Common Drug Review
Clinical Review Report (Resubmission)

April 2015

Drug	pirfenidone (Esbriet) (267 mg capsules)
Indication	Treatment of mild to moderate idiopathic pulmonary fibrosis (IPF) in adults
Listing request	As per indication
Manufacturer	Hoffmann-La Roche Limited

Redactions: Confidential information in this document has been redacted at the request of the manufacturer in accordance with the *CADTH Common Drug Review Confidentiality Guidelines.*

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Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

6MWT	six-minute walk test
AE	adverse event
CDEC	Canadian Drug Expert Committee
CDR	CADTH Common Drug Review
CI	confidence interval
CPFF	Canadian Pulmonary Fibrosis Foundation
DL_{CO}	diffusing capacity of the lung for carbon monoxide
FVC	forced vital capacity
HR	hazard ratio
IPF	idiopathic pulmonary fibrosis
MCID	minimal clinically important difference
MD	mean difference
PF	pulmonary fibrosis
PFS	progression-free survival
PP	per-protocol
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
TEAE	treatment-emergent adverse event
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Pirfenidone (267 mg capsules) is indicated for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF) in adults. In 2013, the Canadian Drug Expert Committee (CDEC) recommended that pirfenidone not be reimbursed for this indication. The reason for this recommendation was the inconsistent results of the two randomized controlled trials (RCTs) (CAPACITY-1 and CAPACITY-2, or PIPF-004 and PIPF-006, respectively), in which pirfenidone was compared with placebo.

For the current resubmission, the manufacturer provided data from a new RCT, namely PIPF-016 (the ASCEND study), to complement the data from the CAPACITY studies. The objective of this review was to perform an updated systematic review of the beneficial and harmful effects of pirfenidone for the treatment of mild to moderate IPF in adults, focusing on the new data from PIPF-016.

Indication under review
Treatment of mild to moderate idiopathic pulmonary fibrosis in adults.
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Results and Interpretation

Included Studies

One placebo-controlled trial was identified and included in this report: the ASCEND study, PIPF-016 (N = 555). The ASCEND study evaluated the efficacy and safety of pirfenidone compared with placebo for the treatment of mild to moderate IPF. Patients received either three pirfenidone 267 mg capsules three times per day or matching placebo. The primary outcome was the change in the per cent predicted forced vital capacity (% FVC) at 52 weeks. Secondary outcomes included changes in the 6MWT distance, progression-free survival (PFS), changes in dyspnea, and mortality.

The results of PIPF-016 have several limitations. First, while pirfenidone is indicated for mild to moderate IPF to reflect the study population, the absence of criteria to define the severity of IPF makes it possible that pirfenidone will be used in patients with severe IPF. Therefore, the exclusion of such patients from PIPF-016 limits the generalizability of the available data to patients with severe IPF who are likely to be treated in practice. Similarly, the exclusion from PIPF-016 of patients with exacerbated (or progressive) IPF limits the generalizability of the results to such patients. Finally, the relatively high pill burden associated with pirfenidone treatment (nine capsules daily) requires a high degree of motivation and compliance from patients, which raises the possibility that the results of PIPF-016 might overestimate real-world efficacy.

Efficacy

In PIPF-016, all-cause mortality after 52 weeks of treatment was lower in the pirfenidone-treatment group compared with the placebo-treatment group (4% versus 7.2%, respectively), although the hazard ratio (HR) for the between-treatment effect did not reach statistical significance (HR = 0.55; [95% CI, 0.26 to 1.15]). Quality of life (QoL) was not evaluated in PIPF-016. Acute exacerbation occurred at a lower frequency in the pirfenidone group (8.6%) than in the placebo group (14.4%), and the difference

between groups was statistically significant (*P* = 0.034). After 52 weeks of treatment, pirfenidone was associated with a statistically significantly smaller decline in lung capacity (%FVC) and walking distance (6MWT) compared with placebo. Specifically, the mean difference (MD) in %FVC was 4.8% (95% CI, 2.4% to 7.2%), while the MD in the 6MWT distance was 26.7 m (*P* = 0.036). These differences met the minimal clinically significant difference (MCID) threshold for both of these outcomes, based on an MCID of 2% to 6% for %FVC and 24 m to 45 m for the 6MWT.

Harms

In PIPF-016, the most frequent adverse events (AEs) leading to treatment dose reduction (pirfenidone versus placebo) were rash (7.6% versus 0.4%, respectively), nausea (7.2% versus 1.1%, respectively), anorexia (4.3% versus 0.7%, respectively), pruritus (2.9% versus 0%, respectively), photosensitivity (2.8% versus 0%, respectively), diarrhea (2.9% versus 2.9%, respectively), and weight loss (2.5% versus 0%, respectively). Treatment discontinuations due to AEs were more frequent in the pirfenidone-treatment group compared with the placebo-treatment group (14.4% versus 10.8%, respectively). The most frequent reason for treatment discontinuation in the placebo group was worsening IPF, which occurred in 5.4% of patients (versus 1.1% in the pirfenidone group).

Other Considerations

An analysis of pooled all-cause mortality data obtained at 52 weeks for the ASCEND study (PIPF-016) and the two CAPACITY studies (PIPF-004 and PIPF-006) suggested that pirfenidone treatment is associated with significantly lower mortality compared with placebo (HR = 0.52; [95% CI, 0.31 to 0.87]). Nevertheless, pirfenidone was not associated with statistically significantly lower all-cause mortality at 52 weeks in any of the individual trials. The absence of a statistically significantly effect on survival for the pirfenidone-treated patients in the individual studies has been postulated to be due to a lack of sufficient power, as mortality was not the primary outcome in any of the pirfenidone studies. The longer-term efficacy of pirfenidone is uncertain, as data are available up to 72 weeks only for the two CAPACITY studies (the ASCEND study was only 52 weeks long). An analysis of pooled all-cause mortality data obtained at 72 weeks for the two CAPACITY studies indicated that pirfenidone was not associated with statistically significantly better survival (HR = 0.77; [95% CI, 0.47 to 1.28]). A similar trend was observed for other outcomes that were analyzed by pooling. The results of an ongoing, open-label extension study of the pirfenidone clinical trials (PIPF-012 is) demonstrated that after a median duration of 3.1 years of treatment, 38% of patients discontinued pirfenidone treatment due to AEs, while 23% of patients died.

Patient input received by CADTH indicated that IPF patients hope that pirfenidone will slow disease progression, improve debilitating symptoms that prevent them from participating in daily living activities, and help them live longer. While the effects of pirfenidone on lung capacity and functional capacity (walking distance) clearly meet these expectations, it is less clear whether the effects of pirfenidone on mortality meet patient expectations. Patients also expressed a desire for improvement in QoL and a reduced need for lung transplantation, but there is insufficient evidence available from the ASCEND and CAPACITY studies to determine whether pirfenidone has such effects.

Conclusions

The results of a new study of the effects of pirfenidone versus placebo (the ASCEND study; PIPF-016) demonstrated that 52 weeks of treatment with pirfenidone significantly improved lung function (%FVC) and functional capacity (walking distance) in adults with mild to moderate IPF, and that these differences were sufficiently large to be clinically meaningful. While all-cause mortality in the ASCEND study was substantially lower in pirfenidone-treated patients compared with placebo-treated patients (HR = 0.37),

the difference between treatment groups was not statistically significant. A pooled analysis of the results of the ASCEND study (PIPF-016) and the two previous CAPACITY studies (PIPF-004 and PIPF-006) suggested that pirfenidone is associated with statistically significantly lower mortality at 52 weeks of treatment versus placebo (HR = 0.52), although the effect on mortality was not statistically significant in any of the individual studies.

TABLE 1: SUMMARY OF KEY OUTCOMES

Outcome	Outcome Measure	PIPF-0016	
		Pirfenidone (N = 278)	Placebo (N = 277)
Mortality	**All-cause mortality**[5]		
	N (%)	11 (4.0)	20 (7.2)
	HR (CI), *P* value	0.55 (0.26 to 1.15), 0.10	
Per cent predicted FVC	**Mean change in per cent predicted FVC**[4]		
	Baseline per cent predicted FVC, mean (SD)	67.8 (11.2)	68.6 (10.9)
	Mean change from baseline, mean (SD)	–6.17 (12.11)	–10.95 (16.75)
	Absolute difference (95% CI), *P* value	4.8 (2.4 to 7.2)[b], <0.0001	
Six-minute walk test	**Mean change in 6MWT**[4,6]		
	Baseline 6MWT distance (m), mean (SD)	415.0 (98.5)	420.7 (98.13)
	Change from baseline (m), mean (SD)	–33.6 (95.73)	–60.2 (122.56)
	Difference in mean change from baseline, *P* value[a]	26.7 m, 0.036	
PFS	**PFS**[5]		
	≥ 10% decline in per cent predicted FVC, n (%)	18 (6.5)	49 (17.7)
	≥ 50 m decline in 6MWT, n (%)	46 (16.5)	54 (19.5)
	Death, n (%)	10 (3.6)	14 (5.1)
	Total events, n (%)	74 (26.6)	117 (42.2)
	HR (95% CI), *P* value[a]	0.57 (0.43 to 0.77), 0.0001	
UCSD SOBQ	**Categorical change in dyspnea score**[4,5]		
	Worsening of UCSD SOBQ score ≥ 20 points or death, n (%)	81 (29.1)	100 (36.1)
	Worsening of UCSD SOBQ score < 20 points to 0 points, n (%)	124 (44.6)	115 (41.5)
	No worsening, n (%)	73 (26.3)	62 (22.4)
	P value[a]	0.1577	
SAE	n (%)	55 (19.8)	69 (24.9)
Treatment discontinuation due to AE	n (%)	40 (14.4)	30 (10.8)

6MWT = six-minute walk test; CI = confidence interval; FVC = forced vital capacity; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; PFS = progression-free survival; SD = standard deviation; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

[a] *P* values were calculated with the log-rank test.

[b] CDR calculation.

Source: Clinical Study Report.[4]

1. INTRODUCTION

1.1 Submission History

In 2013, the Canadian Drug Expert Committee (CDEC) issued a negative recommendation for pirfenidone (Do Not List).[1] The reason for this recommendation was due to the inconsistent results of the CAPACITY-1 and CAPACITY-2 trials (PIPF-004 and PIPF-006, respectively).[2,3] Specifically, these two trials were inconsistent with respect to the statistical significance of improvements with pirfenidone of the per cent predicted forced vital capacity (FVC) and the six-minute walk test (6MWT). In addition, there was insufficient evidence to determine if pirfenidone provided clinical benefit for mortality or quality of life (QoL).

In the current resubmission, the manufacturer provided the results of a new randomized controlled trial (RCT), namely the ASCEND study (PIPF-016).[4]

1.2 Drug

Pirfenidone (267 mg capsules) is an orally administered pyridine for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF). In Canada, pirfenidone is the only pharmacological therapy approved for IPF. In the European Union, Esbriet has orphan drug designation.

Pirfenidone 267 mg oral capsules is thought to act by suppressing pulmonary inflammation and excessive collagen disposition through the inhibition of transforming growth factor (TGF-beta)-induced collagen synthesis, and through inhibition of tumour necrosis factor (TNF-alpha). Upon initiating treatment, the dose should be titrated to the recommended daily dose of nine capsules per day (2,403 mg per day) over a 14-day period to improve tolerability. During the first week, it is recommended to use one capsule three times per day; in the second week, two capsules three times per day; and starting from the third week, three capsules three times per day.

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2. OBJECTIVES AND METHODS

2.1 Objectives

To perform an updated systematic review of the beneficial and harmful effects of pirfenidone 267 mg capsules (total daily dose 2,403 mg) for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF) in adults.

2.2 Methods

Studies selected for the systematic review include pivotal trials submitted by the manufacturer in support of the Health Canada indication (IPF) for which the submission was made, in addition to trials meeting the selection criteria presented in Table 2.

Studies included in the previous CADTH Common Drug Review (CDR) were excluded from the current review; however, data from other relevant studies (CAPACITY-1 and CAPACITY-2) are summarized in APPENDIX 6.

TABLE 2: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adults with mild to moderate IPF Subgroup of interest: mild versus moderate disease severity
Intervention	Pirfenidone 267 mg × 3 capsules, TID (2,403 mg/d)
Comparators	• Corticosteroids • The combination of corticosteroids and NAC • Supportive care
Outcomes	**Key efficacy outcomes** • mortality • QoL **Other efficacy outcomes** • incidence of acute exacerbations • lung capacity (including FVC) • 6MWT • PFS • lung transplantation • dyspnea relief **Harms outcomes** SAEs WDAEs AE of special interest: photosensitivity
Study Design	Published and unpublished RCTs
Exclusion Criteria	Phase 2 RCTs

6MWT = six-minute walk test; AE = adverse event; d = day; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; NAC = N-acetylcysteine; PFS = progression-free survival; QoL = quality of life; RCT = randomized controlled trial; SAE = serious adverse event; TID = three times daily; TLC = total lung capacity; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Esbriet (pirfenidone).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on October 6, 2014. Regular alerts were established to update the search until the CDEC meeting on February 18, 2015. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the Grey Matters checklist (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters): health technology assessments, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, and databases. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3; excluded studies (with reasons) are presented in APPENDIX 3.

3. RESULTS

3.1 Findings From the Literature

A total of 381 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 2 and described in Section 3.2. A list of excluded studies is presented in APPENDIX 3.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

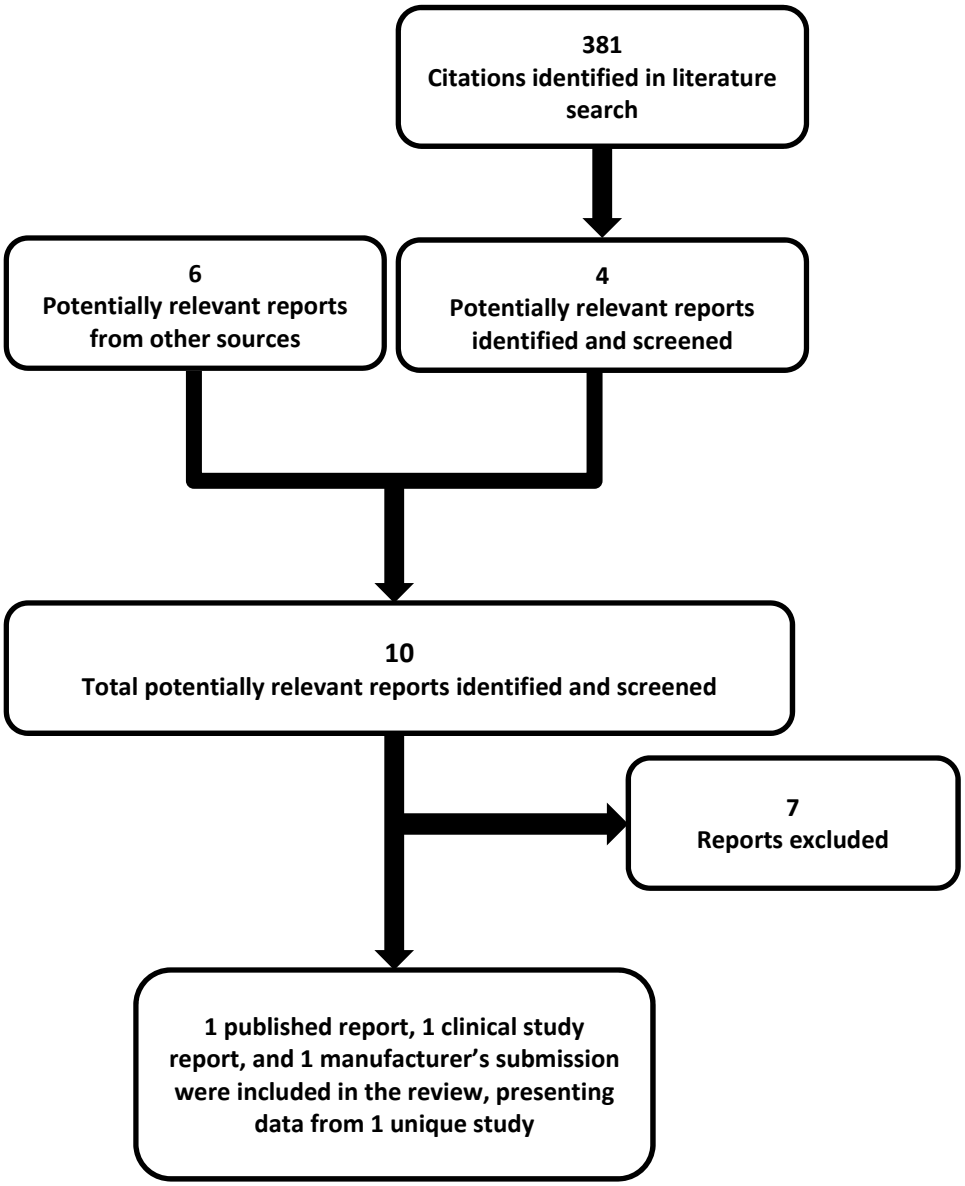


TABLE 3: DETAILS OF INCLUDED STUDY

<table>
<tr><th></th><th></th><th>PIPF-016</th></tr>
<tr><td rowspan="6">DESIGNS AND POPULATIONS</td><td>Study Design</td><td>DB, placebo-controlled, randomized 52-week trial</td></tr>
<tr><td>Locations</td><td>9 countries including the US, Brazil, Mexico, Peru, Australia, New Zealand, Singapore, Israel, and Croatia</td></tr>
<tr><td>Randomized (N)</td><td>555</td></tr>
<tr><td>Inclusion Criteria</td><td>• Age 40 years to 80 years
• Clinical symptoms consistent with IPF of ≥ 12 months duration
• Diagnosis of IPF, defined as the first instance in which a patient was informed of having IPF, at least 6 months before and no more than 48 months before randomization. Diagnosis had been confirmed according to the following criteria:
<table>
<tr><th rowspan="2">Radiology Panel</th><th rowspan="2">Lung Biopsy Not Available</th><th colspan="4">Pathological Assessment</th></tr>
<tr><th>Definite UIP</th><th>Probable UIP</th><th>Possible UIP</th><th>Inconsistent With UIP</th></tr>
<tr><td>Definite UIP</td><td>Eligible</td><td>Eligible</td><td>Eligible</td><td>Eligible</td><td>Not eligible</td></tr>
<tr><td>Possible UIP</td><td>Not eligible</td><td>Eligible</td><td>Eligible</td><td>Not eligible</td><td>Not eligible</td></tr>
<tr><td>Inconsistent With IPF</td><td>Not eligible</td><td>Not eligible</td><td>Not eligible</td><td>Not eligible</td><td>Not eligible</td></tr>
</table>
• Per cent predicted DL_{CO} at entry ≥ 30% and ≤ 90%
• Per cent predicted FVC ≥ 50% and ≤ 90%
• Requirement for an FEV1/FVC ratio ≥ 0.8
• No evidence of improvement in measures of IPF disease severity over the preceding year
• Able to walk ≥ 150 m during the 6MWT at screening</td></tr>
<tr><td>Exclusion Criteria</td><td>• Alternative explanation for interstitial lung disease
• Patients with history of clinically significant liver disease, unstable or deteriorating cardiac or pulmonary disease, or in the opinion of the investigator the patient was likely to die within 2 years after study entry</td></tr>
<tr><td rowspan="2">DRUGS</td><td>Intervention</td><td>3 × 267 mg pirfenidone capsules PO, TID (2,403 mg/day)</td></tr>
<tr><td>Comparator(s)</td><td>Placebo</td></tr>
<tr><td rowspan="4">DURATION</td><td>Washout</td><td>8 weeks to 12 weeks pre-randomization (required only if patients were on a prohibited medication)</td></tr>
<tr><td>Screening</td><td>8 weeks pre-randomization</td></tr>
<tr><td>Double-blind</td><td>52 weeks (including two weeks of dose escalation)</td></tr>
<tr><td>Follow-up</td><td>4 weeks to 5 weeks after last dose of study treatment (required only if patient permanently discontinued study treatment or did not enter extension study PIPF-012)</td></tr>
<tr><td rowspan="2">OUTCOMES</td><td>Primary End Point</td><td>Change in per cent predicted FVC from baseline to Week 52
(treatment effect was presented as the distribution of patients with a decline of ≥ 10% or death, a decline of < 10% to 0%, and no decline)</td></tr>
<tr><td>Other End Points</td><td>Change from baseline to Week 52 in 6MWT distance.
PFS defined as the time to the first occurrence of any of the following events:
• death
• confirmed ≥ 10% decline from baseline in per cent predicted FVC
• confirmed ≥ 50 m decline from baseline in 6MWT distance
Change from baseline at Week 52 in the UCSD SOBQ dyspnea score.
Mortality (all-cause and treatment-emergent disease-related mortality).</td></tr>
</table>

		PIPF-016
NOTES	**Publications**	King et al.[5]

6MWT = six-minute walk test; DB = double-blind; DL_{CO} = diffusing capacity for carbon monoxide; FEV1 = forced expiratory volume in one second; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; PFS = progression-free survival; PO = by mouth; TBBx = transbronchial biopsy; TID = three times daily; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire; UIP = usual interstitial pneumonia.
Source: Clinical Study Report.[4]
Note: One additional report was included (CDR submission{1})

3.2 Included Study

3.2.1 Description of the Study

One RCT met the inclusion criteria for this updated systematic review, namely PIPF-016. The objective of the study was to assess the treatment efficacy and safety of pirfenidone (2,403 mg/day) compared with placebo in patients with mild to moderate IPF. In this study, patients received the blinded study treatments for 52 weeks.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

Eligible patients had a confirmed diagnosis of IPF based on clinical and radiologic data (and histopathological data, if available), without evidence or suspicion of an alternative diagnosis. The study protocol specified 26 exclusion criteria which, in the opinion of the clinical expert, provide an additional aid to determine the appropriate candidates to receive pirfenidone. In addition to the exclusion criteria reported in Table 3, the following criteria were also specified in the study protocol:

1. Significant clinical worsening of IPF between screening and Day 1, in the opinion of the investigator.
2. Not a suitable candidate for enrolment or unlikely to comply with the requirements of this study, in the opinion of the investigator.
3. Forced expiratory volume in one second (FEV1)/FVC ratio < 0.8 after the administration of a bronchodilator at screening, confirmed by central review.
4. Bronchodilator response, defined by an absolute increase of ≥ 12% and an increase of 200 mL in the predicted FEV1 or FVC or both after bronchodilator use compared with the values seen before bronchodilator use at screening, confirmed by central review.
5. Use of any of the following therapies within 28 days before screening:
   a. Investigational therapy, defined as any drug that has not been approved for marketing for any indication in the country of the participating site.
   b. Any cytotoxic, immunosuppressive, cytokine-modulating, or receptor antagonist agent including but not limited to azathioprine, bosentan, ambrisentan, cyclophosphamide, cyclosporine, etanercept, iloprost, infliximab, leukotriene receptor antagonists, methotrexate, mycophenolate mofetil, tacrolimus, montelukast, tetrathiomolybdate, TNF-alpha inhibitors, N-acetylcysteine, imatinib mesylate, interferon gamma-1b (IFN gamma-1b), and tyrosine kinase inhibitors.
   c. Medications that are specifically used for the treatment of IPF, including but not limited to angiotensin-converting enzyme (ACE) inhibitors, colchicine, corticosteroids, heparin, warfarin, and HMG-CoA reductase inhibitors. These drugs may be used if given for a non-IPF indication if there is no clinically acceptable alternative therapy for the same indication.
   d. Fluvoxamine.
   e. Sildenafil (daily use). Note: intermittent use for erectile dysfunction is allowed.

b) Baseline Characteristics

Baseline characteristics for PIPF-016 are summarized inTable 4. A total of 555 patients were randomized in PIPF-016. The majority of patients were males, with a mean age of 68 years. Enrolment of patients was mainly in the US (67%). The mean time from IPF diagnosis to randomization was 1.4 years. Approximately 28% of the included patients used supplemental oxygen at the time of inclusion.

TABLE 4: SUMMARY OF BASELINE CHARACTERISTICS

Characteristics	PIPF-016	
	Pirfenidone (N = 278)	Placebo (N = 277)
Demographics		
Age, years (SD)	68.4 (6.7)	67.8 (7.3)
≥ 75 years, n (%)	57 (20.5)	55 (19.9)
Male, n (%)	222 (79.9)	213 (76.9)
Non-US enrolment	91 (32.7)	93 (33.6)
Race, n (%)		
Caucasian	225 (91.7)	251 (90.6)
Black or African-American	4 (1.4)	2 (0.7)
Asian	2 (0.7)	7 (2.5)
American Indian/Alaskan Native	16 (5.8)	17 (6.1)
Medical history		
UIP diagnosis by HRCT, n (%)		
Definite IPF	266 (95.7)	262 (94.6)
Probable IPF	12 (4.3)	15 (5.4)
SLBx	Available for only 86 patients	Available for only 79 patients
Definite UIP	58 (67.4)	50 (63.3)
Probable UIP	17 (19.8)	14 (17.7)
Possible UIP	11 (12.8)	14 (17.7)
Not UIP pattern	0	1 (1.3)
Time since IPF diagnosis, years, mean (SD)	1.7 (1.05)	1.7 (1.05)
Per cent predicted FVC, mean (SD)	67.8 (11.2)	68.6 (10.9)
DL_{CO} (per cent predicted), mean (SD)	43.7 (10.5)	44.2 (12.5)
6MWT distance, mean (SD)	415.0 (98.5)	420.7 (98.1)
Smoking status, n (%)		
Never (< 100 cigarettes in life)	94 (33.8)	108 (39.0)
Former	184 (66.2)	169 (61.0)
Concomitant medications (medications used during the treatment period)		
Use of supplemental oxygen, n (%)	**78 (28.1)**	**76 (27.4)**
Bronchodilators/COPD drugs, n (%)		
Salbutamol	**238 (85.6)**	**246 (88.8)**
Salbutamol sulfate	**49 (17.6)**	**42 (15.2)**
Systemic corticosteroids, n (%)		
Prednisone	**60 (21.6)**	**71 (25.6)**

6MWT = six-minute walk test; a-a = alveolar-arterial; BAL = bronchoalveolar lavage; COPD = chronic obstructive pulmonary disease; DL_{CO} = carbon monoxide diffusing capacity; FVC = forced vital capacity; HRCT = High-resolution computerized scan; IPF = idiopathic pulmonary fibrosis; SD = standard deviation; SLBx = surgical lung biopsy; UIP = usual interstitial pneumonia.
Source: Clinical Study Report.[4]

3.2.3 Interventions

Patients received either three pirfenidone 267 mg capsules three times per day or matching placebo. In addition to the double-blinded study treatments, PIPF-016 allowed per-protocol (PP) use of other medications for the management of IPF exacerbations. Corticosteroids were used at the discretion of the investigator, without dose restriction, for up to 21 days in patients experiencing acute IPF exacerbation. The study drug was continued during this time if possible.

The following guidelines were offered as a definition of an acute IPF exacerbation, but were not required to be fulfilled. The definition specified that a patient has developed evidence of all of the following criteria within a four-week period:

- a decline of ≥ 5% in resting oxygen saturation by pulse oximetry (SpO2) on room air, or a decline of ≥ 8 mm Hg from the last recorded level in resting partial pressure of arterial oxygen (PaO2) on room air
- a clinically significant worsening of dyspnea or cough, triggering unscheduled medical care (e.g., clinic visit, hospitalization)
- new, superimposed ground-glass opacities or consolidation on computed tomography (CT) scan or new alveolar opacities on chest X-ray
- no clinical or microbiologic evidence of infection (i.e., absence of grossly purulent sputum and no fever > 39°C orally)
- all other causes excluded (e.g., pneumothorax, cardiac event, infection, thromboembolism).

3.2.4 Outcomes

The primary efficacy outcome variable was the change in per cent predicted FVC from baseline to Week 52. Secondary outcomes included change in 6MWT distance from baseline to Week 52. FVC and the 6MWT appear to be valid outcome measures in patients with mild or moderate IPF. An absolute change of at least 5% or 10% in the per cent predicted FVC is predictive of mortality. Estimates of the MCID range from 2% to 6% for the per cent predicted FVC, and from 24 m to 45 m for the 6MWT (APPENDIX 4).

Progression-free survival (PFS) was another secondary outcome, and it was defined as the time to the first occurrence of any of the following:

- death
- confirmed ≥ 10% absolute decline from baseline in per cent predicted FVC
- confirmed ≥ 50 m decline from baseline in 6MWT distance.

Additional secondary efficacy end points included the following:

- Change in dyspnea, as measured by the University of California, San Diego Shortness of Breath Questionnaire score, from baseline to Week 52.
- Mortality, to include all-cause mortality and treatment-emergent IPF-related mortality as key measures. The results of these two measures were pooled (PP) with results from PIPF-004 and PIPF-006. Supportive end points were IPF-related mortality and treatment-emergent all-cause mortality. Study PIPF-016 assessed the relatedness of death (directly or indirectly) by an independent Mortality Assessment Committee that was blinded to treatment assignment. The causes of death in studies PIPF-004 and PIPF-006 were not adjudicated, but were determined by local clinical trial investigators.

3.2.5 Statistical Analysis

a) Analysis Populations

The efficacy analysis population was the intention-to-treat (ITT) population, consisting of all patients who signed informed consent and who were randomized to study treatment. The safety analysis population included all patients who signed informed consent and who received any amount of study treatment. For this study, the ITT population and safety population were identical.

b) Efficacy Analyses

The study primary outcome (change in per cent predicted FVC) was analyzed using a fixed-effect rank analysis of covariance (ANCOVA) comparing pirfenidone and placebo in the ITT population, with ranked baseline per cent predicted FVC value as a covariate. This analysis was tested at an alpha level of 0.0498, adjusting for the two interim mortality analyses. Supportive analysis for the primary outcome included a repeated-measures, mixed linear model for rank change from baseline in per cent predicted FVC, using ranks calculated for change to Weeks 13, 26, 39, and 52. The mixed model included fixed effects for treatment, ranked baseline per cent predicted FVC as a covariate, and a repeated effect of assessment week, unstructured covariance structure, and patient as the subject factor. A sensitivity analysis for the primary outcome was conducted using the last observation carried forward (LOCF) for imputing Week 52 per cent predicted FVC data, if it was missing for reasons other than death.

3.3 Patient Disposition

Table 5 summarizes patient disposition in PIPF-016. Treatment discontinuation was higher in the pirfenidone-treatment group (19.8%) than in the placebo-treatment group (14.1%). Adverse events (AEs) were the main reason for these discontinuations, and AEs occurred more frequently in the pirfenidone-treatment group than in the placebo-treatment group (12.6% versus 8.7%, respectively). Death was the main reason for study discontinuation, and the death rate was slightly lower in the pirfenidone-treatment group than in the placebo-treatment group (4.3% versus 6.9%, respectively).

TABLE 5: PATIENT DISPOSITION

	PIPF-016	
	Pirfenidone	Placebo
Screened, N	1562	
Randomized, N (%)	555	
	278	277
Completed study treatment, n (%)	223 (80.2)	238 (85.9)
Discontinued, n (%)	55 (19.8)	39 (14.1)
AEs	35 (12.6)	24 (8.7)
Withdrawal by patient	9 (3.2)	7 (2.5)
Death	4 (1.4)	5 (1.8)
Lung transplantation	6 (2.2)	1 (0.4)
Other	1 (0.4)	1 (0.4)
Lost to follow-up	0	1 (0.4)
Completed the study, n (%)	243 (87.4)	241 (87.0)
Withdrew early from the study, n (%)	35 (12.6)	36 (13.0)
Death	12 (4.3)	19 (6.9)
AEs	6 (2.2)	7 (2.5)
Withdrawal by patient	4 (1.4)	4 (1.4)
Withdrew consent	4 (1.4)	3 (1.1)
Lung transplant	6 (2.2)	1 (0.4)

	PIPF-016	
	Pirfenidone	Placebo
Lost to follow-up	2 (0.7)	1 (0.4)
Physician's decision	1 (0.4)	0
Sponsor's decision	0	1 (0.4)
ITT, N	278	277
Safety, N	278	277

AE = adverse event; ITT = intention-to-treat.

Source: Clinical Study Report,[4] King et al.[5]

3.4 Exposure to Study Treatments

All randomized patients received at least one dose of study treatment, and 88.8% of study patients took ≥ 80% of their prescribed dose (Table 6). Treatment compliance was lower in the pirfenidone-treatment group compared with the placebo-treatment group. The proportion of patients in the pirfenidone-treatment group that took ≥ 80% of their prescribed dose was lower than in the placebo-treatment group (85.3% versus 92.4%, respectively).

TABLE 6: TREATMENT COMPLIANCE IN PIPF-016 (ALL RANDOMIZED PATIENTS)

Treatment Compliance	PIPF-016	
	Pirfenidone (N = 278)	Placebo (N = 277)
	Number of Patients, n (%)	
Patients who received any amount of study treatment, n (%)	278 (100)	277 (100)
Per cent compliance/patient		
80% to 100%	237 (85.3)	256 (92.4)
60% to < 80%	14 (5.0)	7 (2.5)
40% to < 60%	11 (4.0)	6 (2.2)
< 40%	16 (5.8)	8 (2.9)

Source: Clinical Study Report,[4] King et al.[5]

3.5 Critical Appraisal

3.5.1 Internal Validity

a) Selection Bias

Patients were randomly allocated to receive either pirfenidone or placebo in a 1:1 ratio using permuted block randomization, without stratification on any variable. However, the randomization process was not reported.

b) Performance Bias

The PP criteria for using supportive therapies and concurrent interventions did not differentiate between treatment groups, and this is important to limit the performance bias. However, treatment allocation was potentially unblinded due to AEs. Treatment-emergent AEs (TEAEs) and discontinuation due to AEs occurred more frequently in the pirfenidone group than in the placebo group. This discrepancy in AEs between groups might have affected the assessment of patient-reported outcomes such as dyspnea relief. As recognized, the outcome measures based on spirometry would be affected by subjectivity as well, as would the outcome measures based on the 6MWT. The performance of spirometry is highly dependent on patient co-operation and effort. Less effort could be exerted by patients who knew they were not on the treatment. Conversely, those patients who knew they were on the

treatment might have exerted more effort in those tests. This would have led to an overestimate of the treatment effect in terms of both per cent predicted FVC and 6MWT.

c) Attrition Bias

More patients in the pirfenidone group than in the placebo group discontinued the trial treatment; however, the rate of study withdrawal was similar in both groups, and was consistently less than 15%.

d) Validity of Outcome Measures

The trial evaluated the changes in FVC and 6MWT; according to the clinical expert consulted by CDR, these are two important outcomes used in practice for the evaluation of IPF patients. The validity of these two measures, as evaluated in APPENDIX 4, confirmed that FVC and the 6MWT are valid outcome measures in patients with mild to moderate IPF. An absolute change of at least 5% to 10% in the per cent predicted FVC is predictive of mortality. Estimates of the MCID range from 2% to 6% for the per cent predicted FVC, and from 24 m to 45 m for the 6MWT.

3.5.2 External Validity

Patients were recruited from nine countries; although Canada was not one of these countries, the clinical expert estimated that the clinical practice and IPF patients' characteristics are not expected to differ substantially from the Canadian setting.

Pirfenidone is indicated for mild to moderate IPF; however, the approved product monograph does not provide criteria that can be used to define the severity of IPF, nor is such information available from the published literature. Therefore, differences between definitions of mild to moderate IPF versus severe IPF in practice might have differed from those used in the included trial, which could have undermined the generalizability of the results.

Furthermore, the included study trial protocol excluded patients who were in the exacerbation phase during the screening process. Therefore, the generalizability of the study results to patients with acute exacerbation of IPF is limited.

The pirfenidone treatment regimen requires a high degree of patient motivation and compliance. Pirfenidone is prescribed as three capsules that must be taken orally three times a day (nine capsules in total per day). The results of the included study reflect a high degree of patient compliance, which is likely higher than real-world compliance.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See Table 7 for a summary of efficacy data.

3.6.1 Mortality (Survival)

a) All-Cause Mortality

In the PIPF-016 study, there were fewer all-cause deaths reported in the pirfenidone group compared with the placebo group (4% versus 7.2%, respectively) (Table 7). The hazard ratio (HR) between treatment groups did not reach statistical significance (HR = 0.55; [95% CI, 0.26 to 1.15]; *P* = 0.10).

b) IPF-Related Mortality

In the PIPF-016 study, there were fewer cases of IPF-related mortality in the pirfenidone group compared with the placebo group (1.1% versus 1.5%, respectively) (Table 7); however, the HR was not statistically significant (HR = 0.44; [95% CI, 0.18 to 1.04]; *P* = 0.23).

3.6.2 Quality of Life

Quality of life (QoL) was not an outcome assessed in PIPF-016, the included study.

3.6.3 Incidence of Acute Exacerbations

Acute exacerbation was reported to have occurred at a lower frequency in the pirfenidone group (8.6%) than in the placebo group (14.4%). The difference between groups was statistically significant (*P* = 0.034).

3.6.4 Lung Capacity

a) Mean Change in Per Cent Predicted FVC From Baseline

The results of PIPF-016 showed that, at 52 weeks, pirfenidone reduced the decline in the per cent predicted FVC more than placebo did (6.17% versus 10.95%, respectively) (Table 7); the mean difference (MD) between the two treatment groups was 4.8%; (95% CI, 2.4% to 7.2%). This would appear to exceed the MCID for this outcome, which is estimated to lie between 2% and 6%.

b) Categorical Change in Per Cent Predicted FVC From Baseline

The categorical assessment of change from baseline in per cent predicted FVC revealed that a significantly lower proportion of pirfenidone patients, as compared with placebo patients, had a > 10% decline in FVC or death (16.5% versus 31.8%, respectively, Table 7). The same analysis showed that a higher proportion of pirfenidone patients, as compared with placebo patients, had a < 10% decline in FVC (60.8% versus 58.2%, respectively), or had no decline (22.7% versus 9.7%, respectively). The log-rank analysis of covariance (ANCOVA) analysis showed that the difference between groups was statistically significant (*P* value < 0.00001).

3.6.5 Six-Minute Walk Test

a) Mean Change in 6MWT From Baseline

Table 7 summarizes the mean changes in the 6MWT distance. In PIPF-016, the mean decline in the 6MWT distance test distance was smaller for patients treated with pirfenidone (33.6 m) compared with placebo (60.2 m). The difference between groups was statistically significant, with a MD of 26.7 m; (95% CI, 8.3 m to 44.9 m). These differences met the MCID threshold that ranges from 24 m to 45 m.

b) Categorical Change in 6MWT From Baseline

Categorical analysis revealed that at Week 52 in PIPF-016, there was a statistically significantly smaller proportion of patients who experienced a decline from baseline in 6MWT distance performance in the pirfenidone-treatment group compared with the placebo-treatment group (*P* = 0.0360; rank ANCOVA; Table 7). Specifically, 25.9% of patients in the pirfenidone-treatment group either had a decline from baseline of ≥ 50 m or died, compared with 35.7% of patients in the placebo-treatment group. The proportion of patients in the two groups with no decline in 6MWT distance performance from baseline was similar: 37.8% versus 35.0%, respectively, for pirfenidone-treated versus placebo-treated patients. A higher proportion of patients in the pirfenidone-treatment group (36.3%) had a decline > 0 m but < 50 m compared with the placebo-treatment group (29.2%).

3.6.6 Progression-Free Survival

In PIPF-016, pirfenidone treatment was associated with statistically significant benefits in terms of the proportion of patients who had progression-free survival (PFS) (26.6%) compared with placebo treatment (42.2%) (Table 7); HR = 0.57; (95% CI, 0.43 to 0.77).

3.6.7 Lung Transplantation

In PIPF-016, eight patients had lung transplants, and most of these cases (seven cases) were in the pirfenidone-treatment group. However, no conclusion can be inferred from these results due to the limited number of events.

3.6.8 Dyspnea Relief

In PIPF-016, at Week 52, there was a non-statistically significant reduction in worsening of the University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ) score (dyspnea score) in the pirfenidone group compared with the placebo group (*P* = 0.1577, rank ANCOVA). The proportion of patients whose dyspnea score worsened by ≥ 20 points was smaller in patients receiving pirfenidone than in patients receiving placebo (29.1% versus 36.1%, respectively). A higher proportion of patients in the pirfenidone group compared with the placebo group had a worsening of their dyspnea score by < 20 (44.6% versus 41.5%, respectively), or had no worsening (26.3% versus 22.4%, respectively) (Table 7).

TABLE 7: KEY EFFICACY OUTCOMES

Outcome	Outcome Measure	PIPF-0016	
		Pirfenidone (N = 278)	Placebo (N = 277)
Mortality	**All-cause mortality**[5]		
	N (%)	11 (4.0)	20 (7.2)
	HR (CI), *P* value	0.55 (0.26 to 1.15), 0.10	
	Treatment-emergent IPF-related mortality[5]		
	N (%)	3 (1.1)	7 (1.5)
	HR (CI), *P* value[a]	0.44 (0.11 to 1.72), 0.23	
Per cent predicted FVC	**Mean change in per cent predicted FVC**[4]		
	Baseline per cent predicted FVC, mean (SD)	67.8 (11.2)	68.6 (10.9)
	Mean change from baseline, mean (SD)	–6.17 (12.11)	–10.95 (16.75)
	Absolute difference (95% CI), *P* value	4.8 (2.4 to 7.2)[b], <0.0001	
	Categorical change in per cent predicted FVC[4]		
	Decline of ≥ 10% or death, n (%)	46 (16.5)	88 (31.8)
	Decline of < 10% to 0%, n (%)	169 (60.8)	162 (58.5)
	No decline, n (%)	63 (22.7)	27 (9.7)
	P value[a]	< 0.00001	
Six-minute walk test	**Mean change in 6MWT**[4,6]		
	Baseline 6MWT distance (m), mean (SD)	415.0 (98.5)	420.7 (98.13)
	Change from baseline (m), mean (SD)	–33.6 (95.73)	–60.2 (122.56)
	Difference in mean change from baseline, *P* value[a]	26.7 m, 0.036	
	Categorical change in 6MWT[4,5]		
	Decline of ≥ 50 m or death, n (%)	72 (25.9)	99 (35.7)
	Decline of < 50 m to 0%, n (%)	101 (36.3)	81 (29.2)
	No decline, n (%)	105 (37.8)	97 (35.0)
	P value[a]	0.0360	

Outcome	Outcome Measure	PIPF-0016	
		Pirfenidone (N = 278)	Placebo (N = 277)
PFS	**PFS**[5]		
	≥ 10% decline in per cent predicted FVC, n (%)	18 (6.5)	49 (17.7)
	≥ 50 m decline in 6MWT, n (%)	46 (16.5)	54 (19.5)
	Death, n (%)	10 (3.6)	14 (5.1)
	Total events, n (%)	74 (26.6)	117 (42.2)
	HR (95% CI), *P* value[a]	0.57 (0.43 to 0.77), 0.0001	
UCSD SOBQ	**Categorical change in dyspnea score**[4,5]		
	Worsening of UCSD SOBQ score ≥ 20 points or death, n (%)	81 (29.1)	100 (36.1)
	Worsening of UCSD SOBQ score < 20 points to 0 points, n (%)	124 (44.6)	115 (41.5)
	No worsening, n (%)	73 (26.3)	62 (22.4)
	P value[a]	0.1577	

6MWT = six-minute walk test; CI = confidence interval; FVC = forced vital capacity; HR = hazard ratio; IPF = idiopathic pulmonary fibrosis; PFS = progression-free survival; SD = standard deviation; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

[a] *P* values were calculated with the log-rank test.

[b] CDR calculation.

Source: Clinical Study Report.[4]

3.7 Harms

Only those harms identified in the review protocol are reported below. See APPENDIX 7 for detailed harms data.

3.7.1 Adverse Events

Table 8 lists the common treatment-emergent adverse events (TEAEs) that occurred in ≥ 5% of patients in the pirfenidone-treatment group and were reported more frequently than in the placebo-treatment group during the 52 weeks.

In the PIPF-016 study, almost all patients in the pirfenidone and the placebo groups experienced at least one TEAE (99.6% versus 98.2%, respectively). TEAEs reported at a frequency of 5% or more in the pirfenidone group as compared with the placebo group were nausea (36.0% versus 13.4%, respectively), dyspepsia (17.6% versus 6.1%, respectively), anorexia (15.8% versus 6.5%, respectively), dysgeusia (9% versus 4%, respectively), rash (28.1% versus 8.7%, respectively), and photosensitivity (5.8% versus 0.4%, respectively).

3.7.2 Serious Adverse Events

At 52 weeks in PIPF-016, serious adverse events (SAEs) were reported less frequently in the pirfenidone-treatment group (19.8%) than in the placebo-treatment group (24.9%) (Table 8). The following SAEs were reported more in the pirfenidone group, with no cases were reported in the placebo-treatment group: nausea (1.1% versus 0%, respectively), angina pectoris (1.1% versus 0%, respectively), congestive cardiac failure (0.7% versus 0%, respectively), and rib fracture (0.7% versus 0%, respectively). (Detailed harm results are reported in APPENDIX 7.)

3.7.3 Withdrawals Due to Adverse Events

a) Adverse Events Leading to Treatment Discontinuation

At 52 weeks in PIPF-016, a larger proportion of patients in the pirfenidone-treatment group than in the placebo-treatment group discontinued study treatment early as a result of a TEAE (14.4% versus 10.8%, respectively) (Table 8). The most common reason for study discontinuation (i.e., worsening IPF), was less frequent in the pirfenidone-treatment group than in the placebo-treatment group (three patients versus 15 patients, respectively). In addition to IPF, at least two patients in both the pirfenidone and placebo groups discontinued treatment as a result of the following events: pneumonia (three patients versus one patient, respectively), increased hepatic enzymes (three patients versus zero patients, respectively), decreased weight (three patients versus zero patients, respectively), rash (three versus zero patients), nausea (two patients versus zero patients, respectively), dysgeusia (two patients versus zero patients, respectively), and upper abdominal pain (zero patients versus two patients, respectively).

b) Adverse Events Leading to Dose Reduction or Treatment Interruption

More patients in the pirfenidone-treatment group than in the placebo-treatment group had a dose reduction or interruption due to a TEAE (106 [38.1%] and 37 [13.4%], respectively) (Table 8). The most common reasons for dose reduction or interruption in the pirfenidone group versus the placebo group were gastrointestinal events (nausea [7.2% versus 1.1%, respectively] and anorexia [4.3% versus 0.7%, respectively]), and rash (7.6% versus 0.4%, respectively).

TABLE 8: SUMMARY OF HARMS IN PIPF-016

TEAEs	Pirfenidone (N = 278)	Placebo (N = 277)
Subjects with > 0 TEAEs, n (%)	**277 (99.6)**	**272 (98.2)**
Most common TEAEs[a]		
Nausea	100 (36.0)	37 (13.4)
Rash	78 (28.1)	24 (8.7)
Dyspepsia	49 (17.6)	17 (6.1)
Anorexia	44 (15.8)	18 (6.5)
Gastroesophageal reflex	33 (11.9)	18 (5.6)
Dysgeusia	25 (9.0)	11 (4.0)
Photosensitivity	16 (5.8)	1 (0.4)
SAEs		
Subjects with > 0 SAEs, N (%)	**55 (19.8)**	**69 (24.9)**
Most common SAEs[b]		
Pneumonia	11 (4.0)	14 (5.1)
IPF	7 (2.5)	27 (9.7)
Angina pectoris	3 (1.1)	0
Nausea	3 (1.1)	0
Treatment discontinuation due to AEs		
N (%)	**40 (14.4)**	**30 (10.8)**
Most common reasons		
Pneumonia	3 (1.1)	1 (0.4)
Hepatic enzyme increased	3 (1.1)	0
Weight decreased	3 (1.1)	0
IPF	3 (1.1)	15 (5.4)

TEAEs	Pirfenidone (N = 278)	Placebo (N = 277)
Rash	3 (1.1)	0
TEAEs resulting in study treatment dose reduction or interruption		
N (%)	**106 (38.1)**	**37 (13.4)**
Most common reasons		
Nausea	20 (7.2)	3 (1.1)
Diarrhea	8 (2.9)	8 (2.9)
Weight increased	7 (2.5)	0
Anorexia	12 (4.3)	2 (0.7)
Rash	21 (7.6)	1 (0.4)
Pruritus	8 (2.9)	0

IPF = idiopathic pulmonary fibrosis; SAE = serious adverse event; TEAE = treatment-emergent adverse event.
[a] Occurring at a frequency of ≥ 5% in the pirfenidone-treatment group as compared with the placebo-treatment group.
[b] Occurring in at least in 1% of the pirfenidone-treatment group.
Source: Clinical Study Report.[4]

4. DISCUSSION

4.1 Summary of Available Evidence

One placebo-controlled RCT (the ASCEND study; PIPF-016) was included in this review, in which 555 patients with mild to moderate IPF were randomized to receive either pirfenidone at a dose of 2,403 mg/day (278 patients) or placebo (277 patients) for 52 weeks. These data complement the results of two previous studies in similar patients, namely CAPACITY-1 and CAPACITY-2 (PIPF-004 and PIPF-006, respectively). Patients who completed the ASCEND study (along with patients from the CAPACITY studies) were eligible for enrolment in PIPF-012, an ongoing, open-label extension study that is summarized in APPENDIX 5.

Both CAPACITY studies had identical designs (see Table 13), and while the design of the ASCEND study was similar to that of the CAPACITY studies, there were two notable differences. First, the inclusion criteria for the ASCEND study were such that patients were required to have had IPF for a longer duration and were expected to have a greater risk of disease progression compared with patients in the CAPACITY studies. For example, the minimum per cent predicted DL_{CO} at entry was 30% in ASCEND versus 35% in the CAPACITY studies. Although these differences in design might have led to the discrepancies in baseline lung function (%FVC) and dyspnea scores that were observed in the ASCEND study compared with the CAPACITY studies, it is not clear how this might affect the comparison of the three studies. The second important difference between the designs of the three studies was duration: while the ASCEND study was 52 weeks long, the CAPACITY studies were 72 weeks long. Therefore, comparison of the outcomes across the three studies is limited to the 52-week time point; similarly, combining the data (pooling) for the three studies can only be done for the outcomes at 52 weeks (see APPENDIX 8).

The ASCEND study was intended to provide data that would clarify the efficacy of pirfenidone in IPF patients, because the results of the previous CAPACITY studies (see APPENDIX 6) were discordant with respect to the effects of pirfenidone on lung capacity (%FVC) and functional performance (6MWT distance). For instance, in both CAPACITY studies, %FVC was statistically significantly improved in pirfenidone-treated patients after 48 weeks; however, in one study (PIPF-006), this effect was not statistically significant beyond 48 weeks. In addition, while pirfenidone appeared to reduce mortality in the CAPACITY studies, this effect failed to reach statistical significance, raising doubt as to whether this treatment effectively reduces mortality in IPF patients. In designing and carrying out the ASCEND study, it was the manufacturer's intent to pool data from the ASCEND study and the two CAPACITY studies to increase statistical power and provide a more robust estimate of the effects of pirfenidone on lung capacity, functional capacity, and mortality.

4.2 Interpretation of Results

4.2.1 Efficacy

The results of the ASCEND study demonstrated that 52 weeks of treatment with pirfenidone was associated with lower all-cause mortality compared with placebo (4% versus 7%, respectively; HR = 0.6; [95% CI, 0.3 to 1.2]), although this effect was not statistically significant. In addition, pirfenidone treatment was associated with statistically and clinically significantly improved lung function, as reflected by the slower decline in lung capacity [6% versus 11% decline in %FVC for pirfenidone versus placebo, respectively; MD = 4.8; [95% CI, 2.4 to 7.2]). Pirfenidone treatment was also associated with a slower decline in functional performance, as demonstrated by the better performance of pirfenidone-treated patients in the 6MWT (MD versus placebo = 26.7; [*P* = 0.036]).

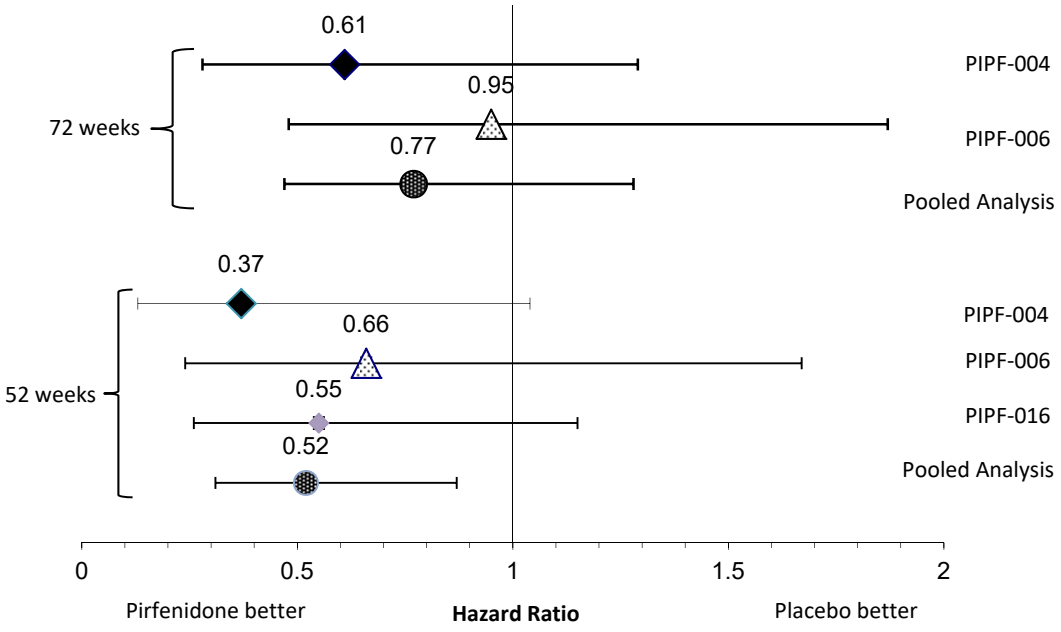
4.2.2 Harms

The most common AEs reported in the ASCEND study were nausea, rash, dyspepsia, anorexia, gastroesophageal reflex, and photosensitivity. These AEs were also common in the CAPACITY studies. Pirfenidone- and placebo-treated patients in the ASCEND study had similar incidences of AEs. Pirfenidone was associated with a higher rate of discontinuation due to AEs, but was associated with fewer SAEs. The most frequent reason for discontinuation in placebo-treated patients was worsening IPF. These results are similar to those of the two CAPACITY studies, as well as being similar to the harms reported for patients who participated in a long-term, open-label extension study, PIPF-012, for patients who had completed the ASCEND or CAPACITY studies (see APPENDIX 5).

4.2.3 Other Considerations

Data for several outcomes from the ASCEND study were pooled with data from the two CAPACITY studies in an analysis provided by the manufacturer; these data are presented in APPENDIX 8. As noted above, and as discussed in the previous CDR report, mortality in pirfenidone-treated patients in both of the CAPACITY studies was not statistically significantly lower than mortality in patients who received placebo (see APPENDIX 6), and this remained so even after pooling the data from the two CAPACITY studies (see APPENDIX 8). Specifically, the HR for the pooled treatment effect of pirfenidone compared with placebo at 72 weeks was 0.77; (95% CI, 0.47 to 1.28). The manufacturer's rationale for this absence of a statistically significant reduction in mortality was that there was insufficient statistical power to detect such a difference, as mortality was not the primary outcome in these studies. Therefore, in designing an additional study, the protocol of the ASCEND study included a pre-specified analysis of pooled data for mortality obtained from PIPF-016 (ASCEND) and the CAPACITY studies (PIPF-004 and PIPF-006). Of note, the analysis was carried out using the pooled data from the 52-week time point (the duration of the ASCEND study) rather than the 72-week time point available from both CAPACITY studies. As was the case for the CAPACITY studies, pirfenidone failed to statistically significantly reduce mortality in the ASCEND study; however, the results of the analysis of pooled data from the three studies suggested that pirfenidone-treated patients had a statistically significantly lower chance of death than did placebo-treated patients (Figure 2). Specifically, the HR for the treatment effect of pirfenidone compared with placebo on all-cause mortality after 52 weeks was 0.52; (95% CI, 0.31 to 0.87) (see APPENDIX 8). A similarly significant reduction in IPF-related mortality was observed in the analysis of pooled data (APPENDIX 8). Therefore, the pooling of data from the ASCEND and CAPACITY studies appears to provide evidence that mortality is significantly reduced after one year in patients with mild to moderate IPF treated with pirfenidone. Whether the aforementioned survival benefit extends beyond 52 weeks is less clear due to insufficient evidence; indeed, the only evidence available (72 weeks of treatment in the CAPACITY studies) failed to demonstrate a statistically significant reduction in mortality.

FIGURE 2: HAZARD RATIO FOR ALL-CAUSE MORTALITY IN PIPF-004, PIPF-006 AND PIPF-016, AND THE ANALYSIS OF POOLED DATA.



Patient input received by CADTH indicated that IPF patients hope that pirfenidone will slow disease progression, improve debilitating symptoms that prevent them from participating in daily living activities, and help them live longer. While the effects of pirfenidone on lung capacity and functional capacity (walking distance) clearly meet these expectations, it is less clear whether the effects of pirfenidone on mortality meet patient expectations. Patients also expressed a desire for improvement in QoL and a reduced need for lung transplantation, but there is insufficient evidence available from the ASCEND and CAPACITY studies to determine whether pirfenidone has such effects.

The clinical expert consulted by CDR for the purpose of this review believes that the patients included in the ASCEND and CAPACITY studies are reflective of those seen in clinical practice in Canada. Nevertheless, there is some uncertainty related to whether pirfenidone will be as effective in real-world practice as it was in the RCTs, because there are no clear diagnostic clinical criteria to distinguish severe IPF from moderate IPF, and pirfenidone has not been studied in patients with severe IPF. In addition, the relatively high pill burden associated with pirfenidone treatment (nine capsules daily) requires a high degree of motivation and compliance from patients, which might be lower in a real-world setting. Therefore, it is possible that the efficacy of pirfenidone in the ASCEND and CAPACITY studies might be greater than the efficacy that would be observed in clinical practice.

5. CONCLUSIONS

The results of a new study of the effects of pirfenidone versus placebo (the ASCEND study; PIPF-016) demonstrated that 52 weeks of treatment with pirfenidone significantly improved lung function (%FVC) and functional capacity (walking distance) in adults with mild to moderate IPF, and that these differences were sufficiently large to be clinically meaningful. While all-cause mortality in the ASCEND study was substantially lower in pirfenidone-treated patients compared with placebo-treated patients (HR = 0.37), the difference between treatment groups was not statistically significant. A pooled analysis of the results of the ASCEND study (PIPF-016) and the two previous CAPACITY studies (PIPF-004 and PIPF-006) suggested that pirfenidone is associated with statistically significantly lower mortality at 52 weeks of treatment versus placebo (HR = 0.52), although the effect on mortality was not statistically significant in any of the individual studies.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

One patient group submitted input.

The Canadian Pulmonary Fibrosis Foundation (CPFF) is a charitable organization with a mandate to support patients diagnosed with pulmonary fibrosis (PF) and their caregivers, to raise public awareness about PF, to be the "patient voice" for PF, and to raise funds for PF research. InterMune Canada has provided funding to CPFF. The CPFF has declared no conflicts of interest in the preparation of this submission.

2. Condition and Current Therapy-Related Information

The information for this section was gathered through an online survey (with responses from 217 individuals, primarily patients living with idiopathic pulmonary fibrosis [IPF], and some caregivers), telephone interviews and direct interactions with patients and caregivers, and the personal experience of one respondent who is a PF patient.

Idiopathic pulmonary fibrosis (IPF) is a progressive and life-threatening condition that has no cure. All patients diagnosed with IPF experience many problems and symptoms as a result of the illness. As the disease progresses, patients will have different symptoms and an increasing severity of symptoms. The most common symptoms include breathlessness, fatigue, loss of energy, reduced physical activity, and a chronic cough. Additionally, patients have to manage psychosocial issues associated with their prognosis. The stress of the diagnosis and prognosis greatly affects patients' quality of life (QoL) and mental well-being, even among those with mild disease and minimal symptoms. The symptoms of PF may limit patients' ability to stay physically active, to work, to participate in social activities, and to continue their usual daily activities and household chores. For some, leaving the house takes a lot of planning and energy, and therefore taking trips are avoided, leading to social isolation.

PF affects the whole family, not just the individual with the disease. Caregivers worry about their loved one's prognosis, and feel helpless, depressed, and anxious. They may limit their own social activities and employment in order to take on more of the household chores, and to provide care for, and attend medical appointments with, their loved one. Caregivers also worry about coverage for Esbriet if their health care insurance plans stop paying for the drug.

There are few supportive treatments available to manage symptoms of PF. The patients surveyed reported using oxygen, N-acetylcysteine, prednisone, azathioprine, and pulmonary rehabilitation. These treatments were somewhat effective in a portion of patients, but were also accompanied with unwanted side effects which added to their stress. Lung transplantation is an option that is available to few patients. Esbriet is the only available drug specifically approved for IPF; however, it is currently available only to Canadian patients who have private insurance.

3. Related Information About the Drug Being Reviewed

Patients who have no experience with Esbriet recognize that Esbriet is not a cure, but they hope that it will slow disease progression and their most debilitating symptoms, and help them live longer. Patients want an improved quality of life (QoL), a slowed disease progression with fewer exacerbations, and increased energy to participate in activities of daily living. Patients' expectations are that by taking Esbriet, the need for a lung transplant will be delayed or not required.

In patients who have received the drug, Esbriet improved their breathing and energy levels. Some patients reported that it helped maintain their lung function and they had less coughing, fewer exacerbations, and no need for prednisone or antibiotics. Side effects included digestive issues, fatigue, photosensitivity, and severe rash. Some patients found that adverse effects were reduced with a lower dosage of Esbriet. Patients were willing to tolerate the side effects for a treatment that would slow disease progression and improve QoL.

4. Additional Information

None to declare.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to 2014 October 03 MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations MEDLINE Daily **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	October 6, 2014
Alerts:	Search updated biweekly (every other week) until February 18, 2015.
Study Types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded
SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt .po	Publication type Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
	MEDLINE search
1	(Esbriet* or pirfenidon* or Pirespa* or Pirfenex* or Deskar* or Fibridoner* or AMR-69 or AMR69 or BRN-1526549 or BRN1526549 or S-7701 or S7701).ti,ab,ot,sh,rn,hw,nm.
2	53179-13-8.rn.
3	or/1-2
4	3 use pmez
	Embase search
5	*pirfenidone/

MULTI-DATABASE STRATEGY	
6	(Esbriet* or pirfenidon* or Pirespa* or Pirfenex* or Deskar* or Fibridoner* or AMR-69 or AMR69 or BRN-1526549 or BRN1526549 or S-7701 or S7701).ti,ab.
7	or/5-6
8	7 use oemezd
9	8 not conference abstract.pt.
	Combine MEDLINE & Embase results, removing non-human results and duplicates
10	4 or 9
11	exp animals/
12	exp animal experimentation/ or exp animal experiment/
13	exp models animal/
14	nonhuman/
15	exp vertebrate/ or exp vertebrates/
16	animal.po.
17	or/11-16
18	exp humans/
19	exp human experimentation/ or exp human experiment/
20	human.po.
21	or/18-20
22	17 not 21
23	10 not 22
24	remove duplicates from 23

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	September 26–29, 2014
Keywords:	Pirfenidone (Esbriet), pulmonary fibrosis, & synonyms
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Interim clinical study report: PIPF-012. An open-label extension study of the long-term safety of pirfenidone in patients with idiopathic pulmonary fibrosis (IPF [Confidential internal manufacturer's report]. Brisbane (CA): InterMune Inc.; 2014.	Not RCTs
King et al. Am J Respir Crit Care Med 2014;189(7):825-31	
Arai et al. Respir Investig 2014;52(2):136-43	Intervention and study design not appropriate
Valeyre et al. Respirology 2014;19(5):740-7	Studies included in the previous review
Clinical study report: PIPF-004. A randomized, double-blind, placebo-controlled, phase 3, three-arm study of the safety and efficacy of pirfenidone in patients with IPF [confidential internal manufacturer's report]. Brisbane (CA): InterMune Inc.; 2009.	
Clinical study report: PIPF-006. A randomized, double-blind, placebo-controlled, phase 3 study of the safety and efficacy of pirfenidone in patients with IPF [confidential internal manufacturer's report]. Brisbane (CA): InterMune Inc.; 2009.	
Health Canada reviewer's report: Esbriet (pirfenidone) [confidential internal report]. Ottawa: Therapeutic Products Directorate, Health Canada; 2012.	

IPF = idiopathic pulmonary fibrosis; RCT = randomized controlled trial.

APPENDIX 4: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- forced vital capacity (FVC)
- six-minute walk test (6MWT)

Findings

TABLE 9: OUTCOME MEASURES

Instrument	Type	Validated?	MCID	References
FVC	Measures total expiratory volume; usually reported as a percentage of predicted FVC for persons of same size, age, and sex	Yes	2% to 6%	Du Bois[7]
6MWT	Distance (m) walked in six minutes on a flat surface	Yes	28 m 24 m to 45 m 29 m to 34 m	Swigris[8] Du Bois [9] Holland[10]

6MWT = six-minute walking test; FVC = forced vital capacity; m = metres; MCID = minimal clinically important difference.

Forced Vital Capacity

Forced vital capacity (FVC) is the volume of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. It is usually reported as the percentage of the volume predicted for a person of the same size, age, and sex. The test properties of FVC were examined using data from two randomized controlled trials (RCTs) in patients with mild to moderate idiopathic pulmonary fibrosis (IPF).[7] FVC results showed good within-person reliability when repeated after a short interval (intraclass correlation = 0.93).[7] Validity was tested by comparing the FVC with other measures of IPF severity and the per cent predicted FVC, and was found to be weakly correlated with measures of functional status (6MWT), gas exchange, dyspnea, and health-related quality of life (HRQoL).[7] Similar results were found when the change in %FVC was correlated with the change in these measures.[7] Baseline FVC has been shown to have an inconsistent relationship with mortality.[11] The change in per cent predicted FVC, however, was found to be predictive of mortality in patients with IPF.[7,11-14] A six-month absolute decrease in the per cent predicted FVC ≥ 10% was associated with a 2.8-fold to 4.8-fold increase in the risk of mortality relative to those with stable disease (defined as < 5% change in per cent predicted FVC), and with a two-fold increased risk of mortality relative to those with < 10% change in per cent predicted FVC.[13] An absolute decline of 5% to < 10% in per cent predicted FVC was associated with a two-fold increased risk of death relative to those with stable FVC values.[7,12]

The minimal clinically important difference (MCID) for the per cent predicted FVC was between 2% and 6%, using anchor and distribution-based methods in a population with mild to moderate IPF.[7]

Six-Minute Walk Test

The six-minute walk test (6MWT) assesses submaximal functional capacity. It measures the distance a patient can walk on a flat surface over six minutes.[8] In two studies, the 6MWT results showed good within-person reliability when repeated after a short interval.[9,15] The correlation between the 6MWT and physiologic, functional, dyspnea, and HRQoL measures were in the expected direction, but were weak.[9] Changes in 6MWT showed responsiveness in predicting mortality.[9] The risk of death was 4.3 times higher in patients who had a > 50 m decrease in 6MWT, and 3.6 times higher in those with a 26 m

to 50 m decrease in distance walked, compared with those with up to a 25 m decrease.[9] Shorter distances walked during a 6MWT were predictive of mortality in some studies.[16,17]

The MCID of the 6MWT in patients with IPF was evaluated in three studies using anchor and distribution-based methods.[8-10] Although the methods used varied, the MCID estimates were similar across studies and ranged from 24 m to 45 m.[8-10] It should be noted that other factors that are unrelated to pulmonary disease, such as lower extremity pain, may limit the distance walked during a 6MWT.[18]

Critical Appraisal

Of the studies evaluating FVC[7,12-14] and 6MWT,[8-10,15,17] five were post hoc analyses of data from RCTs of bosentan,[8] interferon gamma-1b,[7,9,17] or exercise programs.[10] The others were cohort studies.[12-16] Four of the five studies reported using standardized methods to conduct the 6MWT.[8-10,15,17] Limitations of the studies include a small sample size (< 100 patients),[10,12-15] and enrolment of mixed populations including patients with other forms of interstitial lung disease or those that may not meet the American Thoracic Society (ATS) criteria for IPF.[10,12,13,15,16] The MCID estimate in one study[10] may have been biased by the exercise intervention the patients received. All studies[7-10,12-15,17] but one[16] excluded patients with severe IPF; thus, the generalizability of the test performance or MCID estimates to patients with severe disease may be limited.

Conclusion

FVC and the 6MWT appear to be valid outcome measures in patients with mild to moderate IPF. An absolute change of at least 5% to 10% in the per cent predicted FVC is predictive of mortality. Estimates of the MCID range from 2% to 6% for the per cent predicted FVC, and from 24 m to 45 m for the 6MWT.

APPENDIX 5: SUMMARY OF EXTENSION STUDY

Aim

To summarize the ongoing open-label extension study, PIPF-012.[19]

Study Characteristics

Patients were eligible for study PIPF-012 (RECAP) if they completed a qualifying InterMune clinical trial (PIPF-004, PIPF-006, or PIPF-016). The inclusion of participants from PIPF-016 was based on a protocol amendment in May 2012. The data summarized in this report are based on an interim analysis (data cut-off August 7, 2013) and relate only to those patients previously enrolled in PIPF-004 or PIPF-006 (CAPACITY-1 and CAPACITY-2).[19] The analysis excluded patients previously enrolled in PIPF-016 (ASCEND) because, at the time of this interim analysis, few patients from PIPF-016 had enrolled in PIPF-012, and their follow-up time was short (number of patients and length of follow-up was not reported).

The patients included in this summary had completed the last study visit of trial PIPF-004 or PIPF-006, had not permanently discontinued the study drug during PIPF-004 or PIPF-006, and were at least 80% compliant with the study medication. Similar exclusion criteria regarding the use of medications for IPF as used in PIPF-004 or PIPF-006 were continued during PIPF-012. The study is planned to continue until Esbriet is available commercially in several regions.

A total of 603 patients enrolled in the extension study were treated with open-label pirfenidone 2,403 mg/day. Approximately 77% of patients from PIPF-004 and PIPF-006 enrolled, and these patients had a similar age and sex distribution as were reported for PIPF-004, PIPF-006, and PIPF-016. The baseline per cent predicted FVC was 70.9% (SD = 16.7) in study PIPF-012 compared with approximately 75% for all patients in PIPF-004 and PIPF-006, and was 68% for those patients in PIPF-016.

TABLE 10: SUMMARY OF PIPF-012 STUDY CHARACTERISTICS (INTERIM ANALYSES, AUGUST 2013)

Study Design	Population	Intervention	Outcomes
PIPF-012[19] Non-randomized, open-label study Interim analysis at Week 228 (4.4 years) 103 sites in the US, Italy, Canada, Germany, Spain, Australia, France, the UK, Poland, Belgium, and Mexico	Patients who completed PIPF-004 or PIPF-006, and were 80% compliant with treatment N = 603 (77% of 779 enrolled in PIPF-004 and PIPF-006) Male: 72% Mean age: 68 years (SD = 7.8, range: 42 years to 83 years) Previous treatment, n (%): Pirfenidone 1,197 mg/d: 68 (11%) Pirfenidone 2,403 mg/d: 261 (43%) Placebo: 274 (45%)	Pirfenidone 2,403 mg/day (801 mg, TID)	AEs Withdrawals Death Per cent predicted FVC Per cent predicted DL_{CO}

AE = adverse event; d = day; DL_{CO} = carbon monoxide diffusing capacity; FVC = forced vital capacity; SD = standard deviation; TID = three times per day.
Source: Clinical Study Report .[19]

Findings

In PIPF-012, the median duration of treatment was 163.3 weeks (range: 1 to 257; 1,727 patient-years) at a median dose of 2,332 mg/day. By August 2013, 386 patients (64%) had discontinued treatment (Table 11). AEs were the most common reason for stopping treatment (n = 232, 38%). A total of 141 patients (23%) died, and 30 (5%) underwent lung transplantation between September 2008 and August 2013.

Most patients (98%) reported experiencing an AE during follow-up, the most common being related to the respiratory, gastrointestinal, or nervous systems. The incidence of SAEs (62%) was higher in PIPF-012 than in PIPF-004/PIPF-006 (31% to 33%) or PIPF-016 (20%). The most common AEs and SAEs in PIPF-012 are listed in Table 11.

TABLE 11: SAFETY OUTCOMES REPORTED AT INTERIM ANALYSIS (AUGUST 2013) IN STUDY PIPF-012

Outcome	(N = 603) n, (%)	Description
Discontinuation of therapy	386 (64)	Reason for discontinuation of therapy, n (%): AE: 232 (38%) Death: 46 (8%) Withdrawal by patient: 60 (10%) Lung transplantation: 30 (5%) Physician's decision: 10 (2%) Withdrawal of consent: 5 (1%) Other: 3 (< 1%)
Baseline AE (onset during PIPF-004/PIPF-006)	542 (89)	Most common AE (%): cough (23%); fatigue (19%); dyspnea (16%)
TESAE[a]	376 (62)	Most common TESAE (≥ 2%) (%): worsening IPF (23%); pneumonia (8%); bronchitis (5%); respiratory failure (4%); acute respiratory failure (3%); atrial fibrillation (3%); coronary artery disease (2%); pulmonary embolism (2%); hypoxia (2%); syncope (2%), cerebrovascular accident (2%), myocardial infarction (2%)
TEAE[a]	599 (99)	Most common TEAE (≥ 15%) (%): dyspnea (37%); cough (36%); IPF (35%); URTI (34%); nausea (33%); bronchitis (33%); nasopharyngitis (27%); diarrhea (27%); fatigue (26%); dizziness (22%); headache (19%); back pain (17%); pulmonary hypertension (16%); vomiting (16%); rash (16%); peripheral edema (16%); sinusitis (16%); dyspepsia (15%); decreased weight (15%)
Death (all-cause)	141 (23)	Cause of death (%): IPF (13%); other respiratory causes (4%); infections (1.5%); cardiac (1.7%); cancer (1.5%)

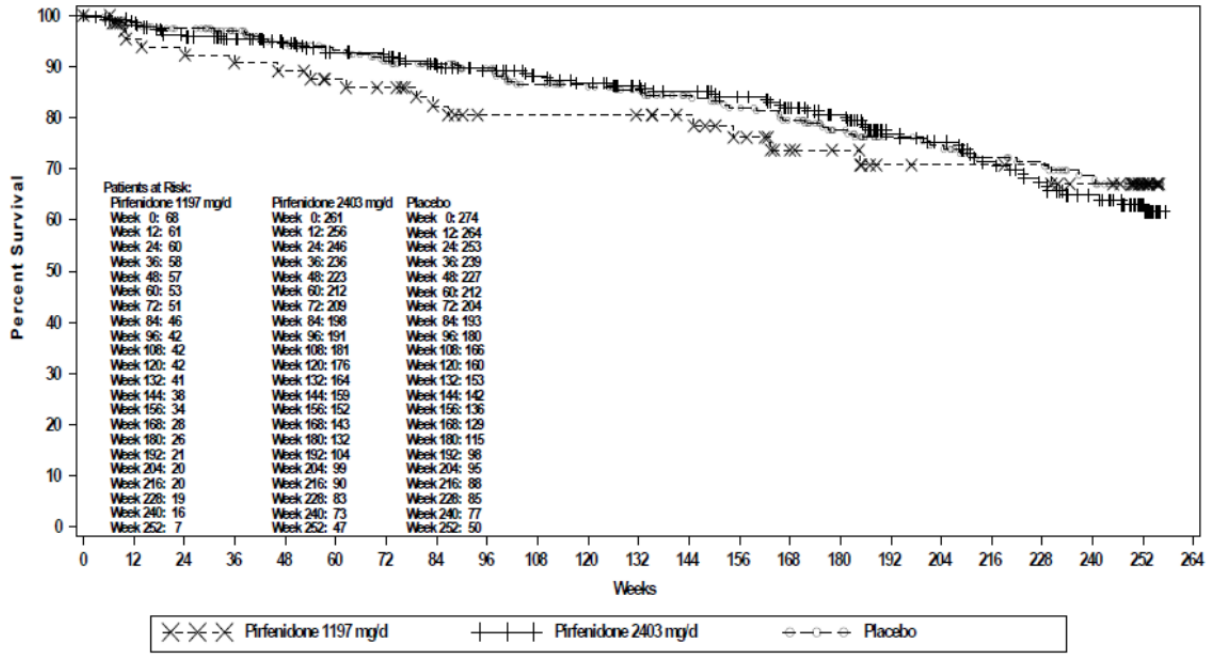
AE = adverse event; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; SAE = serious adverse event; TEAE = treatment-emergent adverse event; TESAE = treatment-emergent serious adverse event; URTI: upper respiratory tract infection.

[a] Includes AEs with an onset during PIPF-012 or pre-existing AEs that worsened during PIPF-012.

Source: Clinical Study Report .[19]

The Kaplan-Meier survival estimate was 96% at Week 36, 89% at Week 84, 85% at Week 132, 79% at Week 180, and 69% at Week 228 for the overall cohort. The survival curves shown in Figure 3 are for the subgroups based on prior treatment exposure.

FIGURE 3: KAPLAN-MEIER SURVIVAL ESTIMATE



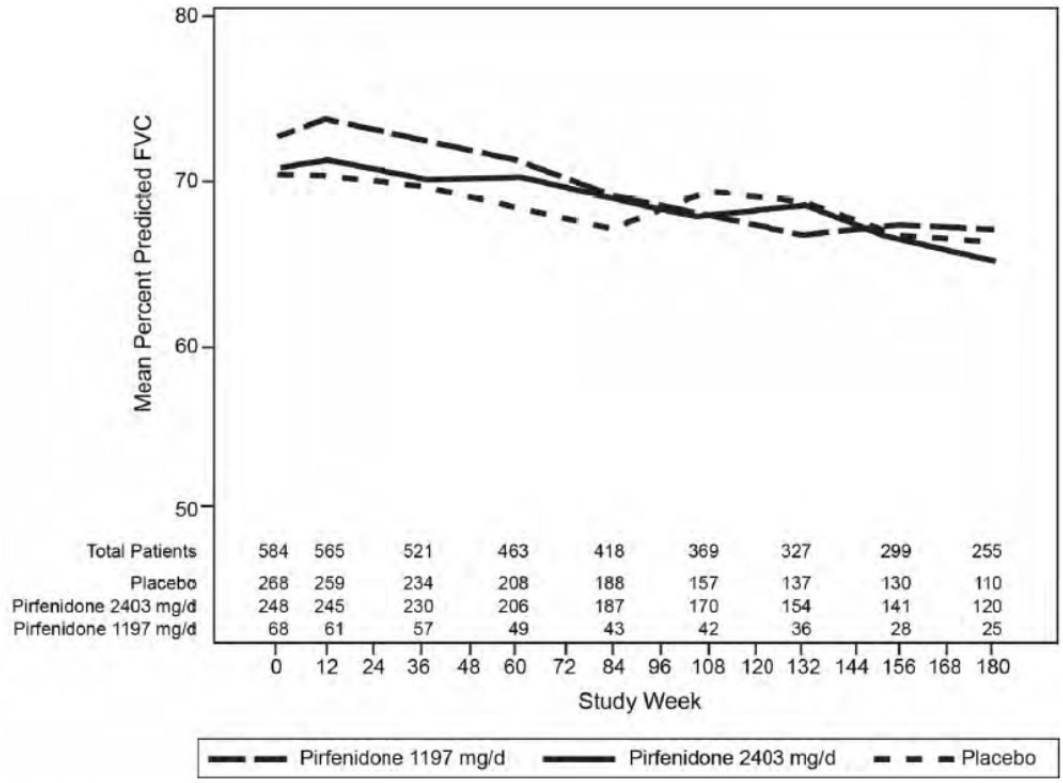
Notes: Data are presented by PIPF-004/006 treatment assignment; for all patients in PIPF-012, the target dose was 2403 mg/d of pirfenidone.

Source: CSR for PIPF-012.[19]

The observed FVC and DL_{CO} data are presented in Figure 4 and Table 12. The analyses were based on the available data, meaning that there was no imputation for missing data; patients with missing data were dropped from the analysis. Scheduled FVC and DL_{CO} testing was eliminated with the protocol amendment in May 2012.

At Week 84, the absolute decrease in per cent predicted FVC was 5.2% (available case analysis). This decrease was less than the 8.5% decrease reported over 72 weeks in the pooled pirfenidone 2,403 mg/day group in PIPF-004/PIPF-006, and the 6.2% decrease after 52 weeks in PIPF-016. However, it should be noted that only 67% of those enrolled in PIPF-012 had FVC outcome data at 84 weeks. Moreover, in PIPF-004, PIPF-006 and PIPF-016, patients who died were assigned a per cent predicted FVC value of 0; thus, the mean FVC at the end of treatment would have been lower compared with PIPF-012, which excluded these patients.

FIGURE 4: MEAN PER CENT PREDICTED FVC IN STUDY PIPF-012



Note: Data are presented by PIPF-004/006 treatment assignment; for all patients in PIPF-012, the target dose was 2403 mg/d of pirfenidone.

Source: CSR for PIPF-012.[19]

Data for hemoglobin-corrected, carbon monoxide diffusing capacity in Table 12 shows a decline in diffusing capacity over time.

TABLE 12: SUMMARY OF EFFICACY OUTCOMES

Time Point	Per Cent Predicted FVC[a]		Absolute Change From Baseline[a]	
	N	Mean (SD)	N	Mean (SD)
Baseline	584	70.9 (16.7)	--	--
Week 12	565	71.2 (16.8)	551	–0.3 (4.5)
Week 36	521	70.2 (17.2)	507	–1.9 (5.6)
Week 60	463	69.7 (17.1)	451	–3.3 (5.7)
Week 84	418	68.1 (17.3)	406	–5.2 (6.9)
Week 108	369	68.7 (17.7)	358	–5.6 (7.0)
Week 132	327	68.4 (17.5)	316	–6.4 (7.0)
Week 156	299	66.7 (17.7)	288	–8.4 (8.3)
Week 180	255	65.9 (16.9)	246	–9.6 (9.4)
Time Point	**Hgb Corrected Per Cent Predicted DL_{CO}[a]**		**Absolute Change From Baseline[a]**	
	N	**Mean (SD)**	**N**	**Mean (SD)**
Baseline	542	41.2 (12.4)	—	—
Week 12	556	40.7 (12.0)	511	–1.1 (7.0)
Week 36	517	39.9 (12.2)	476	–2.6 (7.8)
Week 60	460	39.5 (12.0)	425	–3.9 (8.0)
Week 84	409	37.7 (12.0)	378	–6.1 (7.4)
Week 108	364	37.5 (12.7)	335	–6.9 (8.5)
Week 132	318	37.1 (12.5)	293	–7.7 (10.0)
Week 156	287	35.9 (12.8)	263	–8.9 (8.9)
Week 180	243	35.6 (12.9)	224	–9.8 (9.4)

DL_{CO} = carbon monoxide diffusing capacity; FVC = forced vital capacity; Hgb = hemoglobin; SD = standard deviation.
[a] No imputation for missing data.
Source: Clinical Study Report.[19]

Summary

PIPF-012 is an ongoing, open-label extension study of the pirfenidone clinical trials. Data were presented for 603 patients who were treated with pirfenidone 2,403 mg/day for a median duration of 3.1 years. The incidence of AEs and SAEs was higher in PIPF-012 than during the 72-week PIPF-004/PIPF-006 trials or the 52-week PIPF-016 study. Thirty-eight per cent of patients discontinued pirfenidone due to AEs. During the 4.4 years of follow-up, 23% of the patients died and 5% underwent lung transplantation. The mean per cent predicted FVC and DL_{CO} decreased over time. The study was limited by the lack of a control group and the open-label administration of the study drug.

APPENDIX 6: SUMMARY OF PREVIOUS CDR REVIEW OF PIRFENIDONE

Aim

To describe the characteristics and the main results of the clinical trials included in the previous CDR.

Study Characteristics

Two double-blind (DB), randomized controlled trials (RCTs) (PIPF-004 and PIPF-006) met the inclusion criteria (Table 13). Both phase 3 trials used the same inclusion and exclusion criteria and enrolled patients with mild to moderate idiopathic pulmonary fibrosis (IPF) who were 40 years of age to 80 years of age. Patients were randomized to 72 weeks of therapy with placebo, pirfenidone 2,403 mg per day (PIPF-004 and PIPF-006), or pirfenidone 1,197 mg per day (PIPF-004).

TABLE 13: STUDY CHARACTERISTICS OF PIPF-004 AND PIPF-006

<table>
<tr><th></th><th></th><th colspan="4">PIPF-004</th><th colspan="2">PIPF-006</th></tr>
<tr><td rowspan="8">DESIGNS AND POPULATIONS</td><td>Study design</td><td colspan="6">DB, placebo-controlled, randomized 72-week trials</td></tr>
<tr><td>Locations</td><td colspan="4">US, Canada (9 centres), Mexico, UK, France, Italy, Poland, Australia</td><td colspan="2">US, Australia, Belgium, Germany, Ireland, Spain, Switzerland</td></tr>
<tr><td>Randomized (N)</td><td colspan="4">435</td><td colspan="2">344</td></tr>
<tr><td>Inclusion criteria</td><td colspan="6">• age 40 years to 80 years
• clinical symptoms consistent with IPF of 3-months duration, including the insidious onset of otherwise unexplained dyspnea on exertion
• diagnosis of IPF within 48 months of randomization. Diagnosis confirmed according to the following criteria:</td></tr>
<tr><td></td><td colspan="2">Patients ≥ 50 years</td><td colspan="2">Patients < 50 years</td></tr>
<tr><td>HRCT findings</td><td>Definitive IPF</td><td>Probable IPF</td><td>Definitive IPF</td><td>Probable IPF</td></tr>
<tr><td>Pathologic findings</td><td>Non-diagnostic TBBx or BAL, or SLBx with UIP</td><td>SLBx with UIP</td><td>SLBx with UIP</td><td>SLBx with UIP</td></tr>
<tr><td colspan="6">Mild to moderate IPF as determined by the following:
• FVC ≥ 50% at screening visit and Day 1 (before randomization)
• DL_{co} (hemoglobin-corrected) ≥ 35%
• FVC or DL_{co} (hemoglobin-corrected) ≤ 90%
• no evidence of improvement in IPF over the previous year
• distance ≥ 150 m with O_2 saturation ≥ 83% on ≤ 6 L/min of O_2 during 6MWT</td></tr>
<tr><td>Exclusion criteria</td><td colspan="6">• obstructive airway disease
• connective tissue disease
• alternative explanation for interstitial lung disease
• patients with history of clinically significant liver disease, unstable or deteriorating cardiac or pulmonary disease, or in the opinion of the investigator, were likely to die within 2 years after study entry</td></tr>
<tr><td rowspan="2">DRUGS</td><td>Intervention</td><td colspan="4">3 × 267 mg pirfenidone TID PO (2,403 mg/d)
or
3 × 133 mg pirfenidone TID PO (1,197 mg/d)</td><td colspan="2">3 × 267 mg pirfenidone TID PO (2,403 mg/d)</td></tr>
<tr><td>Comparator(s)</td><td colspan="6">Placebo</td></tr>
</table>

		PIPF-004	PIPF-006
DURATION	**Phase:**	3	3
	Washout	4 weeks (Day –70 to Day –43)	
	Screening	6 weeks (Day –42 to Day –2)	
	DB	Dose escalation phase: 2 weeks	
		Maintenance phase: 72 weeks from the inclusion date of the last patient	
	Follow-up	3 to 4 weeks after treatment completion visit	
OUTCOMES	**Primary end point**	Absolute change in per cent predicted FVC from baseline to Week 72 for the pirfenidone 2,403 mg/d treatment group compared with placebo	

	Other end points	• time to worsening of IPF: time to acute IPF exacerbation, IPF-related death, lung transplantation, or respiratory-related hospitalization, whichever comes first
		• PFS: time to first occurrence of either
		  • 10% absolute decline in per cent predicted FVC, or
		  • 15% absolute decline in per cent predicted DL_{co}, or
		  • death.
		• 6MWT
		• HRQoL	

NOTES	**Publications**	Nobel et al.;[20,21] Costabel et al.;[22] Albera et al.;[23] and Valeyre et al.[24]	

6MWT = six-minute walk test; BAL = bronchoalveolar lavage; d = day; DB = double-blind; DL_{CO} = carbon monoxide diffusing capacity; FVC = forced vital capacity; HRCT = high-resolution computerized tomography; HRQoL = health-related quality of life; IPF = idiopathic pulmonary fibrosis; PFS = progression-free survival; PO = by mouth; SLBx = surgical lung biopsy; TBBx = transbronchial biopsy; TID = three times per day; UIP = usual interstitial pneumonia.
Sources: CSRs{57,58}

The primary outcome was the absolute change in the per cent predicted forced vital capacity (FVC) from baseline to Week 72 for the pirfenidone 2,403 mg/day group compared with the placebo group, which was tested using rank analysis of covariance (ANCOVA). A secondary analysis was conducted using a categorical assessment of absolute change in per cent predicted FVC from baseline to Week 72 (severe decline: ≥ 20% decrease in FVC, death, or lung transplantation; moderate decline: 10% to 20% decrease in FVC; mild decline: 0% to 10% decrease in FVC; mild improvement: 0% to 10% increase in FVC; or moderate improvement: ≥ 10% increase in FVC).

Survival was pre-specified as an exploratory end point, and the analysis included all deaths except those occurring after lung transplantation or after completion of the treatment period. IPF-related mortality was estimated in a post hoc analysis. The cause of death was not adjudicated: it was assessed by the investigator who remained masked to treatment assignment.

Quality of life (QoL) was included as an exploratory outcome in both studies, and was measured by the World Health Organization (WHO) QoL questionnaire and by the St. George's Hospital Respiratory Questionnaire (SGRQ). The WHO QoL scores range from 4 to 20, with lower scores indicating a lower QoL. SGRQ scores range from 0 to 100, where 0 is best possible score and 100 is worst possible score.[25] The MCID for SGRQ in patients with chronic obstructive lung disease (COPD) has been reported to be a difference of four or more points in the total SGRQ score from baseline or versus placebo at study end.[26]

Progression-free survival (PFS) was defined as the time to first occurrence of either a 10% absolute decline in per cent predicted FVC, a 15% absolute decline in per cent predicted DL_{co}, or death. Other outcomes included 6MWT, time to worsening of IPF, and dyspnea relief. Dyspnea was measured using the University of California, San Diego Shortness of Breath Questionnaire (UCSD SOBQ).

Patient Characteristics

The characteristics of the patients enrolled in PIPF-004 and PIPF-006 are listed in Table 14. The studies enrolled 348 and 344 patients in PIPF-004 and PIPF-006, respectively, to either the placebo-treatment group or to the 2,403 mg per day pirfenidone-treatment group. The patient characteristics were generally balanced between and within trials. The mean age per treatment group ranged from 65.7 years to 67.0 years, and the proportion of males ranged from 68% to 74%. More patients in PIPF-006 than in PIPF-004 used supplemental oxygen (28% versus 16%, respectively). The mean per cent predicted FVC ranged from 73.1% to 76.2%, and the 6MWT ranged from 378 m to 411 m across the treatment groups in both trials.

Overall, treatment discontinuation was similar in the PIPF-004 and PIPF-006 trials (20% and 19%, respectively). AEs were the main reason for treatment discontinuation in both trials, and this occurred more frequently in the pirfenidone-treatment groups than in the placebo-treatment groups (13% and 8%, respectively).

TABLE 14: SUMMARY OF BASELINE CHARACTERISTICS FOR PIPF-004 AND PIPF-006

Characteristics	PIPF-004		PIPF-006	
	Pirfenidone 2,403 mg/d	Placebo	Pirfenidone 2,403 mg/d	Placebo
Randomized, N	174	174	171	173
Demographics				
Age, years (SD)	65.7 (8.2)	66.3 (7.5)	66.8 (7.9)	67.0 (7.8)
Male, n (%)	118 (68)	128 (74)	123 (72)	124 (72)
Smoking status, n (%)				
Never	56 (32)	51 (29)	59 (35)	64 (37)
Former	110 (63)	114 (66)	112 (65)	101 (58)
Current	8 (5)	9 (5)	0	8 (5)
Medical history				
IPF diagnosis by HRCT, n (%)				
Definite IPF	159 (91)	164 (94)	149 (87)	158 (91)
Probable IPF	14 (8.0)	10 (5.7)	20 (11.8)	15 (8.7)
Uncertain	1 (0.6)	0	1 (0.6)	0
FVC (per cent predicted), mean (SD)	74.5 (14.5)	76.2 (15.5)	74.9 (13.2)	73.1 (14.2)
DL_{co} (per cent predicted), mean (SD)	46.4 (9.5)	46.1 (10.2)	47.8 (9.8)	47.4 (9.2)
6MWT distance, mean (SD)	411.1 (91.8)	410.0 (90.9)	378.0 (82.2)	399.1 (89.7)
Concomitant medications (medications used during the treatment period)				
Supplemental oxygen, n (%)	29 (17)	25 (14)	48 (28)	49 (28)
Bronchodilators/COPD drugs, n (%)	84 (48.3)	87 (50.0)	89 (52.0)	97 (56.1)
Salbutamol	45 (25.9)	53 (30.5)	48 (28.1)	70 (40.5)
Salmeterol	23 (13.2)	28 (16.1)	5 (2.9)	4 (2.3)
Systemic corticosteroids, n (%)	38 (21.8)	52 (29.9)	42 (24.6)	50 (28.9)

6MWT = six-minute walk test; COPD = chronic obstructive pulmonary disease; d = day; DL_{CO} = carbon monoxide diffusing capacity; FVC = forced vital capacity; HRCT = high-resolution computerized scan; IPF = idiopathic pulmonary fibrosis.
Sources: Nobel et al. 2011;[20] Sahn et al.;[27] FDA Briefing,[28]

Summary of Critical Appraisal

Both studies randomized patients using an interactive voice response system, and blinded all participants to treatment allocation until after the final database lock. The attrition rate was similar between treatment groups in both studies. There were some differences between the pirfenidone-treatment group and the placebo-treatment group in the proportion of patients who received salbutamol and systemic corticosteroids, potentially leading to performance bias. Data on IPF-related mortality should be viewed with caution, as the cause of death was determined by the investigator and was not adjudicated. In addition, the analysis of secondary and exploratory outcomes had a possible inflated type I error due to multiplicity, leading to an overstatement of the treatment effect if inference was based on a statistical significance level of $P < 0.05$.

In terms of external validity, the clinical management and patient characteristics of those enrolled in PIPF-004 and PIPF-006 were expected to be similar to the Canadian setting. Of note, the trials excluded patients with severe IPF and those who showed worsening pulmonary function during the screening process; therefore, the findings may not be generalizable to these patients. As with most clinical trials, the high adherence to therapy during the trials may not be observed in clinical practice, and this may impact treatment response.

Summary of Results

There was no evidence of differential rates of all-cause mortality between pirfenidone-treated patients and placebo-treated patients; overall, 9.3% of pirfenidone-treated patients and 10.7% of placebo-treated patients died during both trials. An exploratory pooled analysis of IPF-related mortality suggested that pirfenidone was associated with a statistically significant higher probability of survival compared with placebo (pooled hazard ratio [HR] = 0.48; [95% CI, 0.24 to 0.95]), but IPF-related [mortality was not significantly lower in either of the individual trials. An analysis of pooled data also suggested that pirfenidone significantly increased PFS versus placebo (pooled HR = 0.74; [95% CI, 0.57 to 0.96]); however, there was a significant increase in PFS in only one of the two trials (PIPF-004).

There were no statistically significant differences between pirfenidone and placebo in any of the QoL outcomes.

Results for %FVC and the six-minute walk test (6MWT) were not consistent between the two trials. In PIPF-004, pirfenidone statistically significantly improved %FVC versus placebo [mean difference (MD) = 4.4%; [95% CI, 0.7 to 9.1]); however, in the same trial, there was no effect on the 6MWT. By contrast, in PIPF-006 there was no difference between pirfenidone and placebo for change in %FVC, but there was a statistically significant difference in favour of pirfenidone for change in the 6MWT (MD = 31.8 m; [$P = 0.001$]). When the data for each of these two outcomes from the two individual trials were combined in a pooled analysis, pirfenidone was associated with a statistically significant improvement in %FVC and a significant improvement in 6MWT compared with placebo (MD = 2.5%; [$P = 0.005$] and 24.0 m [$P < 0.001$], respectively).

Both trials failed to demonstrate statistically significant differences between pirfenidone and placebo for time to worsening of IPF, respiratory-related hospitalizations, dyspnea, gas transfer, and the need for supplemental oxygen.

TABLE 15: SUMMARY OF RESULTS FROM PIPF-004, PIPF-006, AND THE POOLED ANALYSIS

Outcome	PIPF-004		PIPF-006		Pooled Analysis	
	Pirfenidone	Placebo	Pirfenidone	Placebo	Pirfenidone	Placebo
Number of patients	**174**	**174**	**171**	**173**	**345**	**347**
All-cause mortality						
n (%)	11 (6.3)	17 (9.8)	16 (9.4)	17 (9.8)		
HR (CI), *P* value	0.61 (0.28 to 1.29), 0.191		0.95 (0.48 to 1.87), 0.872		0.77 (0.47 to 1.28), 0.315	
NNH	29		213		51	
QoL — SGRQ, score						
Baseline, mean (SD)	15.1 (2.74)	15.0 (2.58)	14.8 (2.76)	15.1 (2.51)		
Change from baseline, mean (SD)	–1.1 (3.22)	–1.3 (3.43)	–1.2 (3.24)	–1.3 (3.53)		
MD (CI), *P* value	0.2 (NR), 0.684		0.1 (NR), 0.628		NR	
Per cent predicted FVC						
Baseline, mean (SD)	74.5 (14.5)	76.2 (15.5)	74.9 (13.2)	73.1 (14.2)		
Change from baseline, mean (SD)	–8.0% (16.5)	–12.4% (18.5)	–9.0% (19.6)	–9.6% (19.1)		
MD (CI), *P* value	4.4% (0.7 to 9.1), 0.001		0.6% (–3.5 to 4.7), 0.501		2.5% (NR), 0.005	
6MWT, m						
Baseline, mean (SD)	411.1 (170)	410.0 (170)	378.0 (169)	399.1 (168)		
Change from baseline, mean (SD)	–60.4 (120.6)	–76.8 (135.4)	–45.1 (139.8)	–76.9 (127.5)		
MD (CI), *P* value	16.4 (NR), 0.171		31.8 (NR), 0.001		24.0 (NR), < 0.001	
Completed study						
n (%)	146 (83.9)	144 (82.8)	139 (81.3)	146 (84.4)	285 (82.6)	290 (83.6)
SAEs						
n (%)	60 (34.5)	58 (33.3)	53 (31.0)	51 (29.5)	113 (32.8)	109 (31.4)
NNH	87		66		75	
WDAEs						
n (%)	28 (16.1)	16 (9.2)	23 (13.5)	14 (8.1)	51 (14.8)	30 (8.6)
NNH	15		19		16	

6MWT = six-minute walk test; FVC = forced vital capacity; HR = hazard ratio; MD = mean difference; SAE = serious adverse event; NNH = number needed to harm; NR = not reported; QoL = quality of life; SD = standard deviation; SGRQ = St. George's Respiratory Questionnaire; WDAE = withdrawal due to adverse event.
Source: CSRs,{57,58} Nobel et al.;[20,21] Costabel et al.;[22] Albera et al.;[23] and Valeyre et al.[24]

The pooled results of two placebo-controlled trials (PIPF-004 and PIPF-006) suggest that pirfenidone improves lung function (FVC) and functional capacity (walking distance) in adults with mild to moderate IPF. However, the results of the individual trials were discordant with respect to these outcomes, with a significant improvement for FVC and walking distance reported in only one of the two trials. There was no conclusive evidence that pirfenidone reduced mortality or improved QoL.

APPENDIX 7: DETAILED HARM DATA FOR PIPF-016

TABLE 16: TREATMENT-EMERGENT ADVERSE EVENTS REPORTED IN 5% OR MORE OF PATIENTS IN EITHER TREATMENT GROUP IN PIPF-016

Common TEAEs	Number of Patients, n (%)	
System Organ Class Preferred Term	Pirfenidone (N = 278)	Placebo (N = 277)
Patients with any TEAE	**277 (99.6)**	**272 (98.2)**
Cardiac disorders	**37 (13.3)**	**26 (9.4)**
Ear and labyrinth disorders	**11 (4.0)**	**10 (3.6)**
Eye disorders	**23 (8.3)**	**16 (5.8)**
Gastrointestinal disorders	**215 (77.3)**	**171 (61.7)**
Nausea	100 (36.0)	37 (13.4)
Diarrhea	62 (22.3)	60 (21.7)
Dyspepsia	49 (17.6)	17 (6.1)
Vomiting	36 (12.9)	24 (8.7)
Gastroesophageal reflex disease	33 (11.9)	18 (6.5)
Constipation	32 (11.5)	38 (13.7)
Stomach discomfort	24 (8.6)	12 (4.3)
Abdominal pain upper	20 (7.2)	12 (4.3)
Flatulence	12 (4.3)	17 (6.1)
General disorder and administration site conditions	**111 (39.9)**	**116 (41.9)**
Fatigue	58 (20.9)	48 (17.3)
Asthenia	16 (5.8)	11 (4.0)
Pyrexia	6 (2.2)	17 (6.1)
Infection and infestation	**189 (68.0)**	**187 (67.5)**
URTI	61 (21.9)	56 (20.2)
Bronchitis	39 (14.0)	36 (13.0)
Nasopharyngitis	33 (11.9)	30 (10.8)
Pneumonia	21 (7.6)	24 (8.7)
Sinusitis	20 (7.2)	24 (8.7)
UTI	9 (3.2)	17 (6.1)
Influenza	14 (5.0)	13 (4.7)
LRTI	12 (4.3)	19 (6.9)
Investigations	**75 (27.0)**	**66 (23.8)**
Weight decreased	35 (12.6)	22 (7.9)
Metabolism and nutrition disorders	**88 (31.7)**	**61 (22.0)**
Anorexia	44 (15.8)	18 (6.5)
Decreased appetite	20 (7.2)	10 (3.6)
Musculoskeletal and connective tissue disorders	**97 (34.9)**	**108 (39.0)**
Arthralgia	26 (9.4)	20 (7.2)
Back pain	30 (10.8)	37 (13.4)
Pain in extremity	14 (5.0)	16 (5.8)
Musculoskeletal pain	14 (5.0)	9 (3.2)
Nervous system disorders	**145 (52.2)**	**108 (39.0)**

Common TEAEs	Number of Patients, n (%)	
System Organ Class Preferred Term	Pirfenidone (N = 278)	Placebo (N = 277)
Headache	72 (25.9)	64 (23.1)
Dizziness	49 (17.6)	36 (13.0)
Dysgeusia	25 (9.0)	11 (4.0)
Psychiatric disorders	**53 (19.1)**	**50 (18.1)**
Insomnia	31 (11.2)	18 (6.5)
Depression	9 (3.2)	14 (5.1)
Anxiety	8 (2.9)	14 (5.1)
Respiratory, thoracic, and mediastinal disorders	**151 (54.3)**	**173 (62.5)**
Cough	70 (25.2)	82 (29.6)
Dyspnea	41 (14.7)	49 (17.7)
IPF (worsening)	26 (9.4)	50 (18.1)
Productive cough	9 (3.2)	14 (5.1)
Pharyngolaryngeal pain	14 (5.0)	20 (7.2)
Skin and subcutaneous tissue disorders	**141 (50.7)**	**80 (28.9)**
Rash	78 (28.1)	24 (8.7)
Photosensitivity	16 (5.8)	1 (0.4)
Pruritus	27 (9.7)	19 (6.9)
Vascular disorders	**31 (11.2)**	**28 (10.1)**

IPF = idiopathic pulmonary fibrosis; LRTI = lower respiratory tract infection; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection.
Source: PIPF-016 Clinical Study Report[4]

TABLE 17: TREATMENT-EMERGENT SERIOUS ADVERSE EVENTS REPORTED IN PIPF-016 IN TWO OR MORE PATIENTS IN EITHER TREATMENT GROUP

Adverse Events	Number of Patients, n (%)	
	Pirfenidone (N = 278)	Placebo (N = 277)
Patients with any TESAE	55 (19.8)	69 (24.9)
IPF (worsening)	7 (2.5)	27 (9.7)
Pneumonia	11 (4.0)	14 (5.1)
Prostate cancer (percentage among male patients)	2 (0.9)	4 (1.9)
Angina pectoris	3 (1.1)	0
Nausea	3 (1.1)	0
Atrial fibrillation	1 (0.4)	2 (0.7)
Bronchitis	1 (0.4)	2 (0.7)
Dyspnea	1 (0.4)	2 (0.7)
Pulmonary embolism	1 (0.4)	2 (0.7)
Septic shock	1 (0.4)	2 (0.7)
Cardiac failure, congestive	2 (0.7)	0
Rib fracture	2 (0.7)	0
Aortic aneurysm	0	2 (0.7)
Gastroenteritis, viral	0	2 (0.7)

IPF = idiopathic pulmonary fibrosis; TESAE = treatment-emergent serious adverse event.
Source: PIPF-016 Clinical Study Report[4] .

TABLE 18: TREATMENT-EMERGENT ADVERSE EVENTS IN PIPF-016 LEADING TO TREATMENT DISCONTINUATION (OCCURRING IN MORE THAN 1% OF PIRFENIDONE-TREATMENT GROUP)

Adverse Events	Number of Patients, n (%)	
	Pirfenidone (N = 278)	Placebo (N = 277)
Patients with at least one TEAE	277 (99.6)	272 (98.2)
Patients with a TEAE resulting in study treatment discontinuation	40 (14.4)	30 (10.8)
Pneumonia	3 (1.1)	1 (0.4)
Hepatic enzyme increased	3 (1.1)	0
Weight decreased	3 (1.1)	0
IPF (worsening)	3 (1.1)	15 (5.4)
Rash	3 (1.1)	0

IPF = idiopathic pulmonary fibrosis; TEAE = treatment-emergent adverse event.
Source: PIPF-016 Clinical Study Report[4]

TABLE 19: TREATMENT-EMERGENT ADVERSE EVENTS IN PIPF-016 LEADING TO DOSE REDUCTION OR TREATMENT INTERRUPTION (OCCURRING IN MORE THAN 1% OF PIRFENIDONE-TREATMENT GROUP)

Adverse Events	Number of Patients, n (%)	
	Pirfenidone (N = 278)	Placebo (N = 277)
Patients with at least one TEAE	277 (99.6)	272 (98.2)
Patients with a TEAE resulting in study treatment dose reduction or interruption	106 (38.1)	37 (13.4)
Nausea	20 (7.2)	3 (1.1)
Diarrhea	8 (2.9)	8 (2.9)
Stomach discomfort	5 (1.8)	2 (0.7)
Dyspepsia	5 (1.8)	1 (0.4)
Vomiting	4 (1.4)	2 (0.7)
Gastroesophageal reflux disease	3 (1.1)	1 (0.4)
Abdominal pain upper	3 (1.1)	1 (0.4)
Fatigue	3 (1.1)	1 (0.4)
Weight increase	7 (2.5)	0
Anorexia	12 (4.3)	2 (0.7)
Decrease appetite	3 (1.1)	0
Dizziness	3 (1.1)	2 (0.7)
Headache	4 (1.4)	0
Rash	21 (7.6)	1 (0.4)
Pruritus	8 (2.9)	0
Photosensitivity	7 (2.5)	0

TEAE = treatment-emergent adverse event.
Source: PIPF-016 Clinical Study Report[4]

APPENDIX 8: RESULTS OF POOLED DATA ANALYSIS OF MORTALITY (PIPF-004, PIPF-006, PIPF-016)

TABLE 20: ALL-CAUSE MORTALITY ANALYSIS IN PIPF-004, PIPF-006, PIPF-016, AND THE POOLED ANALYSIS (ALL RANDOMIZED PATIENTS)

	PIPF-004		PIPF-006		PIPF-16		Pooled Analysis	
	Pirfenidone (N = 174)	Placebo (N = 174)	Pirfenidone (N = 171)	Placebo (N = 173)	Pirfenidone (N = 278)	Placebo (N = 277)	Pirfenidone	Placebo
Results at 52 weeks of treatment							**(N = 623)**	**(N = 624)**
Events,[a] n (%)	5 (2.9)	13 (7.5)	6 (3.5)	9 (5.2)	11 (4.0)	20 (7.2)	22	42
HR (95% CI), *P* value	0.37 (0.13 to 1.04), 0.06		0.66 (0.24 to 1.67), 0.435		0.55 (0.26 to 1.15), 0.1045		0.52 (0.31 to 0.87)	
Results at 72 weeks of treatment							**(N = 345)**	**(N = 347)**
Events,[b] n (%)	11 (6.3)	17 (9.8)	16 (9.4)	17 (9.8)			27 (7.8)	34 (9.8)
HR[c] (95% CI), *P* value	0.61 (0.28 to 1.29), 0.191		0.95 (0.48 to 1.87), 0.872				0.77 (0.47 to 1.28), 0.315	

[a] Includes deaths that occurred within 52 weeks of treatment. Source: Nobel et al. 2014.[29]
[b] Includes deaths that occurred within 72 weeks of treatment. Sources: Nobel et al. 2011;[30] Albera et al.;[23] and FDA Briefing,[31]
[c] Hazard ratio and *P* values were adjusted by geographic region (US and rest of the world).

TABLE 21: IPF-RELATED MORTALITY ANALYSIS IN PIPF-004, PIPF-006, PIPF-016, AND THE POOLED ANALYSIS (ALL RANDOMIZED PATIENTS)

	PIPF-004		PIPF-006		PIPF-16		Pooled Analysis	
	Pirfenidone (N = 174)	Placebo (N = 174)	Pirfenidone (N = 171)	Placebo (N = 173)	Pirfenidone (N = 278)	Placebo (N = 277)	Pirfenidone	Placebo
Results at 52 weeks of treatment							**(N = 623)**	**(N = 624)**
Events,[a] n (%)	2	10	4	6	7	16	13	30
HR[b] (95% CI), *P* value	0.20 (0.04 to 0.90), 0.04		0.67 (0.19 to 2.35), 0.54		0.44 (0.18 to 1.04), 0.06		0.42 (0.22 to 0.81), 0.009	
Results at 72 weeks of treatment							**(N = 345)**	**(N = 347)**
Events,[c] n (%)	6 (3.4)	13 (7.5)	12 (7.0)	15 (8.7)			18 (5.2)	28 (8.1)
HR[d] (95% CI), *P* value	0.45 (0.17 to 1.19), 0.108		0.79 (0.37 to 1.69), 0.542				0.63 (0.35 to 1.14), 0.130	

[a] Sources: Clinical Study Reports: PIPF-004,[2] 16.2.7-3, pages 1686-1969/1987; PIPF-006,[3] 16.2.7-3, pages 1280–1292/1529; and PIPF-016[4] – 16.2.7.4, pages 1938-1961/2120.
[b] CDR calculation.
[c] Includes deaths that occurred during the trial period. Source: FDA Briefing,[31] pages 150 and 155/185.
[d] Hazard ratio and *P* values were adjusted by geographic region (US and rest of the world).

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