodular rash, rash, rash erythematous, rash generalized, rash macular, rash maculo-papular, rash papular, rash pruritic, rash follicular, exfoliative rash, solar dermatitis, solar urticaria, sunburn and erythema and dry skin.
f QTcF interval >500 ms or >60 ms change from baseline, a repeat ECG within 24 hours.
Source: Table 14.3.1.1.1.

The time to onset of the selected adverse events, nausea, diarrhoea, weight decreased, fatigue, decreased appetite, photosensitivity, rash, and SOC GI disorders, is also presented in Kaplan-Meier plots. The analysis was in line with experience from the three pivotal IPF clinical studies, and no new safety concerns were noted. These AESIs were consistent with the safety profile of pirfenidone.

CHMP comment

Recently, drug-induced liver injury (DILI) has been identified as an ADR of pirfenidone. Cases of severe drug-induced liver injury, including isolated cases with fatal outcome, have been reported post-marketing. Hence DILI was appointed as an AESI. There were no AESIs of drug-induced liver injury or transmission of infectious agent reported.

Furthermore, 8 AEs were appointed as selected AEs. The time of onset of the 8 selected AEs was presented in 8 separate Kaplan-Meyer graphs. At a glance, the timing of these selected AEs was consistent with the safety profile of pirfenidone of the pooled phase III studies (Module 2.7.4, Appendix 2, Figure 3). However, no other description or clear tables are provided to compare with the pooled Phase III clinical trials (PIPF-004/006/016). To have a clear view on these selected AEs, the applicant is requested to provide a similar graph as for the pooled Phase III clinical trials (PIPF-004/006/016) or a plain table with the results. (**OC**)

The proposed changes to the SmPC:

Table 1 Summary of Adverse Drug Reactions per frequency category

	Frequency	
System Organ Class preferred term	**Idiopathic Pulmonary Fibrosis (n=623)**	**Unclassifiable Interstitial Lung Disease (n=127)**
Study Duration	52-72 weeks	24 weeks
Infections and infestations		
Upper respiratory tract infection	Common	Common
Urinary tract infection	Common	Common
Blood and lymphatic system disorders		
Agranulocytosis[1][2]	~~Rare~~Uncommon[2]	Uncommon[2]
Immune system disorders		
Angioedema[1][2]	Uncommon[2]	Uncommon[2]
Anaphylaxis[1]	Uncommon[1] ~~Not known~~	Uncommon[1]
Metabolism and nutrition disorders		
~~Anorexia~~	~~Very common~~	
Weight decreased	Common	Common
Decreased appetite	~~C~~Very common	Very common
Hyponatraemia[1]	Uncommon[1]	Common[1]
Psychiatric disorders		
Insomnia	Common	Common
Nervous system disorders		
Headache	Very common	Very common
Dizziness	Common	Common
Somnolence	Common	Uncommon
Dysgeusia	Common	Uncommon
Lethargy	Common	Not reported
Vascular disorders		
Hot flush	Common	Common

Respiratory, thoracic and mediastinal disorders		
Dyspnoea	Common	Very common
Cough	Common	Very common
Productive cough	Common	Uncommon
Gastrointestinal disorders		
Dyspepsia	Very common	Very common
Nausea	Very common	Very common
Diarrhoea	Very common	Very common
Gastroesophageal reflux disease	Common	Common
Vomiting	Common	Very common
Abdominal distension	Common	Uncommon
Abdominal discomfort	Common	Common
Abdominal pain	Common	Common
Abdominal pain upper	Common	Common
Stomach discomfort	Common	Common
Gastritis	Common	Uncommon
Constipation	Common	Common
Flatulence	Common	Common
Hepatobiliary disorders		
ALT increased	Common	Common
AST increased	Common	Uncommon
Gamma glutamyl transferase increased	Common	Common
Total serum bilirubin increased in combination with increases of ALT and AST[1]	Uncommon[1]	Uncommon[1]
Drug-induced liver injury[2]	Uncommon[2]	Uncommon[2]
Skin and subcutaneous tissue disorders		
Photosensitivity reaction	Very common	Common
Rash	Very common	Common
Pruritus	Common	Common
Erythema	Common	Common
Dry skin	Common	Common
Rash erythematous	Common	Common
Rash macular	Common	Uncommon
Rash pruritic	Common	Common
Musculoskeletal and connective tissue disorders		
Myalgia	Common	Common
Back pain	Very common	Common
Arthralgia	Common	Common
General disorders and administration site conditions		
Fatigue	Very common	Very common
Asthenia	Common	Common
Non-cardiac chest pain	Common	Common
Injury poisoning and procedural complications		
Sunburn	Common	Common

1. Identified through post-marketing surveillance, frequency category based on the highest incidence observed during the pivotal IPF and UILD clinical trials.
2. Identified through post-marketing surveillance, not reported during the pivotal clinical trials. The frequency category for ADRs observed only in the post-marketing setting is defined as the upper limit of the 95% confidence interval calculated on the basis of the total number of patients exposed to Esbriet in the IPF and UILD pivotal trials.

The applicant proposed the update to section 4.8 of the SmPC and include two lists of ADRs per indication.

This approach is not supported. In line with the guideline, only 1 table (or tabulated list) should list all adverse reactions with respective frequency category. This applies to the SmPC as well as the package leaflet. Separate frequencies/tables are only acceptable in exceptional cases where the safety profiles markedly differ depending on the use of the product; e.g. for a product used for very different indications or at different posologies.

In addition, it should be noted that the proposed revision of section 4.8 – summary of the safety profile doesn't comply with the SmPC guideline. Section 4.8 should be based upon best-evidence assessment of all safety information from all clinical trials, PASS and spontaneous reporting and should be updated as necessary during the life-cycle of the product. It is not expected to describe the initial clinical safety data set, which will be shortly outdated after marketing authorisation. Also, frequencies of adverse reactions cited in the summary of safety profile should be stated as accurately as possible, e.g. by including % in brackets. The SmPC needs to be corrected **(OC).**

Comparison of the safety of pirfenidone in patients with IPF with patients with UILD

The safety of pirfenidone in patients with IPF has been evaluated in three randomized, double-blind, placebo-controlled, completed Phase III studies: PIPF-004, PIPF-006, and PIPF-016.

The safety data presented below are focused on the comparison between the pooled IPF studies (004/006/016) and the UILD study (MA39189) double-blind safety data. As these studies were of differing durations (52-72 weeks in IPF vs. 24 weeks in UILD), this analysis is based both on the following:

- Exposure-adjusted data
- The first 24 weeks of treatment (taking into account the skewed temporal distribution of many AEs), which has been shown to be the time interval whereby the most common pirfenidone-related AEs tend to occur

Overall, similar rates per 100-patient years (PY) were observed between the IPF and UILD safety populations (967.76 [CI: 945.98, 989.55] vs. 1051.87 [CI: 971.13, 1132.61], respectively) when considering the totality of the data

When focusing on the 24-week treatment period following an exposure-adjusted approach, the safety profile of pirfenidone emerging from the UILD study is in line with that established in IPF, with TEAEs of similar nature and an overall lower frequency (rate per 100 PY in UILD = 1127.94 [CI:1036.22, 1219.66]; rate per 100 PY in IPF 1503.93 [CI: 1458.29, 1549.56].

Table 37 ***Safety overview regarding AEs in IPF versus UILD (Safety populations)***

Roche-MA39189-uILD Final Analysis (Database Snapshot Date:06-Apr-2020)

Table 20.3: Safety overview regarding AEs (Safety population)

	Idiopathic Pulmonary Fibrosis (N=623)	Unclassifiable Interstitial Lung Disease (N=127)
Overall (DBP)		
Duration in Study (PY)	783.46	61.98
Patients* (Number of Events)	617 (7582)	120 (652)
Rate per 100 PY	967.76	1051.87
95%-CI	945.98 : 989.55	971.13 : 1132.61
Week 0-24		
Duration in Study (PY)	277.41	51.51
Patients* (Number of Events)	605 (4172)	120 (581)
Rate per 100 PY	1503.93	1127.94
95%-CI	1458.29 : 1549.56	1036.22 : 1219.66

DBP: Double -blind period; PY: Patient years; CI: Confidence interval.
Overall (DBP) is first dose to last dose plus 28 days irrespective of duration of exposure.
Week 0-24 is day 1 of exposure to last day of exposure or day 168 whatever came first.
*Patients with at least one event
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In addition, the nature of TEAEs in > 5% of the safety populations across IPF and UILD was shown to be similar over the 24-week treatment period, and the affected SOCs between the two safety populations turned out to be the same.

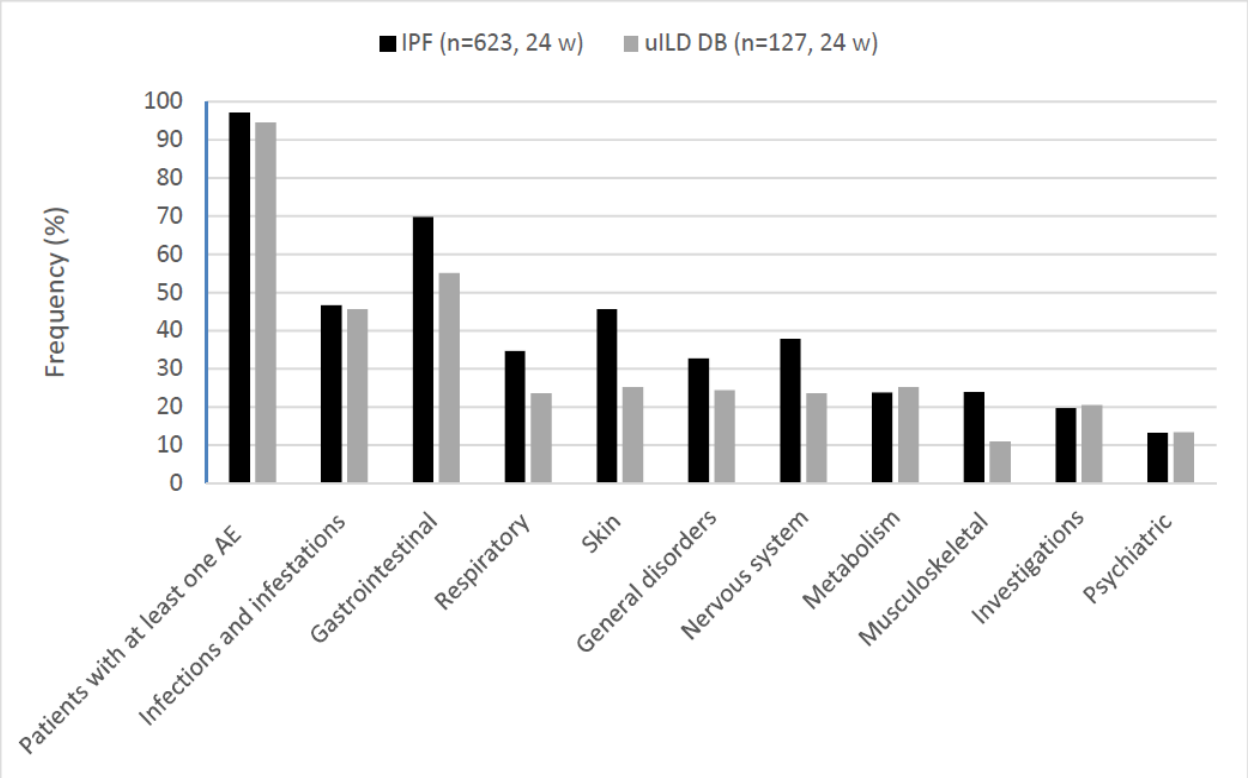
The most frequently reported all grade AEs occurring in ≥ 5% of the safety population for both IPF and UILD were previously known adverse drug reactions of pirfenidone. The proportion of patients with at least one TEAE was similar between the IPF and UILD safety populations (97.1% vs. 94.5%, respectively)

More specifically, the SOC with the most frequently reported TEAEs for both IPF and UILD safety populations was GI disorders, followed by infections and infestations, and skin and subcutaneous tissue disorders. The corresponding AE frequency for each SOC was higher or similar in IPF as compared to UILD (69.8% vs. 55.1%, 46.7% vs. 45.7% and 45.7% vs. 25.2% respective).

Overall, the most common PTs reported occurred with higher or similar frequency in IPF as compared to UILD (nausea 32.1% vs. 31.5%, diarrhoea 20.2% vs. 16.5%, dyspepsia 15.2% vs. 13.4%, upper respiratory tract infection 12.8% vs. 8.7%, rash 25% vs. 6.3% headache 18.3% vs. 10.2%, dizziness 14.3% vs. 8.7%, cough 15.7% vs. 11.8% and fatigue 18.1% vs. 16.5%, anorexia 10.8% vs. not reported, respectively
AE occurrence with lower frequency in IPF vs. UILD (e.g. depression) consists of isolated events and is considered chance finding.

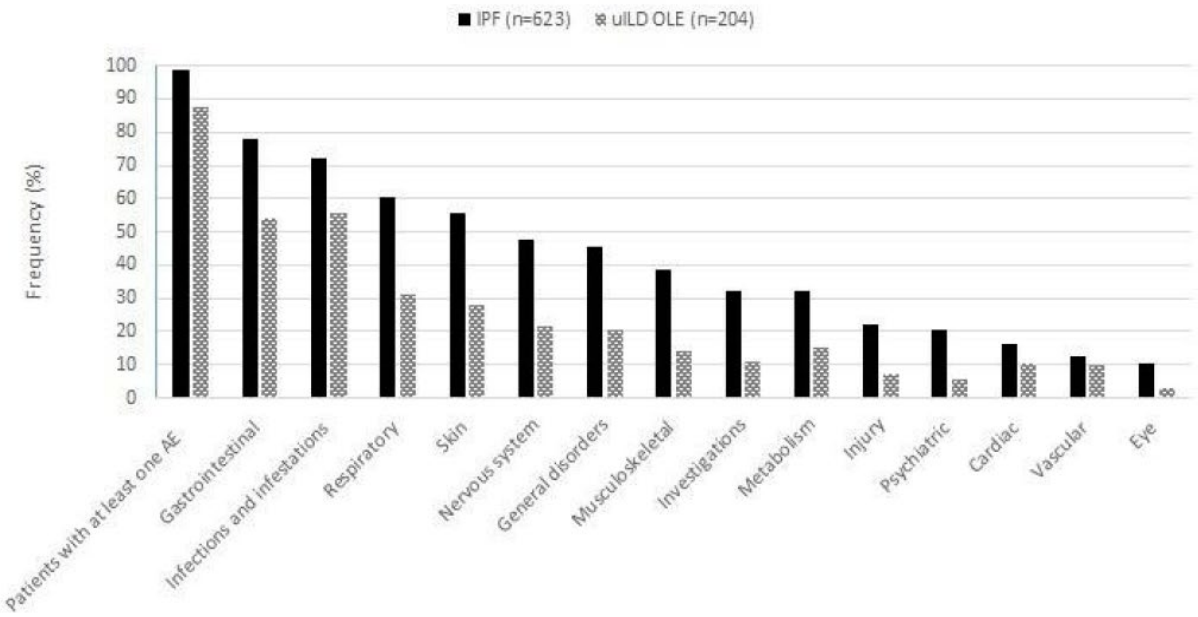
Figure below shows the distribution of all TEAEs occurring with ≥5% frequency between the IPF studies with 52-72 weeks duration and the 52 weeks safety follow-up period of Study MA39189. With due consideration to the underlying differences in study design, this shows that the most commonly affected SOCs remained the same, and that the frequency of TEAEs in the OLE phase of the UILD study was consistently lower than that observed in the IPF studies.

Figure 6 ***Distribution of TEAEs in Patients Treated with Esbriet in IPF Clinical Trials vs. Double-Blind Treatment Phase of MA39189 (≥5% Frequency, 24-Week data)***



DB: Double-blind; IPF: Idiopathic pulmonary fibrosis; TEAE: Treatment emergent adverse event; UILD: Unclassifiable interstitial lung disease

Figure 7 ***Distribution of TEAEs in Patients Treated with Esbriet in IPF Clinical Trials vs. Open-Label Extension Phase of MA39189 (≥5% Frequency)***



CHMP comment: The event rates per 100 PY in the pooled IPF studies (004/006/016) was generally comparable to the event rates per 100 PY in the double-blinded period of UILD study MA39189. In the 24-week treatment period, the safety profile of pirfenidone emerging from the UILD study is somewhat lower in UILD (rate per 100 PY = 1127.94) than in IPF (rate per 100 PY in IPF 1503.93).

In the 24-week treatment period, more events occurred in PTs lower respiratory tract infections and respiratory tract infections in SOC Infections and Infestations, PT decreased appetite in SOC Metabolism and Nutrition Disorder and PT weight decreased in SOC Investigations during treatment in patients with UILD. The applicant is requested to discuss. Kaplan-Meier plots of time to onset of the AE plotted as in Module 2.7.4, Appendix 2 Figure 2 are requested for these events. (**OC**)

Laboratory findings

During double-blind treatment period

Hematology

Small fluctuations in hematology parameters were observed over time, but there were no clinically meaningful and notable changes from baseline in any hematology parameter.

Table 38 ***Laboratory data - CTCAE gradable parameters - Hematology: Frequencies of Grade 1 - 4, Grade 3 - 4 and Grade 4 Shifts from Baseline (Safety Population)***

Parameter	Pirfenidone (N=127) Shift of			Placebo (N=124) Shift of		
	1 - 4 grades n (%)	3 - 4 grades n (%)	4 grades n (%)	1 - 4 grades n (%)	3 - 4 grades n (%)	4 grades n (%)
White blood cell (WBC) count [10^9/L]: Hypo	1 (0.8)	0	0	1 (0.8)	0	0
Haemoglobin [g/L]: Hyper	4 (3.1)	0	0	4 (3.2)	0	0
Haemoglobin [g/L]: Hypo	11 (8.7)	0	0	16 (12.9)	0	0
Platelet count [10^9/L]: Hypo	5 (3.9)	0	0	2 (1.6)	0	0
Neutrophils (Absolute count) [10^9/L]: Hypo	1 (0.8)	1 (0.8)	0	0	0	0
Lymphocytes (Absolute count) [10^9/L]: Hyper	2 (1.6)	0	0	1 (0.8)	0	0
Lymphocytes (Absolute count) [10^9/L]: Hypo	15 (11.8)	0	0	10 (8.1)	0	0

Chemistry

There were no clinically meaningful and notable changes from baseline in any chemistry parameter. Grade 3/4 elevation in ALT was reported in 1 patient (0.8%) each in the pirfenidone and placebo groups, and Grade 3/4 elevation in AST was reported in 1 patient (0.8%) in the pirfenidone group.

Table 39 ***Laboratory data - CTCAE gradable parameters - Chemistry: Frequencies of Grade 1 - 4, Grade 3 - 4 and Grade 4 Shifts from Baseline (Safety Population)***

Parameter	Pirfenidone (N=127) Shift of			Placebo (N=124) Shift of		
	1 - 4 grades n (%)	3 - 4 grades n (%)	4 grades n (%)	1 - 4 grades n (%)	3 - 4 grades n (%)	4 grades n (%)
Sodium [mmol/L]: Hyper	5 (3.9)	0	0	2 (1.6)	0	0
Sodium [mmol/L]: Hypo	12 (9.4)	1 (0.8)	0	14 (11.3)	0	0
Potassium [mmol/L]: Hyper	8 (6.3)	1 (0.8)	0	9 (7.3)	1 (0.8)	0
Potassium [mmol/L]: Hypo	13 (10.2)	0	0	6 (4.8)	0	0
Bicarbonate [mmol/L]: Hypo	12 (9.4)	0	0	16 (12.9)	0	0
Glucose [mmol/L]: Hyper	41 (32.3)	1 (0.8)	0	37 (29.8)	0	0
Glucose [mmol/L]: Hypo	2 (1.6)	0	0	7 (5.6)	1 (0.8)	1 (0.8)
Albumin [g/L]: Hypo	5 (3.9)	0	0	6 (4.8)	0	0
Phosphorus [mmol/L]: Hypo	28 (22.0)	3 (2.4)	0	25 (20.2)	0	0
Calcium [mmol/L]: Hyper	9 (7.1)	0	0	10 (8.1)	0	0
Calcium [mmol/L]: Hypo	6 (4.7)	0	0	7 (5.6)	1 (0.8)	1 (0.8)
Total bilirubin [umol/L]: Hyper	4 (3.1)	0	0	5 (4.0)	0	0
Alkaline phosphatase [U/L]: Hyper	7 (5.5)	0	0	5 (4.0)	0	0
ALAT (SGPT) [U/L]: Hyper	19 (15.0)	1 (0.8)	1 (0.8)	15 (12.1)	0	0
ASAT (SGOT) [U/L]: Hyper	22 (17.3)	0	0	22 (17.7)	0	0
Uric acid [umol/L]: Hyper	11 (8.7)	2 (1.6)	0	17 (13.7)	2 (1.6)	0

CHMP comment:
Haematology.

Small fluctuations in hematology parameters were observed over time, but the applicant claimed that these changes were not clinically meaningful. Nevertheless, the applicant should comment on the fact that more patients in the pirfenidone group as compared to the placebo group reported grade 1 – 4 decrease in the level of platelets (3.9% versus 1.6 %) and white blood cells (especially lymphocytes-11.8 versus 8.1 %). For these parameters there was a shift to lower values during the study. Of note, agranulocytosis is currently listed as a ADR in section 4.8 of the SmPC. Further updates to the adverse reactions list within the SOC Blood and lymphatic system disorders should be considered **(OC).**

Chemistry

The applicant claimed that there were no clinically meaningful and notable changes from baseline in any chemistry parameter.
However, it is noted that a significantly higher percentage of patients in the pirfenidone group reported grade 1 – 4 hypokalemia (10.2 % in the pirfenidone group and 4.8% in the placebo group). This could be linked to the fact that more patients treated with pirfenidone reported GI related AEs and poor nutrition. The applicant should discuss and consider updating section 4.8 of the SmPC (OC). Currently only hyponatraemia is listed in this section. In addition, the applicant should provide a general discussion on changes in other chemistry parameters which could be observed in patients with poor nutrition. The chemistry results reported in the MA39189 study should be reviewed in this context **(OC).**

There were 2 grade 4 events, one of hypocalciaemia, and one of hypoglaemia. The applicant is requested to discuss the details of these patients. (**OC**)

As described in the SmPC, elevated transaminases have been commonly reported in patients treated with pirfenidone. There is no section in the CSR that describes the course of the transaminases during the study. As the events of elevation of ASAT/ALAT were present, the applicant is requested to provide the numbers of patients who had elevated transaminases, in accordance with the definitions of protocol,

- patients with a >3 to <5 × ULN increase in ALT or AST levels without hyperbilirubinemia
- For patients with a >3 to <5 × ULN increase in ALT or AST levels with symptoms or hyperbilirubinemia
- For patients with a >5 × ULN increase in ALT or AST levels. (**OC**)

Other Safety Tests

Electrocardiograms

All patients had QTcF intervals <500 ms at baseline, except 1 patient in the pirfenidone group for whom the QTcF value was missing, and there were no QTcF intervals ≥500 ms reported at Week 28 or early discontinuation.

Table 40 ***ECG - Maximum QTcF Interval and change from baseline by category (Safety Population)***

	Parameter Category	Baseline n (%)	Week 12 n (%)	Week 24 n (%)	Week 28 n (%)	Early Disc. n (%)
Pirfenidone (N=127)	QTcF interval					
	<500 ms	127 (100)	107 (84.3)	100 (78.7)	95 (74.8)	20 (15.7)
	500 to 550 ms	0	0	0	0	0
	>550 ms	0	0	0	0	0
	Missing	0	4 (3.1)	1 (0.8)	4 (3.1)	3 (2.4)
	Change from Baseline QTcF interval					
	<=30 ms		103 (81.1)	98 (77.2)	95 (74.8)	19 (15.0)
	31 to 60 ms		3 (2.4)	2 (1.6)	0	1 (0.8)
	>60 ms		1 (0.8)	0	0	0
	Missing		4 (3.1)	1 (0.8)	4 (3.1)	3 (2.4)
Placebo (N=124)	QTcF interval					
	<500 ms	124 (100)	113 (91.1)	113 (91.1)	106 (85.5)	5 (4.0)
	500 to 550 ms	0	1 (0.8)	0	0	0
	>550 ms	0	0	0	0	0
	Missing	0	1 (0.8)	1 (0.8)	7 (5.6)	2 (1.6)
	Change from Baseline QTcF interval					
	<=30 ms		109 (87.9)	102 (82.3)	100 (80.6)	5 (4.0)
	31 to 60 ms		4 (3.2)	11 (8.9)	6 (4.8)	0
	>60 ms		1 (0.8)	0	0	0
	Missing		1 (0.8)	1 (0.8)	7 (5.6)	2 (1.6)

CHMP comment

There were no QTcF intervals ≥500 ms reported. However, 1 patient treated with pirfenidone had a change from baseline QTcF interval >60 ms. A change from baseline QTcF interval >60 ms is only relevant when it is accompanied with clinical features of an AE. The applicant is requested to discuss the details of this patient. (**OC**)

Double-Blind Treatment Period

Vital Signs

Variations were observed in vital signs, including weight, over time, but overall changes were very small except in weight. Among the patients who completed 24 weeks of treatment, there was a decrease in mean (SD) weight from baseline to Week 24 in the pirfenidone group (-1.976 [4.2612]) kg and the placebo group (-0.091 [2.4324]) kg, which is in line with the known safety profile of pirfenidone.

12-Month Safety Follow-Up Period

Overall changes in vital signs were minor and did not raise any safety concerns.

CHMP comment

Treatment with pirfenidone is known to cause weight loss in some patients. This is already sufficiently addressed in the SmPC.

Safety follow–up

Laboratory Data

No patients previously treated with pirfenidone had Grade 4 shifts, in LFT parameters and 1 patient (0.9%) previously treated with placebo had Grade 4 shifts in ALP, ALT, and AST levels. 1. Grade 3/4 elevations in ALP, ALT, and AST levels were reported in 1 patient previously treated with placebo. No patients in any group had Grade ¾ elevations in total bilirubin levels.
There were no clinically meaningful or notable changes from baseline in any chemistry

Safety in special populations

Subgroup analyses of safety were performed for the double-blind treatment period.

Intrinsic Factors

During the double-blind treatment period, there were no clinically meaningful differences in the safety profile in different subgroups (split by age, gender, weight).

Extrinsic Factors

Subgroup analyses include summaries of safety profile for the following subgroups:

- Patients with/without lung biopsy
- Presence/absence of IPAF
- MMF treatment
- Deaths according to concomitant MMF subgroup
- FVC at baseline
- DL_{CO} at baseline

The applicant claims that during double-blind treatment period, there were no clinically meaningful differences in the safety profile in different subgroups (split by age, gender, weight, concomitant MMF, presence/absence of IPAF, or baseline FVC or DLco).

Table 41 ***Summary of safety profile by MMF treatment (Safety Population)***

	Pirfenidone n(%)	Placebo n(%)
MMF treatment Yes (N=45)	23	22
Number of patients experiencing any TEAEs	22 (95.7)	19 (86.4)
Number of patients experiencing any related TEAEs	19 (82.6)	11 (50.0)
Number of patients experiencing any serious TEAEs	5 (21.7)	2 (9.1)
Number of patients experiencing any related serious TEAEs	0	0
Number of patients experiencing any severe TEAEs	5 (21.7)	2 (9.1)
Number of patients experiencing any related severe TEAEs	0	0
Number of patients experiencing any TEAEs of special interest [a]	0	0
Number of patients experiencing any related TEAEs of special interest [a]	0	0
Number of patients experiencing any GI disorder [b]	16 (69.6)	12 (54.5)
Number of patients experiencing any related GI disorder [b]	15 (65.2)	7 (31.8)
Number of patients experiencing any hepatic side effects [c]	0	0
Number of patients experiencing any photosensitivity [d]	2 (8.7)	1 (4.5)
Number of patients experiencing any related photosensitivity [d]	2 (8.7)	1 (4.5)
Number of patients experiencing any rash [e]	4 (17.4)	4 (18.2)
Number of patients experiencing any related rash [e]	3 (13.0)	3 (13.6)
Number of patients experiencing any Increase in QT interval [f]	0	0
Number of patients experiencing any Angioedema	0	0
Number of patients experiencing any related Angioedema	0	0
Number of patients experiencing any Dizziness	1 (4.3)	4 (18.2)
Number of patients experiencing any related Dizziness	1 (4.3)	0
Number of patients experiencing any Weight decreased	4 (17.4)	1 (4.5)
Number of patients experiencing any related Weight decreased	4 (17.4)	0
Number of patients experiencing any Fatigue	3 (13.0)	2 (9.1)
Number of patients experiencing any related Fatigue	3 (13.0)	1 (4.5)
Number of patients experiencing TEAEs leading to death	1 (4.3)	0
Number of patients experiencing related TEAEs leading to death	0	0
Number of patients experiencing TEAEs leading to treatment discontinuation	4 (17.4)	1 (4.5)
Number of patients experiencing related TEAEs leading to treatment discontinuation	3 (13.0)	0

	Pirfenidone n(%)	Placebo n(%)
MMF treatment No (N=206)	104	102
Number of patients experiencing any TEAEs	98 (94.2)	82 (80.4)
Number of patients experiencing any related TEAEs	71 (68.3)	46 (45.1)
Number of patients experiencing any serious TEAEs	13 (12.5)	17 (16.7)
Number of patients experiencing any related serious TEAEs	1 (1.0)	1 (1.0)
Number of patients experiencing any severe TEAEs	24 (23.1)	24 (23.5)
Number of patients experiencing any related severe TEAEs	6 (5.8)	2 (2.0)
Number of patients experiencing any TEAEs of special interest [a]	0	0
Number of patients experiencing any related TEAEs of special interest [a]	0	0
Number of patients experiencing any GI disorder [b]	56 (53.8)	38 (37.3)
Number of patients experiencing any related GI disorder [b]	45 (43.3)	25 (24.5)
Number of patients experiencing any hepatic side effects [c]	1 (1.0)	0
Number of patients experiencing any photosensitivity [d]	8 (7.7)	1 (1.0)
Number of patients experiencing any related photosensitivity [d]	8 (7.7)	1 (1.0)
Number of patients experiencing any rash [e]	15 (14.4)	9 (8.8)
Number of patients experiencing any related rash [e]	10 (9.6)	6 (5.9)
Number of patients experiencing any Increase in QT interval [f]	1 (1.0)	1 (1.0)
Number of patients experiencing any Angioedema	0	0
Number of patients experiencing any related Angioedema	0	0
Number of patients experiencing any Dizziness	10 (9.6)	9 (8.8)
Number of patients experiencing any related Dizziness	9 (8.7)	4 (3.9)
Number of patients experiencing any Weight decreased	7 (6.7)	5 (4.9)
Number of patients experiencing any related Weight decreased	6 (5.8)	2 (2.0)
Number of patients experiencing any Fatigue	18 (17.3)	17 (16.7)
Number of patients experiencing any related Fatigue	13 (12.5)	11 (10.8)
Number of patients experiencing TEAEs leading to death	0	2 (2.0)
Number of patients experiencing related TEAEs leading to death	0	0
Number of patients experiencing TEAEs leading to treatment discontinuation	15 (14.4)	4 (3.9)
Number of patients experiencing related TEAEs leading to treatment discontinuation	13 (12.5)	1 (1.0)

CHMP comment:

It is noted that the safety profile of pirfenidone seemed to be worse in patients receiving concomitantly MMF. For example, GI symptoms were reported in 70% of patients receiving concomitantly MMF as compared to 54% of patients without this concomitant treatment. The applicant should discuss and consider adding this information to the SmPC **(OC).**

Safety related to drug-drug interactions and other interactions

No new information is available

Discontinuation due to adverse events

- **During double-blind treatment period**

Overall, 19 patients (15.0%) in the pirfenidone group and 5 patients (4.0%) in the placebo group discontinued study treatment due to a total of 33 and 6 TEAEs, respectively.

The most commonly reported TEAEs that led to treatment discontinuation included nausea, fatigue, decreased appetite, LFT increased, and photosensitivity reaction, all events known to be associated with pirfenidone. Of 19 patients in the pirfenidone group, 2 patients (Patients and) had SAEs of Grade ≥3, whereas 1 patient (Patient) had non-serious Grade 3 TEAEs that led to study treatment discontinuation. Of 5 patients in the placebo group, 2 patients (Patients and) had SAEs with Grade ≥3 that led to study treatment discontinuation. The remaining patients in the pirfenidone and placebo group had Grade <3 AEs that led to study treatment discontinuation.

- **Safety – follow up**

Overall, 7 patients (7.4%) previously treated with pirfenidone and 14 patients (12.7%) previously treated with placebo, discontinued pirfenidone treatment due to a total of 9 and 19 AEs, respectively. The most commonly reported AEs that led to pirfenidone discontinuation included nausea, vomiting, ileus, dizziness,
spinal cord compression, pulmonary embolism, respiratory failure, decreased appetite, and rash pruritic.

Patient was hospitalized for left lung transplant on Study Day 355 and underwent left lung transplant on Study Day 356. The patient had stopped treatment one day before lung transplant (i.e., Study Day 355) but the investigator labelled the treatment discontinuation incorrectly as worsening of interstitial lung disease (Grade 4) and not the lung transplant.

Post marketing experience

As of 27 February 2020, pirfenidone has been globally approved for the treatment of IPF.

The Roche worldwide regulatory status of Esbriet (including approved indications) and the overall cumulative safety experience with pirfenidone is presented in the most recent PBRER.

In addition, to adverse reactions identified from clinical trials the following adverse reactions: agranulocytosis, angioedema, anaphylaxis, hyponatraemia, bilirubin increased in combination with

increases of ALT and AST and DILI. Important safety update and new recommendations to prevent Drug-Induced Liver Injury (DILI).

Because these reactions may be reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency. No potential serious drug interactions were identified during post-marketing.

Analysis of Adverse Events in Patients Treated with Pirfenidone in Other ILD Trials

A qualitative assessment of available safety data from other clinical trials in ILD (Studies LOTUSS, RELIEF and TRAIL1) is provided below. Details on key study design features for each clinical trial is provided in **Error! Reference source not found.**.

PSSc-001 (LOTUSS)

Safety Overview

The LOTUSS study is complete. The duration of the study was 10.5 months (first patient enrolled: 31 October 2013; last patient completed study: 16 September 2014). Overall, 521 TEAEs were reported in 61 patients (96.8%).

The safety profile observed in the LOTUSS study is largely similar to what was observed in IPF and UILD patients. Severe TEAEs were reported in 19% of the patients enrolled in the LOTUSS trial vs. 22.8% of those administered pirfenidone in the MA39189 study (21% of those administered placebo). Serious AEs occurred with higher frequency in the MA39189 study (14.2% vs. 4.8% in the LOTUSS study), most likely due to the underlying clinical conditions as indicated by the 15% rate of SAEs in the placebo control arm of the UILD study. No death occurred during the LOTUSS study, whereas 2 deaths (both unrelated to treatment, one in the pirfenidone arm and the other in the placebo arm) were reported in the MA39189 study. Overall, the nature of TEAEs reported during the LOTUSS study is similar to what was observed in the UILD study, whereas their frequency tends to be higher. GI disorders such as nausea and diarrhea were the most frequently reported TEAEs (77.8% vs. 56.7% reported in the UILD study), followed by the nervous system disorders (57.1% vs. 24.4% in the UILD study), general disorders (57.1% vs. 26.8% in the UILD study), and skin disorders SOCs (49.2% vs. 26.8% in the UILD study).

ML29884 (RELIEF)

The RELIEF study was terminated early in 2018 based on the result of an efficacy futility analysis. The duration of the study was 30 months (the first patient enrolled on 05 April 2016, date of the last patient completed 04 October 2018). In total, 127 were recruited in this study, of which 64 were in the pirfenidone arm and 63 in the placebo arm.

The Sponsor of the study concluded that pirfenidone treatment was generally well tolerated, with incidence rates of typical adverse drug reactions comparable to those observed in the Phase III IPF program with pirfenidone.

In conclusion, the nature of the TEAEs reported during the RELIEF study is in line with the safety profile of pirfenidone in IPF patients and the results of the MA39189 study, whereas their frequency (including the proportion of SAEs) appears to be lower in study MA39189. Notably, the population in RELIEF was generally more advanced with respect to lung function compared to Study MA39189.

ML30171 (TRAIL1)

The TRAIL study is still ongoing at the time of authoring of this SCS, and only limited safety information is currently available from the Sponsor's Development Safety Update Report (DSUR) (Report Nr. 1097798), which has been made available to the Agency and covers the period from 18 August 2018 to 24 October 2019:

At the data lock point (DLP) of the DSUR (24 October 2019), 101 subjects were randomized, 51 subjects were exposed to pirfenidone arm and 50 to placebo arm.

During the reporting interval, 2 unrelated SAEs resulting in death were reported. A total of 12 SAEs were reported, including 1 SAE meeting the criteria for a suspected unexpected serious adverse reaction (SUSAR). Of the remaining 11 SAEs, none were considered related to study drug either by the Principal Investigator or the Sponsor. A total of 6 patients discontinued the study drug due to an AE and these included the 2 SAEs that had a fatal outcome.

CHMP comment

No new safety signals have emerged from analysis of sparse available safety data from other clinical trials in ILD (Studies LOTUSS, RELIEF and TRAIL1).

Report Nr. 1097798 (ML30171 (TRAIL1) has not been found. As this report will not change this assessment, it will not be requested.

4.5.1. Discussion on clinical safety

The safety data on pirfenidone in patients with unclassifiable interstitial lung disease (UILD) is derived from one study (MA39189) which enrolled 253 patients (127 in the pirfenidone group and 126 in the placebo group).

In addition, pooled safety data from pirfenidone Phase III studies in patients with idiopathic pulmonary fibrosis (IPF) are presented, in order to provide context for the safety assessment of pirfenidone treatment in UILD.

The data cut-off of MA39189 Primary CSR for the analyses of safety data (data cut-off 18 December 2018) do not match the statement in the item 'under conduct of the study. This discrepancy needs to be explained. (**OC**)

Exposure

The study consisted of the double – blind period (24 weeks) and the safety follow-up (12 months). A total of 102 patients (80.3%) in the pirfenidone group and 114 patients (90.5%) in the placebo group completed the double-blind treatment period of the study, whereas 159 (59.1% previously treated with pirfenidone and 66.7% previously treated with placebo) completed the whole study period.

During the double–blind period, the mean (SD) treatment duration, including dose interruptions, was 21.47 [6.359] weeks in the pirfenidone group vs. 23.04 [4.492] weeks in the placebo group. During the safety follow-up the mean [SD] treatment duration, including dose interruptions, was 44.01 weeks. A significant proportion of patients on pirfenidone had at least one dose interruption (31.5% in double – blind period and 28.4% in safety follow up) and at least one dose modification (40.2% in double – blind period and 49.5% in safety follow up). Of note, AEs were the most commonly reported reason for dose modification and dose interruption.

In the double-blind period of study MA39189, the median daily dose of pirfenidone was close to the full dose, and similar for pirfenidone (2281.62 mg/day) and placebo (2299.80 mg/day). During the 12-month safety follow-up period, mean (SD) treatment duration, including dose interruptions, was similar between treatment groups.

Overview of Treatment-Emergent Adverse Events (TEAEs)

In study MA39189, during the double-blind treatment period, more patients treated with pirfenidone experienced at least 1 TEAE than placebo patients (94.5% vs. 81.5%). These TEAEs were generally mild to moderate in severity. In addition, there was higher rates of AEs leading to discontinuation (15% vs. 5.2%), treatment-related TEAEs (70.9% vs. 46.0%) in the pirfenidone group as compared to the placebo group.

There were no significant differences between the treatment groups in the percentage of patients experiencing serious (14.2% versus 15.3%) and severe TEAEs (22.8% versus 21.0%).

During the 12 month safety – follow up 88% of patients experienced at least 1 TEAE, 57% treatment-related TEAEs, 26% serious and 32% severe TEAEs.

During the double-blind treatment period the SOCs with the highest incidence of TEAEs were GI disorders (72 patients [56.7%] in the pirfenidone group and 50 patients [40.3%] in the placebo group), followed by infections and infestations (58 patients [45.7%] in the pirfenidone group and 53 patients [42.7%] in the placebo group), and respiratory, thoracic and mediastinal disorders (36 patients [28.3%] in the pirfenidone group and 43 patients [34.7%] in the placebo group). The same SOCs had the highest incidence of TEAEs also during the 12 month safety – follow up.

The most common AEs observed in the pirfenidone group and occurring with a higher incidence compared with placebo were nausea (32.3% vs. placebo 7.3%), fatigue (16.5 % vs. 15.3%), decreased appetite (15.7 % vs. placebo 8.9%), cough (15.7% vs. placebo 12.9%), dyspepsia (13.4% vs. placebo 5.6%) vomiting (11% vs. placebo 4.8), headache (10.2% vs. placebo 3.2%), upper respiratory tract infection (9.4% vs. placebo 7.3%), gastrooesophageal reflux disease (7.9% vs. placebo 4.8%), weight decreased (8.7% vs. placebo 4.8%), bronchitis (7.9 % vs. placebo 2.4%), rash (7.1% vs. placebo 6.5%), back pain (6.3% vs. placebo 2.4%), photosensitivity reaction(6.3 % vs. placebo 0%), constipation(6.3% vs. placebo 3.2%) Of note, nausea, fatigue, decreased appetite were also the most frequently reported TEAEs leading to the treatment discontinuation.

An additional graph in order to make the onset of these selected AEs better visible is requested. (**OC**)

All these TEAEs, with an exception of back pain and bronchitis are already included in section 4.8 of the SmPC.

Back pain is proposed to be added to the list of ADRs as a part of this procedure, which is supported. In relation to bronchitis, the applicant should discuss whether this AE should be included in the table of ADRs or provide the relevant justification, if otherwise **(OC).**

The applicant should also discuss imbalances which were observed in relation to the frequency of depression reported in the study i.e 5.5% of patients in the pirfenidone group and 0 patients receiving placebo. It is noted that one case of depression was considered related to the study drug by an investigator **(OC).**

Further discussion is also required in relation to the long term safety of pirfenidone. There was no comparator arm during the 12 month safety follow up. Therefore, the applicant is requested to compare the exposure-adjusted incidence rates (EAIRs) for TEAEs reported during the safety follow up with the exposure-adjusted incidence rates (EAIRs) for TEAEs reported in the placebo group in the double- blind period. This should done for all patients enrolled to the safety follow up and also separately for those previously treated with placebo and those previously treated with pirfenidone. Any imbalances need to be commented by the applicant. This comparison should be also done for SAEs. **(OC).**

In addition, the applicant should investigate whether there was any increase in the rate of TEAEs over time. Therefore, the exposure-adjusted incidence rates (EAIRs) for TEAEs reported in the double- blind period should be compared to the exposure-adjusted incidence rates (EAIRs) for TEAEs reported during the safety follow up **(OC).**

Related TEAEs

70.9 % of patients in the pirfenidone group and 46% in the placebo group reported treatment-emergent related adverse events. At the PT level, the related TEAEs with the highest incidence were nausea (38 patients [29.9%] in the pirfenidone group and 6 patients [4.8%] in the placebo group), followed by decreased appetite (19 patients [15.0%] in the pirfenidone group and 9 patients [7.3%] in the placebo group), diarrhea (16 patients [12.6%] in the pirfenidone group and 14 patients [11.3%] in the placebo group), and fatigue (16 patients [12.6%] in the pirfenidone group and 12 patients [9.7%] in the placebo group). During the safety follow up the related TEAEs was reported in 57.4 % of patients.

It is noted that the related TEAEs which were reported in more than one patient are already captured in the SmPC.

Deaths

During the double blind period, 2 subjects died: 1 in the pirfenidone group and 1 in the placebo group. During the 12-month safety follow-up period, 17 patients died. None of these deaths were considered related to pirfenidone by investigators. However, further clarifications from the Applicant are requested. The table in the study report states that an adverse event was a primary cause of death in 13 patients. The applicant should provide the list of these events and discussion on their potential relationship to the study drug **(OC).**

Serious TEAEs

During the double–blinded period, the incidence of SAEs was 14.2% in the pirfenidone group and 15.3% in the placebo group. Exacerbation of ILD, pneumonia, dyspnea and cardiac failure congestive were among the most frequent SAEs. Only one case of decreased appetite was considered to be related to pirfenidone and this ADR is already listed in the SmPC.

During the safety follow–up 53 patients (26.0%) experienced SAEs. For two patients SAEs were considered related the study drug i.e one patient had Grade 2 decreased appetite and 1 patient had Grade 3 ALT increased. Again these ADRs are already listed in the SmPC.

Pneumonia and exacerbation of ILD was the most frequently reported SAEs (8 patients each) followed by dyspnoea and lower respiratory tract infection (5 patients). A total 10 SAEs within the SOP of cardiac disorders were reported. It is noted that cases of atrial fibrillation, cerebrovascular accidents and myocardial infarction were discussed during the last PSUR procedure and it was agreed with the MAH that no further action is necessary at this time and these topics can remain under routine pharmacovigilance.

The patients who experienced TEAEs of severity Grade ≥3 were also similar (22.8% in the pirfenidone group and 21.0% in the placebo group). However, the nature of the most severe TEAEs (grade 4 and 5) is not clearly presented and needs to be provided (OC).

The proportion of patients with at least 1 dose modification

The proportion of patients with at least 1 dose modification was higher in the pirfenidone group (40.2%) than in the placebo group (27.4%). Similarly, the proportion of patients with at least 1 dose interruption was higher in the pirfenidone group (31.5%) than in the placebo group (9.7%). An adverse event was the most commonly reported reason for dose modification and dose interruption and possibly led to a higher proportion of subjects in the pirfenidone group modifying or interrupting their doses due to the expected safety profile of pirfenidone. During the 12-month safety follow-up period, the median daily dose in the previously treated with pirfenidone group was higher than in the previously treated placebo group, which could be because the patients previously treated with pirfenidone included more patients who were able to tolerate pirfenidone (selection bias). The proportion of patients with at least one dose modification and interruption was higher in the previously treated with placebo group than in the previously treated with pirfenidone group. Thus, the safety follow-up population included more patients able to tolerate pirfenidone as a result of the selection bias.

Laboratory tests

Haematology.

Small fluctuations in hematology parameters were observed over time, but the applicant claimed that these changes were not clinically meaningful. Nevertheless, the applicant should comment on the fact that more patients in the pirfenidone group as compared to the placebo group reported grade 1 – 4 decrease in the level of platelets (3.9% versus 1.6 %) and white blood cells (especially lymphocytes-11.8% versus 8.1 %). For these parameters there was a shift to lower values during the study. Of note, agranulocytosis is currently listed as an ADR in section 4.8 of the SmPC. Further updates to the adverse reactions list within the SOC Blood and lymphatic system disorders should be considered **(OC).**

Chemistry

The applicant claimed that there were no clinically meaningful and notable changes from baseline in any chemistry parameter.

However, it is noted that a significantly higher percentage of patients in the pirfenidone group reported grade 1 – 4 hypokalemia (10.2 % in the pirfenidone group and 4.8% in the placebo group). This could be linked to the fact that more patients treated with pirfenidone reported GI related AEs and poor nutrition. The applicant should discuss and consider updating section 4.8 of the SmPC **(OC).** Currently only hyponatraemia is listed in this section. In addition, the applicant should provide a general discussion on changes in other chemistry parameters which could be observed in patients with poor nutrition. The chemistry results reported in the MA39189 study should be reviewed in this context **(OC).**

The numbers of patients with elevated transaminases is not clearly reported and needs to be presented. **(OC).**

ECG parameters

There were no QTcF intervals ≥500 ms reported. However, 1 patient treated with pirfenidone treatment had a change from baseline QTcF interval >60 ms. A change from baseline QTcF interval >60 ms is only relevant when it is accompanied with clinical features of an AE. Further information is requested. (OC)Of note, the Applicant has conducted a single study to measure the QTc pharmacodynamic potential of pirfenidone in healthy subjects (PIPF-007). The results of this study (reviewed during the original application) indicated that pirfenidone does not adversely influence the cardiac conduction system.

Special population

The applicant claimed that during double-blind treatment period, there were no clinically meaningful differences in the safety profile in different subgroups (split by age, gender, weight, concomitant MMF, presence/absence of IPAF, or baseline FVC or DLco).

It is noted, that the safety profile of pirfenidone seemed to be worse in patients receiving concomitantly MMF. For example, GI symptoms were reported in 70% of patients receiving concomitantly MMF as compared to 54% of patients without this concomitant treatment. The applicant should discuss and consider adding the relevant warning regarding to the SmPC. **(OC).**

Interactions

Now new data provided

Pregnancy and lactation

No pregnancies were reported during the study

Comparison to IPF studies

The applicant performed the comparison between the pooled IPF studies (004/006/016) and the UILD study (MA39189) double-blind safety data. Overall, similar rates per 100-patient years (PY) were observed between the IPF and UILD safety populations (967.76 [CI: 945.98, 989.55] vs. 1051.87 [CI: 971.13, 1132.61], respectively) when considering the totality of the data

When focusing on the 24-week treatment period following an exposure-adjusted approach, the safety profile of pirfenidone emerging from the UILD study was in line with that established in IPF, with TEAEs of similar nature and an overall lower frequency (rate per 100 PY in UILD = 1127.94 [CI:1036.22, 1219.66]; rate per 100 PY in IPF 1503.93 [CI: 1458.29, 1549.56].

The proportion of patients with at least one TEAE was similar between the IPF and UILD safety populations (97.1% vs. 94.5%, respectively)

Post-marketing

As of 27 February 2020, pirfenidone has been globally approved for the treatment of IPF. The product is not approved for UILD.
Additional ADRs were identified in the postmarketing setting including agranulocytosis, angioedema, anaphylaxis, hyponatraemia, bilirubin increased in combination with increases of ALT and AST and DILI. Important safety update and new recommendations to prevent Drug-Induced Liver Injury (DILI) was circulated in the last year.
During the last PSUR procedure the applicant was requested to perform a comprehensive evaluation of severe skin disorders including Stevens-Johnson Syndrome. Further, the applicant was requested to comment on the relevance of non-clinical repeat dose toxicity findings for bladder cancer and close monitor cases of bladder cancer.

Updates to the SmPC

The applicant proposed the update to section 4.8 of the SmPC and include two lists of ADRs per indication.

This approach is not supported. In line with the guideline, only 1 table (or tabulated list) should list all adverse reactions with respective frequency category. This applies to the SmPC as well as the package leaflet. Separate frequencies/tables are only acceptable in exceptional cases where the safety profiles markedly differ depending on the use of the product; e.g. for a product used for very different indications or at different posologies.

In addition, it should be noted that the proposed revision of section 4.8 – summary of the safety profile doesn't comply with the SmPC guideline. Section 4.8 should be based upon best-evidence assessment of all safety information from all clinical trials, PASS and spontaneous reporting and should be updated as necessary during the life-cycle of the product. It is not expected to describe the initial clinical safety data set, which will be shortly outdated after marketing authorisation. Also, frequencies of adverse reactions cited in the summary of safety profile should be stated as accurately as possible, e.g. by including % in brackets. The SmPC needs to be corrected **(OC).**

Additional expert consultations

N/A

Assessment of paediatric data on clinical safety

N/A

4.5.2. Conclusions on clinical safety

Overall, no major issues were found in the assessment of the safety profile of pirfenidone However, clarifications on a number of issues are required.

4.5.3. 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

4.5.4. Direct Healthcare Professional Communication

N/A

4.6. Significance of paediatric studies

N/A

5. Risk management plan

The MAH submitted an updated RMP version 11.0, dated 17 November 2020 with this application. The data lock point for this RMP is 01 October 2020. The (main) proposed RMP changes were the following:

- New indication of UILD was added in Part II: Module SI- Epidemiology of the Indication and target population.
- Product Overview Table was updated to include all necessary updates on the new indication of UILD.
- Clinical trial exposure data was added for the new indication of UILD in Part II: Module SIII.
- Part II: Module SIV.1 was updated with Exclusion Criteria in pivotal clinical studies within the development program (Study MA39189) for the indication of UILD.
- Part II: Module SIV.3 was updated with Limitations in Respect to Populations typically under-represented in Clinical Trial Development Program for the indication of UILD.
- Post authorization exposure data was updated for the indication of Idiopathic Pulmonary Fibrosis (IPF).
- Part II: Module SVII.3 was updated with information on UILD for important identified risks, potential risks and missing information.
- Part V Risk Minimization Measures was updated to include indication of UILD.
- Updated Guided Questionnaire for Drug-Induced Liver Injury (DILI) was added to Annex 4 of the RMP.

- Removal of Dear Healthcare Professional (DHPC) & Dear Investigator Letter (DIL) for Clinically Relevant DILI from Annex 6 of the RMP.

Part II: Safety Specification

Module SI: Epidemiology of the indications and target population

PRAC comment: The MAH has updated the RMP, version 11.0, with the epidemiology of unclassifiable interstitial lung disease (UILD) and this is acceptable.

Module SII: Non-clinical

PRAC comment: There were no changes to the non-clinical section of the RMP Part II: Module SII.

Clinical trial exposure

Unclassifiable Interstitial Lung Disease (UILD)

The Pirfenidone Patient Subset contains data from 237 unique patients, followed up for a maximum of 78 Weeks. This includes 127 patients treated with at least one dose of pirfenidone in the double-blind, placebo-controlled phase of the study and 110 patients, who were treated with placebo during the double-blind phase of the study and were treated with at least one dose of pirfenidone in the open-label phase of the study. Patients treated with pirfenidone during double-blind period, who entered the open-label period, are counted only once. The length of treatment duration takes into account all days under pirfenidone treatment. The mean daily dose is calculated from all doses of pirfenidone received during either study period.

PRAC comment: *The Applicant has updated the RMP, version 11.0, with clinical trial exposure in patients with unclassifiable interstitial lung disease. According to the tabulated updates provided by the MAH, overall 127 patients with UILD were treated with at least one dose of pirfenidone (100 patients received placebo) in study MA39189 with 155 patients ⩾65 years and 65 patients ⩾75 years. Treatment duration was of mean duration of 49.39 weeks with a median value of 50.86 weeks. Mean daily dose was calculated at 1987.1mg with a median value of 2238.3mg.*

Summary of the safety concerns

Table 42 ***Summary of the Safety Concerns***

Summary of safety concerns	
Important identified risks	• Photosensitivity and rash • Drug Induced Liver Injury • Gastrointestinal symptoms
Important potential risks	• Severe skin reactions • Risk of medication error in patients transferring between capsules and tablets
Missing information	• QT prolongation • Underlying specific cardiac events

PRAC comment: *There are no changes proposed to the safety concerns for pirfenidone and this is accepted.*

The summary of safety concerns for pirfenidone in the current and proposed indications is acceptable.

Part III: Pharmacovigilance plan

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Other forms of routine pharmacovigilance activities for:

- Photosensitivity Reaction and Rash
- DILI
- GI Symptoms

A guided questionnaire is used to collect DILI case details and information about adherence to liver monitoring.

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 authorities is done as required, based on the nature and strength of the evidence and its impact on benefit risk assessment.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered by the MAH to be sufficient to obtain and analyse relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

A guided questionnaire is used to collect DILI case details and information about adherence to liver monitoring.

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 authorities is done as required, based on the nature and strength of the evidence and its impact on benefit risk assessment.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Routine pharmacovigilance activities are considered by the MAH to be sufficient to obtain and analyse relevant post-marketing safety data for all safety concerns with the aim to fully assess the safety of the product.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Not applicable.

PRAC conclusion: *Routine pharmacovigilance is sufficient to identify and characterise the risks of the product. Routine Pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.*

A follow-up questionnaire was recently introduced during variation EMEA/H/C/002154/II/0066 for events of DILI. This questionnaire has been further updated following FDA and internal expert review to enhance data collection on medication history, medical history and hepatic investigations. The updated questionnaire is included in Annex 4 and is acceptable.

Part IV: Plans for post-authorisation efficacy studies

No post-authorization efficacy studies are planned or ongoing.

Part V: Risk Minimisation Measures

RMP version 11.0, documents the routine risk minimisation measures for pirfenidone.

A Safety Checklist is in place as an additional risk minimisation measures for prescribing physicians to address the safety concerns of photosensitivity and drug-induced liver injury.

PRAC comments: *As an additional risk minimisation measures a safety checklist is in place for the safety concerns for photosensitivity and DILI. This questionnaire was updated during the recent II/066 variation. There are no additional changes proposed to the risk minimisation measures for Esbriet/pirfenidone and this is acceptable.*

Overall conclusions on risk minimisation measures

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indications.

5.1. Elements for a public summary of the RMP

PRAC comment: The MAH have updated the summary of the RMP to include the proposed indication for treatment of patients with unclassifiable interstitial lung disease. The summary of the RMP follows the template guidance and is acceptable.

5.2. Annexes

The annexes have been updated appropriately.

5.3. Overall conclusion on the RMP

☒The changes to the RMP, version 11.0, dated 17 November 2020 are acceptable.

6. Changes to the Product Information

As a result of this variation, section(s) 4.1, 4.2, 4.8 and 5.1 of the SmPC are being updated. The Package Leaflet (PL) is updated accordingly.

6.1.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Esbriet (pirfenidone). The bridging report submitted by the MAH has been found acceptable.

The following justification was provided by the applicant:

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 extend the indication of Esbriet (pirfenidone) to treatment of adult patients

with unclassifiable interstitial lung disease (UILD).

User consultation was conducted in the context of the initial Esbriet Marketing Authorisation Application for the treatment of adult patients with idiopathic pulmonary fibrosis (IPF).

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 follow the same structure and use similar descriptions and terminology as used in the approved package leaflet.
- The target group of users will be similar between the approved indication (IPF patients) and the applied indication (UILD patients), with no significant age difference.
- Moreover, the posology proposed in this application is the same as the currently approved IPF indication.

In light of the above, the MAH considers it justified not to perform a novel User

Consultation for the updated Package Leaflet.

7. Benefit-Risk Balance

7.1. Therapeutic Context

7.1.1. Disease or condition

Interstitial lung disease (ILD) represents a group of diffuse pulmonary parenchymal disorders that are classified together based on specific clinical, radiological, and histopathological features; many of these disorders are associated with significant morbidity and mortality. Approximately 10% of patients evaluated by multi-disciplinary teams (MDT) have characteristics that do not allow them to be classified as a specific subset of ILD (Skolnik and Ryerson 2016). This "unclassifiable ILD" (UILD) population is recognised as a medical entity with an established definition for diagnosis of fibrotic ILD.

7.1.2. Available therapies and unmet medical need

There is a lack of standard of care for patients with UILD. Moreover, most drugs currently used to treat UILD, such as the corticosteroids prednisone, prednisolone and methylprednisolone, and immune-suppressants including MMF and azathioprine, have not been subjected to rigorous clinical testing.

Recently, May 2020, the CHMP approved nintedanib, a protein kinase inhibitor, for the treatment of adult patients with progressive interstitial lung disease.

7.1.3. Main clinical studies

No formal dose-response study has been conducted. The selected dose was based on the efficacy, safety, and dose-findings of the trials of the pirfenidone trials in IPF (EMEA/H/C/002154).

The applicant submitted one study (MA39189) investigating the use of pirfenidone in patients with fibrosing ILD that, following MDT review, could not be classified with either high or moderate confidence as a specific idiopathic interstitial pneumonia or other defined ILD.

MA39189 study had a 24-week double-blind treatment period and 12-month safety follow-up in which patients were receiving open-label pirfenidone. No spirometry or other efficacy assessments were conducted during the 12-month safety follow-up.

7.2. Favourable effects

The primary outcome measure was the FVC decline (mL) from baseline to week 24 measured by daily home spirometry.
The updated analysis (2020) is based on the primary data set, but with the exclusion of data of non-acceptable quality. In these analyses, the mean (95% CI) FVC decline measured by home spirometry for pirfenidone was -90.3 (95% CI=-157.0, -23.7) ml, and for placebo 125.6 (-458.4, 709.6) mL. The mean (95% CI) difference was – 216.0 (803.6, 371.1), p=0.46 using the student's t-test and Wilcoxon test p=0.02 (nominal p value).

The rate of FVC decline from baseline to week 24 and categorical change in FVC of >5% and 10% measured by *clinic* spirometry visits was investigated as secondary endpoints.

The results of the primary analysis as well as updated analysis of this secondary endpoint showed a smaller magnitude of decline in FVC in the pirfenidone as compared to the placebo group.

During the primary analysis (2019), at Week 24, mean predicted *clinic* FVC declines for pirfenidone and placebo were -17.8 mL and -113.0 mL, respectively, with an overall mean difference of 95.3 mL (Student's t-test p=0.0018; 95% CI: 35.9, 154.6).
Over 24 weeks, >5% and >10% categorical declines in FVC (percent predicted) were higher in the placebo group than in the pirfenidone group (>5% decline, odds ratio: 0.42; 95% CI: 0.25, 0.69; p=0.0006; >10% decline, odds ratio: 0.44; 95% CI: 0.23, 0.84 p=0.0114).
Per updated analysis (2020), at Week 24, mean predicted FVC declines for pirfenidone and placebo were -24.8 mL and -109.1 mL, respectively, with an overall mean difference of 84.3 mL (Student's t-test p=0.0096; 95% CI: 20.7, 147.8).
Over 24 weeks, >5% and >10% absolute declines in FVC (percent predicted) were higher in the placebo group than in the pirfenidone group (>5% decline, odds ratio: 0.43; 95% CI: 0.26, 0.71; p=0.0009; >10% decline, odds ratio: 0.46; 95% CI: 0.24, 0.88; p=0.0168).

Change in percent predicted DLco and change in 6MWD in meters were investigated as secondary endpoints.

In relation to the mean changes in DLco (percent predicted) from baseline at Week 24 endpoint there was no difference between the treatment groups. A categorical decline with >15% absolute decrease in DLco (percent predicted) was higher in the placebo group than the pirfenidone group (odds ratio: 0.15; 95% CI: 0.03, 0.69; p=0.0150).

The Mean changes in 6MWD from baseline at Week 24 analysed by rank ANCOVA resulted in a p-value of 0.0299 (showing improvements in patients receiving pirfenidone) however, categorical decline with >50 m absolute decrease in 6MWD was similar between treatment groups (odds ratio: 0.95; 95% CI: 0.55, 1.65; p=0.8574).

7.3. Uncertainties and limitations about favourable effects

There are significant uncertainties in relation to the efficacy results.

The primary efficacy endpoint in this study was the rate of decline in FVC measured in millilitres with daily home spirometer over the 24-week, double-blind treatment period. However, the results of this primary efficacy endpoint are not considered reliable. The original analysis of this endpoint performed in 2019 showed unreliable results with high intra-individual variability and extreme outliers in home spirometry values in both treatment groups. Physiologically implausible values were noted. The results of the updated analysis of the home spirometry measurements performed in 2020 are also questioned i.e. the updated data set is based on 60% of the original data, and is post hoc defined. The updated data set includes still extreme outliners and the conference intervals are very broad. Therefore, it is not

agreed that the results of this endpoint is used by the applicant to claim treatment benefits of pirfenidone in patients with unclassifiable ILDs.

As discussed above some improvements were seen in other secondary endpoints investigated in the study (i.e the rate of FVC Decline from baseline to week 24 measured by clinic spirometry, a categorical decline with >15% absolute decrease in DLco (percent predicted)and the mean changes in 6MWD from baseline at Week 24) however, due to the fact that these endpoints were not included in the multiplicity control strategy these results cannot be considered as pivotal and can be used for descriptive purposes only. In addition, for DLco and 6MWD endpoints robustness of results with respect to missing data assumptions has not been examined.

Further, taking into consideration previous regulatory decisions, it is considered that the duration of the double-blind treatment period was too short as 52 weeks duration of the double-blind treatment period would be expected.

The results of endpoints investigating direct clinical effects were inconclusive. The results of patients reported outcomes, i.e. George's respiratory questionnaire scores, University of California, San Diego–shortness of breath questionnaire scores, Leicester cough questionnaire scores, cough visual analog scale scores have not showed significant differences between the treatment groups.

Events such as acute exacerbations, non-elective hospitalization, deaths were recorded in the study; however, the number of these events was too small to make any meaningful conclusion.

The conduct of the study raises concerns about the validity of the generated database and whether the obtained efficacy results could be used to support the application.

Previous studies showed that the home FVC could be used as primary outcome in clinical trials. However, it is currently insufficiently clarified why study population currently included was unable to generate home spirometry data of sufficient quality. In addition, in relation to the primary efficacy results, it is not clear from the information provided by the applicant why issues relating to the quality of data for home spirometry measurements were not identified during the trial (or if they were identified, why they were not corrected).

Therefore a number of clarifications are required regarding oversight mechanisms, which were in place for both investigators/sites and for the sponsor to ensure that subjects were conducting daily spirometry assessments and to ensure the quality of the results being recorded. Details on how data that was collected through the daily spirometry assessment was handled throughout the study, including any data validation or reconciliation activities need to be provided. Furthermore, the database set of 3 Mar 2019 has been subject to additional cleaning activities not only in relation to the primary endpoint but also secondary endpoints.

The cleaning activities of the primary research dataset need to be further clarified and the applicant is requested to provide all details (Who, What, When, Where and Why) about all cleaning activities after database lock 3 Mar 2019. This applies to both the home FVC as well as to the secondary outcome measures.

Finally, the wording of the indication is not agreed. The applicant is proposing the following indication: Esbriet is indicated in adults for the treatment of unclassifiable interstitial lung disease (UILD). This indication is not supported as the pivotal study was only enrolling patients with progressive disease and mild to moderated disease as reflected by the inclusion criteria of baseline DLCO ≥30% and FVC ≥45%, this need to be reflected in the text of the indication. The study population included patients with a "low confidence on another ILD diagnosis, except IPF". This subgroup is not recognised as a particular subgroup for Unclassifiable ILD patients

Further, the study population was limited to patients with baseline DLCO ≥30% and FVC ≥45%. The applicant should discuss whether this these criteria should be reflected in the text of the indication.

7.4. Unfavourable effects

The AEs presented in general are overall expected with the condition or are already captured in the labelling & RMP. During the double-blind treatment period, more patients treated with pirfenidone experienced at least 1 TEAE than placebo patients (94.5% vs. 81.5%). In addition, there was higher rates of AEs leading to discontinuation (15% vs. 5.2%), treatment-related TEAEs (70.9% vs. 46.0%) in the pirfenidone group as compared to the placebo group.

There were no significant differences between the treatment groups in the percentage of patients experiencing serious (14.2% versus 15.3%) and severe TEAEs (22.8% versus 21.0%).

During the 12 month safety – follow up 88% of patients experienced at least 1 TEAE, 57% treatment-related TEAEs, 26% serious and 32% severe TEAE.

During the double-blind treatment period the SOCs with the highest incidence of TEAEs were GI disorders (72 patients [56.7%] in the pirfenidone group and 50 patients [40.3%] in the placebo group), followed by infections and infestations (58 patients [45.7%] in the pirfenidone group and 53 patients [42.7%] in the placebo group), and respiratory, thoracic and mediastinal disorders (36 patients [28.3%] in the pirfenidone group and 43 patients [34.7%] in the placebo group). The same SOCs had the highest incidence of TEAEs also during the 12 month safety – follow up.

The most common AEs observed in the pirfenidone group and occurring with a higher incidence compared with placebo were nausea (32.3% vs. placebo 7.3%), fatigue (16.5 % vs. 15.3%), decreased appetite (15.7 % vs. placebo 8.9%), cough (15.7% vs. placebo 12.9%), dyspepsia (13.4% vs. placebo 5.6%) vomiting (11% vs. placebo 4.8), headache (10.2% vs. placebo 3.2%), upper respiratory tract infection (9.4% vs. placebo 7.3%), gastrooesophageal reflux disease (7.9% vs. placebo 4.8%), weight decreased (8.7% vs. placebo 4.8%), bronchitis (7.9 % vs. placebo 2.4%), rash (7.1% vs. placebo 6.5%), back pain (6.3% vs. placebo 2.4%), photosensitivity reaction(6.3 % vs. placebo 0%), constipation(6.3% vs. placebo 3.2%). All these TEAEs, with the exception of back pain and bronchitis were considered treatment-related and they are already included in section 4.8 the SmPC. Of note, nausea, fatigue, decreased appetite were also the most frequently reported TEAEs leading to the treatment discontinuation.

During the double blind period, 2 subjects died: 1 in the pirfenidone group and 1 in the placebo group. During the 12-month safety follow-up period, 17 patients died. None of these deaths were considered related to pirfenidone by investigators.

During the double–blinded period, the incidence of SAEs was 14.2% in the pirfenidone group and 15.3% in the placebo group. Exacerbation of ILD, pneumonia, dyspnea and cardiac failure congestive were among the most frequent SAEs. Only one case of decreased appetite was considered to be related to pirfenidone and this ADR is already listed in the SmPC.

During the safety follow–up 53 patients (26.0%) experienced SAEs. For two patients SAEs were considered related the study drug i.e one patient had Grade 2 decreased appetite and 1 patient had Grade 3 ALT increased. Again these ADRs are already listed in the SmPC.

Pneumonia and exacerbation of ILD was the most frequently reported SAEs (8 patients each) followed by dyspnoea and lower respiratory tract infection (5 patients each).

The applicant performed the comparison between the pooled IPF studies (004/006/016) and the UILD study (MA39189) double-blind safety data. In general, the safety profile of pirfenidone emerging from the UILD study was in line with that established in IPF, with TEAEs of similar nature and an overall similar or lower frequency

As of 27 February 2020, pirfenidone has been globally approved for the treatment of IPF.
Additional ADRs were identified in the postmarketing setting including agranulocytosis, angioedema, anaphylaxis, hyponatraemia, bilirubin increased in combination with increases of ALT and AST and DILI. Important safety update and new recommendations to prevent Drug-Induced Liver Injury (DILI) was circulated in the last year.

7.5. Uncertainties and limitations about unfavourable effects

Overall, no major issues were found in the assessment of the safety profile of pirfenidone. The safety profile of pirfenidone emerging from the UILD study was in line with that established in IPF, with TEAEs of similar nature and an overall similar or lower frequency.

However, clarifications on a number of issues are required.

During the 12-month safety follow-up period, the proportion of patients with at least one dose modification and interruption was higher in the previously treated with placebo group than in the previously treated with pirfenidone group, that could be due to the fact that the patients previously treated with pirfenidone included more patients who were able to tolerate pirfenidone (selection bias).

The nature of the most severe TEAEs (grade 4 and 5) is not clearly presented and needs to be provided.

During the Safety Follow-Up period, one patient experienced an AESI, of which the details are lacking and subsequently requested.

Elevated transaminases have been commonly reported in patients treated with pirfenidone treatment in IPF. Therefore, liver function tests (ALT, AST and bilirubin) should be performed frequently during treatment with Esbriet. In the current application for unclassifiable ILD, the numbers of patients with elevated transaminases are not clearly reported and needs to be presented.

There are no indications that pirfenidone causes prolongation of QTc interval. However, 1 patient treated with pirfenidone treatment had a change from baseline QTcF interval >60 ms. A change from baseline QTcF interval >60 ms is only relevant when it is accompanied with clinical features of an AE. Further information is requested.

Although the nature and frequency of pirfenidone emerging TEAEs in the double-blind period of study MA39189 were generally consistent with that observed in earlier IPF studies, the higher frequencies of lower respiratory tract infections and respiratory tract infections, decreased appetite and weight needs to be discussed.

The applicant should consider updating the list of ADRs in section 4.8 of the SmPC in respect to the following AEs: bronchitis, depression, hypokalemia and some hematology parameters.

An additional discussion is required in relation to deaths reported in this study. It is noted that an adverse event was a primary cause of death in 13 patients. The applicant should provide the list of these events and discussion on their potential relationship to the study drug.

Further discussion is also required in relation to the long term safety of pirfenidone. There was no comparator arm during the 12 month safety follow up. Therefore, the applicant is requested to compare the exposure-adjusted incidence rates (EAIRs) for TEAEs reported during the safety follow up with the exposure-adjusted incidence rates (EAIRs) for TEAEs reported in the placebo group in the double-blind period. Any imbalances need to be explained by the applicant.

In addition, the applicant should investigate whether there was any increase in the rate and/or severity of TEAEs overtime. Therefore the exposure-adjusted incidence rates (EAIRs) for TEAEs reported in the double- blind period should be compared to the exposure-adjusted incidence rates (EAIRs) for TEAEs reported during the safety follow up.

Finally, the proposed update to section 4.8 is not in line with the SmPC guidelines. The SmPC needs to be corrected.

7.6. Effects Table

Table 43 ***Effects Table for Esbriet for the treatment of unclassifiable interstitial lung disease (UILD)***

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
FVC decline-home spirometry Updated analysis 2020	Rate of decline in forced vital capacity (FVC) measured in millilitres (mL) by daily handheld spirometer (daily home spirometry) over the 24-week double-blind treatment period	ml	Mean -90.3 mL Median -85.6 mL	Mean 125.6 mL Median -183.5 mL	UNC: The results are not considered reliable and not corrected for multiplicity	Primary endpoint
FVC decline - clinic spirometry Updated analysis 2020	Change in percent predicted FVC and in mL measured by spirometry during clinic visits (clinic spirometry)	ml	Mean -24.8 mL	Mean -109.1 mL	UNC Endpoint not included in the multiplicity control strategy; Choice for this outcome measure might be data driven; Standardisation of spirometry; Data might have been subject to additional cleaning activities Strength: Supported with addional sensitivity analyses	Secondary endpoint
CatDec10% - clinic spirometry Updated analysis	Categorical change in FVC of >10% (absolute change in percent predicted and relative change in mL), measured both by daily home spirometry as well as by clinic spirometry	%	14.2%	26.2%	UNC standardisation of FVC measurement; Comparability of the proportion of patient with baseline FVC >5% ; - method of analyse of reduction FVC 5% from baseline; Not corrected for multiplicity ; Data might have been subject to additional cleaning activities	Secondary endpoint
DLco (% predicted)	Change in percent predicted diffusing capacity of the lung for carbon monoxide (DLco) from baseline to Week 24		-0.65	-2.48	No difference between the groups. Endpoint not included in the multiplicity control strategy Data might have been subject to additional cleaning activities Robustness of results with respect to missing data assumptions has not been examined.	Secondary endpoint
6MWD	Change in 6 minute walking distance	m	-2.0 m	-26.7 m	**UNC** : Endpoint not included in the multiplicity	Secondary endpoint

Effect	Short description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
	(6MWD) in meters from baseline to Week 24				control strategy. Robustness of results with respect to missing data assumptions has not been examined. Data might have been subject to additional cleaning activitiesStandardisation of test, clinical relevance of findings	
Unfavourable Effects						
nausea	GI disorders is a SOC with the highest frequency of AEs	%	32.3%	7.3%		
dyspepsia		%	13.4%	5.6%		
vomiting			11%	4.8%		
fatigue	could led to treatment discontinuation	%	16.5 %	15.3%		
decreased appetite	Is linked to other AEs such as decrease in the body weight. Decreased appetite could be serous and lead to treatment discontinuation	%	15.7 %	8.9%		
photosensitivity reaction		%	6.3%	0%		

7.7. Benefit-risk assessment and discussion

7.7.1. Importance of favourable and unfavourable effects

Pirfenidone is an approved therapy in patients with idiopathic pulmonary fibrosis (IPF), an interstitial lung disease with a rapid disease progression. Patients with various forms of progressive interstitial lung disease may have many comparable characteristics.

The current application is for the treatment of patients with unclassifiable ILD. Unclassifiable ILD is a rare disease with a dismal prognosis, particularly if the patients suffer from a progressive disease like in the patients included in the current trial, Study MA39189

Study MA39189 was conducted to show the efficacy and safety in patients with unclassifiable interstitial lung disease (ILD). When the trial was initiated, there was no approved therapy. Since May 2020, nintedanib had been approved as the first treatment in progressive ILD, including progressive unclassifiable ILD.

Study MA39189 limited the inclusion to patients with progressive unclassifiable interstitial lung disease of mild to moderated severity. It remains to be elucidated if the obtained results could also be applied to patients with less progressive disease. These patients might be less responsive to therapy and the treatment may provide less benefit, while no data has been obtained for the severe population.

The study population consisted of 3 different subpopulations of which one group is not specifically recognised as a subgroup of unclassifiable ILD i.e. the small subgroup defined by "an unlikely other diagnosis of ILD other than IPF". The inclusion of this subgroup could be justified, because the CHMP previously concluded that in the various progressive ILD disease forms, the disease may have similar disease progression and extrapolation might be feasible if a benefit in this population is shown. (EPAR Ofev).

In the pivotal study, the applicant investigated the efficacy and safety of pirfenidone in the treatment of patients with UILD. However, it is considered that the available single pivotal study results are not compelling (CPMP/EWP/2330/99) and do not meet regulatory expectations for the clinical investigation of medicinal products for treatment of interstitial lung disease.

The results of the primary efficacy endpoint are not considered reliable. Some improvements were seen in other secondary endpoints investigated in the study (i.e the rate of FVC Decline from baseline to week 24 measured by clinic spirometry, changes in DLco and in 6MWD). However because that these endpoints were not included in the multiplicity control strategy these results cannot be considered as pivotal and can be used for descriptive purposes only. In addition, for DLco and 6MWD endpoints robustness of results with respect to missing data assumptions has not been examined.

Further, taking into consideration previous regulatory decisions, it is considered that the duration of the double-blind treatment period was too short as a 52 weeks duration of the double-blind treatment period would be expected.

The conduct of the study raises concerns about the validity of the generated database and whether the obtained efficacy results could be used to support the application. There is the lack of clarity why the study population could not generate home FVC of sufficient quality, the concern about the data validity of the generated datasets, and the lack of transparency of the cleaning activities, all together increase the risk that the results for the rate of decline in FVC clinic spirometry and could be a chance finding.

This concern is also supported because it is unclear if the currently defined key secondary outcome was prespecified, while concerns exist which if any of the applied statistical analyses best describe the data, as most of them were performed post-hoc.

Nevertheless, the study showed a statistically significant improvement compared to placebo in rate of FVC decline in clinic spirometry by both data sets of 2019 and 2020, (mean (95% CI) difference 95 ML (35.9-157) mL p=0.002, and 84.3 mL (20.7-147.8) mL, p=0.01, respectively). Although cross-study comparisons are fraud with risk, these results align with the observed rate of FCV decline difference by nintedanib in a subgroup of patients with unclassifiable ILD 68.3 (-31.4-168.1) mL

Also, the proportion of patients with an FVC decline > 5% or > 10% is significantly decreased if treated with pirfenidone compared to placebo. An annual FVC decrease > 10% is associated with an increased mortality, and so slowing the decline to this extend might likely have long term beneficial effects. However, the data of the categorial FVC decline is associated with two main uncertainties which make it hard to interpret: a) the lack of comparison of the proportion of patients with baseline decline FVC >5% and b) the method of analyses of the FVC decline for this outcome measure

The rate of decline in forced vital capacity (FVC), DLco and change in 6-minute walk distance are only surrogate endpoints and therefore it is considered that a positive trend in other endpoints investigating

direct clinical effects needs to be shown in the study. However, the results of endpoints investigating direct clinical effects were inconclusive.

Overall, no major issues were found in the assessment of the safety profile of pirfenidone. The safety profile of pirfenidone emerging from the UILD study was in line with that established in IPF, with TEAEs of similar nature and an overall similar or lower frequency. However, it needs to be noted that treatment with pirfenidone could be poorly tolerated (i.e. 15.0% in the pirfenidone group in the double – blind period discontinued the study treatment due to TEAEs such as nausea, fatigue, decreased appetite, LFT increased, and photosensitivity reaction). In addition, fatal or life-threatening ADRs may occur including agranulocytosis, angioedema, anaphylaxis, and DILI (these ADRs were identified in the post-marketing setting).

7.7.2. Balance of benefits and risks

It is considered that the available single pivotal study results are not compelling (CPMP/EWP/2330/99) and do not meet regulatory expectations for the clinical investigation of medicinal products for treatment of interstitial lung disease.Overall, no major issues were found in the assessment of the safety profile of pirfenidone. The safety profile of pirfenidone emerging from the UILD study was in line with that established in IPF, with TEAEs of similar nature and an overall similar or lower frequency. However, it needs to be noted that treatment with pirfenidone could be poorly tolerated (i.e 15.0% in the pirfenidone group in the double – blind period discontinued the study treatment due to TEAEs such as nausea, fatigue, decreased appetite, LFT increased, and photosensitivity reaction). In addition, fatal or life-threatening ADRs may occur including agranulocytosis, angioedema, anaphylaxis, and DILI (these ADRs were identified in the post-marketing setting).

In addition, the proposed indication is currently not covered by the included study population and needs to be justified.

7.7.3. Additional considerations on the benefit-risk balance

N/A

7.8. Conclusions

The overall B/R of Esbriet in patients with UILD is negative.