IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Pirfenidone – Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Pirfenidon – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 12.12.2011). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institute for Quality and Efficiency in Health Care
Dillenburger Str. 27
51105 Cologne
Germany

Tel: +49-(0)221/35685-0
Fax: +49-(0)221/35685-1
E-mail: berichte@iqwig.de
www.iqwig.de

Medical and scientific advice:

- Anselm Bäumer, Practice for Internal Medicine, Cardiology and Pneumology, Cologne

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

IQWiG employees involved in the dossier assessment:[2]

- Beate Wieseler
- Andreas Gerber
- Ulrich Grouven
- Tatjana Janzen
- Thomas Kaiser
- Michaela Florina Kerekes
- Siw Waffenschmidt
- Carolin Weigel

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[2] Due to legal data protection regulations, employees have the right not to be named.

List of abbreviations

Abbreviation	Meaning
AE	adverse event
BSC	best supportive care
DLco	carbon monoxide diffusing capacity
FVC	forced vital capacity
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Hgb	haemoglobin
IPF	idiopathic pulmonary fibrosis
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
QoL	quality of life
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGRQ	St George's Respiratory Questionnaire
UCSD	University of California at San Diego
WHO QoL	World Health Organization Quality of Life (Questionnaire)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 15.09.2011, in accordance with § 35a SGB (Social Code Book) V, the Federal Joint Committee (G-BA) wrote to IQWiG to commission the benefit assessment of the drug pirfenidone. The assessment was based on a dossier compiled by the pharmaceutical company. The dossier was sent to IQWiG on 15.09.2011.

Pirfenidone is a drug for treating a rare disease ("orphan drug"). In accordance with § 35a SGB V, an added benefit of orphan drugs is deemed as proven by the fact that they have been approved. However, evidence must be presented regarding groups of patients for whom a therapeutically important added benefit exists. For this purpose, the extent of the added benefit of pirfenidone must be assessed.

Research question

- The objective of the present report is to assess the extent of the added benefit of pirfenidone in comparison with *best supportive care* (BSC) as appropriate comparator therapy in patients with mild to moderate idiopathic pulmonary fibrosis (IPF).

The benefit assessment considered studies in which pirfenidone as a monotherapy or in combination with *best supportive care* was compared with treatment consisting of *best supportive care* alone. The assessment was based on the comparison of pirfenidone combined with *best supportive care* (pirfenidone/BSC) with treatment consisting of *best supportive care* alone (placebo/BSC), since these were the treatments investigated in the included studies. The assessment was undertaken based on patient-relevant outcomes and reviewed direct comparative randomized controlled trials (RCTs).

Results

Two relevant studies (PIPF-004 und PIPF-006) were available for the assessment. Both were double-blind RCTs, in which pirfenidone combined with *best supportive care* was compared with placebo in combination with *best supportive care*.

The results of the individual studies were combined in meta-analyses that produced the following results:

Mortality

Analysis of all-cause mortality showed no statistically significant difference between pirfenidone combined with *best supportive care* and *best supportive care* alone. An added benefit of pirfenidone for all-cause mortality is not proven.

Morbidity

Need for supplemental oxygen

Analysis of the need for supplemental oxygen produced no statistically significant difference between pirfenidone/BSC and placebo/BSC. An added benefit of pirfenidone in combination with *best supportive care* compared to *best supportive care* alone is not proven for this outcome.

Exercise tolerance (6-minute walk test)

Exercise tolerance of patients was documented using the 6-minute walk test. An analysis of the proportion of patients who experienced a deterioration in the walk test of ≥ 50 metres during the study showed a statistically significant advantage of pirfenidone/BSC compared to placebo/BSC. Because the responder criterion was established post-hoc, the certainty of results was downgraded from "proof" to "indication". Thus there was an indication of added benefit of pirfenidone in combination with *best supportive care* compared to *best supportive care* alone, in respect of exercise tolerance of the patients.

Health-related quality of life

Health-related quality of life (QoL) was recorded with two questionnaires (St George's Respiratory Questionnaire (SGRQ) and the World Health Organization (WHO) QoL). The analyses showed no statistically significant difference between the treatment groups for either questionnaire. An added benefit of pirfenidone in combination with *best supportive care* compared with *best supportive care* alone is not proven for health-related quality of life.

Adverse events

Comparison of the adverse events and the serious adverse events between the treatment groups produced no statistically significant difference. Greater harm is not proven for these outcomes.

The proportion of patients who discontinued the study because of adverse events was statistically significantly higher under pirfenidone/BSC than under placebo/BSC. Adverse events affecting the gastrointestinal tract, as well as the skin and subcutaneous tissue, were likewise observed statistically significantly more frequently under pirfenidone/BSC than under placebo/BSC. There is thus proof of greater harm of pirfenidone combined with *best supportive care* compared with *best supportive care* alone for these outcomes.

Probability and extent of the added benefit, patient groups with therapeutically important added benefits

Based on the results presented, the extent and probability of an added benefit of the drug pirfenidone is assessed as follows:

The overall conclusion about the extent of added benefit must balance the indication of added benefit for the outcome "exercise tolerance" against proof of greater harm for the outcome

"discontinuation due to adverse events", "adverse events affecting the gastrointestinal tract" and "adverse events affecting the skin and subcutaneous tissue". The aspects to be weighed up against each other have a comparable outcome quality (non-serious / non-severe symptoms and non-serious / non-severe adverse events). The extent of the effect is classed as "minor" for the positive effect and in two cases as "minor" and in one case as "considerable" for the negative effects.

In accordance with § 35a SGB V, an added benefit of orphan drugs is deemed as proven by the fact that they have been approved.

The dossier assessment was undertaken to classify the extent of the added benefit. Since, taken as a whole, the submitted data do not provide an indication of an added benefit of pirfenidone, then on the basis of these data and in accordance with the legal regulations, the extent of the added benefit of pirfenidone is classed as "no proven added benefit".

The procedure for formulating an overall conclusion of the extent of the added benefit is a proposal from IQWiG. The decision regarding the extent of the added benefit is made by the G-BA.

2.2 Research question

Pirfenidone is a drug approved for the treatment of a rare disease (orphan drug). In accordance with § 35a SGB V, an added benefit of orphan drugs is deemed as proven by the fact that they have been approved. However, evidence must be presented about patient groups for whom a therapeutically important added benefit exists. For this purpose, the extent of the added benefit of pirfenidone must be assessed.

The pharmaceutical company named "non-treatment of the disease and its consequences" as the appropriate comparator therapy. On the other hand, the G-BA specified *best supportive care* as the appropriate comparator therapy. IQWiG used the appropriate comparator therapy specified by the G-BA for the benefit assessment of pirfenidone.

The objective of this report is therefore to assess the extent of the added benefit of pirfenidone compared with *best supportive care* as the appropriate comparator therapy in patients with mild to moderately severe idiopathic pulmonary fibrosis (IPF).

The benefit assessment considered studies that compared pirfenidone as monotherapy or in combination with *best supportive care* with treatment consisting of *best supportive care* alone.

In the placebo-controlled studies included in the assessment, patients in the pirfenidone groups as well as those in the placebo groups received concomitant treatment classed as the *best supportive care*. The studies therefore compared the administration of pirfenidone in addition to *best supportive care* with *best supportive care* alone. In order to describe this

comparison clearly in the report, the treatment arms will be named as follows: pirfenidone/BSC and placebo/BSC.

The assessment was carried out in respect of patient-relevant outcomes and reviewed direct comparative RCTs.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.4.4 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled from the following data:

- Studies on pirfenidone in IPF completed by the pharmaceutical company (shown in the dossier)
- Results of a bibliographical literature search and a search in trial registries for pirfenidone and treatment options for interstitial lung diseases (up to June 2011, company searches)
- Independent searches by the Institute for pirfenidone in bibliographical databases and trial registries up to 13.10.2011 to check the company's search results. The searches by the Institute detected no additional studies.

The identified studies corresponded to the study pool of the company. However, not all studies were included in the assessment because not all studies were suitable for a comparison of pirfenidone with the appropriate comparator therapy (*best supportive care*).

Further information about the inclusion criteria for studies in the benefit assessment and the methods of information retrieval can be found in Module 3, Section 3.1 and in Module 4, Section 4.4.4 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.3.1 Studies included in the assessment

The studies listed in Table 1 were included in the benefit assessment.

Table 1: Study pool – RCTs with the drug to be assessed; direct comparison pirfenidone/BSC vs. placebo/BSC

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
PIPF-004	yes	yes	no
PIPF-006	yes	yes	no
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. BSC: *best supportive care*; RCT: randomized controlled trial			

The study pool of RCTs with the drug to be assessed for the benefit assessment of pirfenidone deviated from the company's study pool in that the trials SP2 and SP3 were not taken into account. The reason these two trials were omitted from the assessment is that neither of them used *best supportive care* in the control group (see also Section 2.7.2.3.2 in the full dossier assessment).

In the included studies PIPF-004 and PIPF-006, patients were randomized to treatment with pirfenidone or placebo. In addition, all patients received *best supportive care* as co-medication. Accordingly, the studies undertook a direct comparison of pirfenidone combined with *best supportive care* (pirfenidone/BSC) and *best supportive care* alone (given combined with placebo: placebo/BSC). The company submitted no studies for an indirect comparison.

Section 2.6 contains a list of data sources named by the company for the studies included in its assessment.

Further information about the results of information retrieval and the study pool derived from it can be found in Module 3, Section 3.1. and in Module 4, Section 4.4.4 of the dossier and in Sections 2.7.2.3.2 and 2.7.2.3.1 of the full dossier assessment.

2.3.2 Study characteristics

Table 2 and Table 3 describe the design of the studies reviewed in the benefit assessment. Both studies were double-blind RCTs in which patients with a confirmed diagnosis of IPF were treated with pirfenidone + *best supportive care* or with placebo + *best supportive care*.

In these studies, the patients were randomly allocated to treatment with pirfenidone or placebo. Extensive concomitant treatment was possible in both arms of the study. Drugs necessary for patient well-being could be used at the investigators' discretion. In addition, if a defined deterioration occurred, further drugs to treat the IPF could be used in both groups (see Table 3). Patients in the studies could also receive supplemental oxygen or a lung transplant. This treatment regime is regarded as sufficiently comprehensive and suited to patient needs to qualify as *best supportive care*. Thus these trials compared the additional administration of pirfenidone on the basis of a *best supportive care* with treatment consisting of *best supportive care* alone. In Study PIPF-004, as well as the approved dosage of 2403 mg/day, a lower dose could be used. The corresponding arm of the study was not included in the benefit assessment because of non-conformity with the approved dosage.

In both studies, the patients were to receive the study medication until the last randomized patient had been treated for 72 weeks. Patients who discontinued treatment were to be followed up – if possible – until study completion.

The primary outcome in both studies was a lung function parameter. The secondary outcomes relevant for the benefit assessment investigated mortality, dyspnoea, exercise tolerance of the patients (6-minute walk test), health-related quality of life, the need for supplemental oxygen therapy and adverse events.

Table 2: Characteristics of the assessed studies – pirfenidone/BSC vs. placebo/BSC

Study	Study design	Population	Interventions (number of randomized patients)	Treatment duration[a] Median (min-max)	Location and period of study	Primary outcome; secondary outcomes[b]
PIPF-004	RCT, double-blind, parallel	Adult patients with IPF (diagnosis confirmed)	Pirfenidone 2403 mg/day (n=174) Pirfenidone 1197 mg/day[c] (n=87) Placebo (n=174) In each case + *best supportive care*	Pirfenidone 2403 mg/day: 72 weeks (2-104 weeks) Placebo: 72 weeks (<1-110 weeks)	North and Central America, Europa, Australia July 2006 – November 2008	Primary: Change in forced vital capacity (% of predicted) between start of study and Week 72 Secondary: All-cause mortality, dyspnoea, 6-minute walk test, need for supplemental oxygen, health-related quality of life, adverse events
PIPF-006	RCT, double-blind, parallel	Adult patients with IPF (diagnosis confirmed)	Pirfenidone 2403 mg/day (n=171) Placebo (n=173) In each case + *best supportive care*	Pirfenidone 2403 mg/day: 75 weeks (6-118 weeks) Placebo: 74 weeks (1-120 weeks)	North and Central America, Europe (incl. Germany), Australia April 2006 – October 2008	Primary: Change in forced vital capacity (% of predicted) between start of study and week 72 Secondary: All-cause mortality, dyspnoea, 6-minute walk test, need for supplemental oxygen, health-related quality of life, adverse events

a: Planned duration of study: All patients were to receive the study medication until the last randomized patient had been treated for about 72 weeks. Patients who discontinued treatment were – if possible - to be followed-up until study completion.

b: Extracted primary outcome criteria contain information without consideration of relevance for this benefit assessment. Extracted secondary outcome criteria contain exclusively information on the relevant available outcomes for this benefit assessment.

c: Since this dose does not correspond with the approved dosage, the results of this group were not included in the benefit assessment.

BSC: *best supportive care;* IPF: idiopathic pulmonary fibrosis; max: maximum; min: minimum; RCT: randomized controlled trial

Table 3: Characteristics of the interventions – pirfenidone/BSC vs. placebo/BSC

Study	Pirfenidone arm	Placebo arm
PIPF-004	Test medication: Pirfenidone 2403 mg/day oral, 3 x 267 mg capsules 3 times daily Concomitant medication (in both arms): Drugs considered necessary for the patient's welfare were allowed at the discretion of the investigator. The following treatments for the IPF were permitted: ▪ short courses of steroids for acute respiratory decompensation ▪ azathioprine or cyclophosphamide with or without corticosteroids for IPF exacerbations ▪ corticosteroids, azathioprine, cyclophosphamide or N-acetylcysteine for defined progression of IPF[a] Non-pharmacological concomitant treatment (in both arms) ▪ oxygen therapy (optional) ▪ lung transplantation (optional)[b]	Test medication: Placebo oral, 3 placebo capsules 3 x daily
PIPF-006	As in Study PIPF-004	

a: According to the protocol, medication to treat a defined progression of IPF was not to be used before Week 72. The use of non-protocol-compliant medication was to be documented and use was classified as a protocol violation.

b: Planned lung transplantation at the start of the study was an exclusion criterion, but once enrolled, patients could undergo lung transplantation during the study. On receipt of a lung transplant, these patients were to discontinue treatment, but their vital status was recorded until study completion.

BSC: *best supportive care;* IPF: idiopathic pulmonary fibrosis; RCT: randomized controlled trial

Table 4 shows the characteristics of patients in the assessed studies. Within the studies there were no substantial differences between the treatment groups in the demographic characteristics of the patients and the time since diagnosis of IPF. There were also no relevant differences in these parameters between the two studies. The average age of the patients treated was 66 to 67 years and the majority (about 70%) were men.

Table 4: Characteristics of the study populations – pirfenidone/BSC vs. placebo/BSC

Study Group	N[a]	Age years Mean (SD)	Sex f / m (%)	Caucasian / other (%)	FVC % of predicted Mean (SD)	DLco % of predicted Mean (SD)	Time since diagnosis of IPF (years) Mean (SD)
PIPF-004							
Pirfenidone	174	66 (8)	32/68	97/3	75 (14)	46 (9)	1 (1)
Placebo	174	66 (8)	26/74	97/3	76 (16)	46 (10)	1 (1)
PIPF-006							
Pirfenidone	171	67 (8)	28/72	99/1	75 (13)	48 (10)	1 (1)
Placebo	173	67 (8)	28/72	99/1	73 (14)	47 (9)	1 (1)

a: Number of randomized patients

BSC: *best supportive care;* DLco: carbon monoxide diffusing capacity; f: female; FVC: forced vital capacity; IPF: idiopathic pulmonary fibrosis; m: male; N: number of patients; RCT: randomized controlled trial; SD: standard deviation

Table 5 shows the risk of bias of the two studies at study level.

Table 5: Risk of bias at study level – pirfenidone/BSC vs. placebo/BSC

Study	Adequate randomization sequence generation	Allocation concealment	Blinding		Selective outcome reporting	Other sources of bias	Risk of bias at study level
			Patient	Treating persons			
PIPF-004	yes	yes	yes	yes	no	no	low
PIPF-006	yes	yes	yes	yes	no	no	low
BSC: *best supportive care;* RCT: randomized controlled trial							

The risk of bias at study level was classed as low for both studies. The company did not present any estimation of the risk of bias in its dossier.

Further information about the design of the studies and the study populations can be found in Module 4 Section 4.4.4 of the dossier and in Sections 2.7.2.4.1 and 2.7.2.4.2 of the full dossier assessment.

2.4 Results concerning added benefit

This assessment covers the following patient-relevant outcomes (for more detailed reasoning, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality (all-cause mortality)
- Morbidity
  - Dyspnoea (UCSD Shortness of Breath Questionnaire)
  - Exercise tolerance (6-minute walk test)
  - Need for supplemental oxygen
- Health-related quality of life (SGRQ and WHO QoL)
- Adverse events
  - Overall rate of adverse events
  - Overall rate of serious adverse events
  - Overall rate of adverse events leading to study discontinuation
  - Overall rate of gastrointestinal adverse events
  - Overall rate of adverse events affecting the skin and subcutaneous tissue

Table 6 shows the data available for the particular outcomes in the assessed studies. Table 7 provides the risk of bias for these outcomes.

Table 6: Matrix of outcomes – pirfenidone/BSC vs. placebo/BSC

Study	All-cause mortality	Dyspnoea	Exercise tolerance (6-minute walk test)	Need for supplemental oxygen	Quality of life: SGRQ	Quality of life: WHO QoL	Adverse events[a]	Serious adverse events	Discontinuation due to adverse events
PIPF-004	yes	yes	yes	yes	yes	yes	yes	yes	yes
PIPF-006	yes	yes	yes	yes	yes	yes	yes	yes	yes

a: For adverse events as well as for adverse events affecting the gastrointestinal tract and the skin and subcutaneous tissue

BSC*: best supportive care*; SGRQ: St. George's Hospital Respiratory Questionnaire; WHO QoL: World Health Organization Quality of Life Questionnaire

Table 7: Risk of bias at study and outcome level – pirfenidone/BSC vs. placebo/BSC

Outcome / Study	Risk of bias at study level	All-cause mortality	Dyspnoea	Exercise tolerance (6-minute walk test)	Need for supplemental oxygen	Quality of life: SGRQ	Quality of life: WHO QoL	Adverse events[b]	Serious adverse events	Discontinuation due to adverse events
PIPF-004	L	L	L	H[a]	L	L	L	L	L	L
PIPF-006	L	L	L	H[a]	L	L	L	L	L	L

H: high risk of bias; L: low risk of bias

a: High risk of bias of the responder analysis because of post-hoc definition of response criterion

b: For all adverse events as well as for adverse events affecting the gastrointestinal tract or the skin and subcutaneous tissue

BSC: *best supportive care*; RCT: randomized controlled trial; SGRQ: St. George's Hospital Respiratory Questionnaire; WHO QoL: World Health Organization Quality of Life (Questionnaire)

All the outcomes relevant for the assessment were recorded in both studies. The risk of bias at outcome level was, with one exception, classed as low for all outcomes. The risk of bias of the responder analysis of the 6-minute walk test was estimated as high because, although the response criterion was recorded empirically, it was defined post-hoc (see Section 2.7.2.4.3 of the full dossier assessment for a discussion of the definition of the response criterion).

The pharmaceutical company did not present any estimation of the risk of bias at outcome level in its dossier.

Further information about choice of outcome and risk of bias at outcome level can be found in Module 4, Section 4.4.4 of the dossier and in Sections 2.7.2.2, 2.7.2.4.2, 2.7.2.4.3 and 2.7.2.9.4 of the full dossier assessment.

Tables 8, 9 and 10 summarize the results of the comparison of pirfenidone/BSC and placebo/BSC in patients with idiopathic pulmonary fibrosis. Where necessary, the data from the manufacturer's dossier were supplemented by the Institute's own calculations. In particular, meta-analyses of Studies PIPF-004 and PIPF-006 were carried out because the company's dossier primarily presented the pooled analyses of individual patient data for the treatment arms, which did not take into account the randomization within the individual studies and did not permit any estimation of the heterogeneity of the results. The meta-analyses are available in Appendix A of the full dossier assessment. Heterogeneity was low in all meta-analyses.

The results are presented grouped according to mortality, morbidity, health-related quality of life and adverse events.

Table 8: Results on mortality and morbidity (dichotomous outcomes) – pirfenidone/BSC vs. placebo/BSC

	Pirfenidone/BSC		Placebo/BSC		Pirfenidone/BSC vs. Placebo/BSC	
	Total N	Patients with events n (%)	Total N	Patients with events n (%)	Hazard Ratio[a] [95 %-CI]	p-value
Mortality						
All-cause mortality						
PIPF-004	174	11 (6.3)	174	17 (9.8)	0.61 [0.28; 1.29]	0.191
PIPF-006	171	16 (9.4)	173	17 (9.8)	0.95 [0.48; 1.87]	0.872
Total[b]	345	27 (7.8)	347	34 (9.8)	0.78 [0.47; 1.30]	0.340
Morbidity						
Need for supplemental oxygen[c]						
PIPF-004	145	32 (22)	148	36 (24)	0.88 [0.55; 1.42]	0.602
PIPF-006	123	24 (20)	123	22 (18)	1.16 [0.65; 2.07]	0.614
Total[b]	268	56 (21)	271	58 (21)	0.98 [0.68; 1.42]	0.928
Exercise tolerance (6-minute walk test)[d]					**Relative risk [95 % CI]**	
PIPF-004	170	62 (37)	170	80 (47)	0.78 [0.60; 1.00][b]	0.050[b]
PIPF-006	169	56 (33)	168	79 (47)	0.71 [0.54; 0.92][b]	0.010[b]
Total[b]	339	118 (35)	338	159 (47)	0.74 [0.62; 0.89]	0.001

a: From Cox-proportional hazards model

b: Institute calculations, hazard ratio and/or relative risk from a meta-analysis (see Appendix A of the full dossier assessment), p-value from unconditional exact test (CSZ method according to [1])

c: Only patients without the need for supplemental oxygen at the start of the study were included in the analysis. Of these patients, 1 patient in the placebo group in each of the two studies was not included in the analysis.

d: Responder analysis; proportion of patients in whom the 6-minute walk test worsened by ≥ 50 metres between the start of the study and Week 72; see Table 9 for a further analysis of the walk test

BSC: *best supportive care*; CI: confidence interval; CSZ: convexity, symmetry, z score; IPF: idiopathic pulmonary fibrosis; N: number of patients in the analysis; n: number of patients with event

Table 9: Results on morbidity and health-related quality of life (continuous outcomes) – pirfenidone/BSC vs. placebo/BSC

Outcome Study Group	Total N	Value at baseline Mean (SD)	Change from baseline to Week 72 Mean (SD)	Group difference Mean difference [95 % CI]	p-value
Morbidity					
Dyspnoea (UCSD SOB)[a]					
PIPF-004					
Pirfenidone/BSC	171	33 (22)	12 (24)	-3 [ND]	0.509
Placebo/BSC	169	30 (21)	15 (26)		
PIPF-006					
Pirfenidone/BSC	168	36 (20)	12 (25)	-2 [ND]	0.604
Placebo/BSC	171	37 (22)	14 (28)		
Total[b]					
Pirfenidone/BSC	339			-3 [-6; 1]	0.195
Placebo/BSC	340				
Exercise tolerance (6-minute walk test [metres])					
PIPF-004					
Pirfenidone/BSC	170	411 (92)	-60 (121)	16 [ND]	0.171
Placebo/BSC	170	410 (91)	-77 (135)		
PIPF-006					
Pirfenidone/BSC	169	378 (82)	-45 (140)	32 [ND]	<0.001
Placebo/BSC	168	399 (90)	-77 (128)		
Total[b]					
Pirfenidone/BSC	339			24 [4; 43]	0.018
Placebo/BSC	338				
Health-related quality of life					
SGRQ[c]					
PIPF-004					
Pirfenidone/BSC	163	38 (19)	8 (19)	-1 [ND]	0.495
Placebo/BSC	165	35 (16)	9 (19)		
PIPF-006					
Pirfenidone/BSC	166	38 (15)	7 (17)	0 [ND]	0.766
Placebo/BSC	169	39 (17)	7 (20)		
Total[b]					
Pirfenidone/BSC	329			-1 [-4; 2]	0.611
Placebo/BSC	334				

(continued on next page)

Table 9: Results on morbidity and health-related quality of life (continuous outcomes) – pirfenidone/BSC vs. placebo/BSC (Continuation)

Outcome Study Group	Total N	Value at baseline Mean (SD)	Change from baseline to Week 72 Mean (SD)	Group difference Mean difference [95 % CI]	p-value
Health-related quality of life					
WHO QoL[d]					
PIPF-004					
Pirfenidone/BSC	174	15 (3)	-1 (3)	0 [ND]	0.684
Placebo/BSC	173	15 (3)	-1 (3)		
PIPF-006					
Pirfenidone/BSC	171	15 (3)	-1 (3)	0 [ND]	0.628
Placebo/BSC	170	15 (3)	-1 (4)		
Total[b]					
Pirfenidone/BSC	345			0 [0; 1]	0.554
Placebo/BSC	343				

a: UCSD SOB: The score can assume values from 0 to 120, higher values signify more severe symptoms.

b: Institute calculations, group difference and p-value from a meta-analysis (see Appendix A of the full dossier assessment)

c: SGRQ: The score can assume values from 0 to 100, higher values signify a worse quality of life.

d: WHO QoL: From the company's documents, the range of scores is unclear, lower values signify a worse quality of life.

BSC: *best supportive care*; CI: confidence interval; N: number of patients in the analysis; ND: no data; SD: standard deviation; SGRQ: St. George's Hospital Respiratory Questionnaire; UCSD SOB: University of California at San Diego Shortness-of-Breath Questionnaire; WHO QoL: World Health Organization Quality of Life Questionnaire

Table 10: Results on adverse events – pirfenidone/BSC vs. placebo/BSC

Outcome Study	Pirfenidone/BSC		Placebo/BSC		Pirfenidone/BSC vs. Placebo/BSC	
	Total N	Patients with events n (%)	Total N	Patients with events n (%)	Relative risk[a] [95 % CI]	p-value[a]
AE						
PIPF-004	174	171 (98)	174	169 (97)	1.01 [0.98; 1.05]	0.498
PIPF-006	171	169 (99)	173	170 (98)	1.01 [0.98; 1.03]	0.751
Total[a]	345	340 (99)	347	339 (98)	1.01 [0.99; 1.03]	0.431
SAE						
PIPF-004	174	60 (35)	174	58 (33)	1.03 [0.77; 1.39]	0.881
PIPF-006	171	53 (31)	173	51 (30)	1.05 [0.76; 1.45]	0.827
Total[a]	345	113 (33)	347	109 (31)	1.04 [0.84; 1.29]	0.709
Discontinuation due to AE						
PIPF-004	174	28 (16)	174	16 (9)	1.75 [0.98; 3.12]	0.057
PIPF-006	171	23 (14)	173	14 (8)	1.66 [0.89; 3.12]	0.126
Total[a]	345	51 (15)	347	30 (9)	1.71 [1.12: 2.62]	0.014
AE of gastro-intestinal tract						
PIPF-004	174	137 (79)	174	104 (60)	1.32 [1.14; 1.52]	<0.001
PIPF-006	171	133 (78)	173	99 (57)	1.36 [1.17; 1.58]	<0.001
Total[a]	345	270 (78)	347	207 (59)	1.34 [1.20; 1.48]	<0.001
AE of skin and subcutaneous tissue						
PIPF-004	174	105 (60)	174	62 (36)	1.69 [1.34; 2.14]	<0.001
PIPF-006	171	101 (59)	173	65 (38)	1.57 [1.25; 1.98]	<0.001
Total[a]	345	206 (60)	347	127 (37)	1.63 [1.38; 1.92]	<0.001

a: Institute calculations, relative risk from a meta-analysis (see Appendix A of the full dossier assessment), p-value from unconditional exact test (CSZ method according to [1])

BSC: *best supportive care*; CI: confidence interval, CSZ: convexity, symmetry, z score; N: number of patients in the analysis; n: number of patients with event; SAE: serious adverse event; AE: adverse event

The available data enabled a meta-analysis of the two studies. With one exception, the risk of bias at outcome level was classed as low in both studies. Since no additional outcome-specific aspects that would weaken the informative value of these results were identified for these outcomes, the informative value of the evidence can be classed as high. Proof can be derived from statistically significant results of the meta-analyses.

The exception was the responder analysis of the 6-minute walk test. Because of the post-hoc-definition of the response criterion, the risk of bias of this particular analysis was estimated as high. Therefore if a meta-analysis of this responder analysis produces statistically significant results, only an indication rather than proof can be inferred.

Mortality

In Study PIPF-004, fewer patients died under treatment with pirfenidone/BSC than under treatment with placebo/BSC; in Study PIPF-006 the number of deaths in the two groups was comparable. The meta-analysis of the two studies showed no statistically significant group difference. There is no proof for an added benefit of pirfenidone in combination with *best supportive care* compared with *best supportive care* alone for the all-cause mortality.

The pharmaceutical company derived a moderate prolongation of survival under pirfenidone from the results on IPF-related deaths under treatment and on progression-free survival (first occurrence of either of the following: 10% absolute decline in percent predicted FVC or 15% absolute decline in percent predicted Hgb-corrected DLco or death). The company did not comment on the certainty of results of these data. The Institute does not concur with the assessment of the data by the company (for a discussion of these data, see Section 2.7.2.4.3 of the full dossier assessment).

Morbidity

The 6-minute walk test was classed as a measure of the exercise tolerance of the patients. A meta-analysis of the mean decline in walking distance produced a statistically significant effect in favour of pirfenidone/BSC (mean difference 24 metres, 95% CI 4 to 43 metres). The relevance of this effect is unclear. A meta-analysis of the proportion of patients for whom a deterioration in walking distance of ≥ 50 metres was documented in the study likewise showed a statistically significant advantage of pirfenidone/BSC compared to placebo/BSC. This analysis is potentially biased because the response criterion was defined post-hoc. The certainty of results of the analysis is therefore downgraded from “proof” to “indication”. From this responder analysis, an indication of added benefit of pirfenidone combined with *best supportive care* compared with *best supportive care* alone can be derived solely in respect of exercise tolerance of the patients.

The company also evaluated the result of the responder analysis of the 6-minute walk test as a significant treatment effect. It describes the effect as a perceptible alleviation of the disease, without commenting on the certainty of the result (see Section 2.5.1 for the Institute’s evaluation of the extent of the added benefit).

The meta-analyses produced no statistically significant difference between pirfenidone/BSC and placebo/BSC for either of the outcomes “need for supplemental oxygen” and “dyspnoea” (measured with the UCSD Shortness of Breath Questionnaire). An added benefit of pirfenidone in combination with *best supportive care* compared with *best supportive care* alone is therefore not proven for these outcomes.

The company presents no conclusions in the dossier regarding dyspnoea (measured with the UCSD Shortness of Breath Questionnaire). In relation to the need for supplemental oxygen, the assessment of the Institute does not differ from that of the company, which also derived no added benefit for this outcome.

Health-related quality of life

The health-related quality of life of the patients was recorded in both studies with a specific questionnaire for respiratory diseases (the SGRQ) and with a generic questionnaire (the WHO QoL Questionnaire). The meta-analysis of the two studies showed no statistically significant difference between the treatment groups for the change in quality of life during the study as measured by either questionnaire.

There is thus no proof of added benefit of pirfenidone combined with *best supportive care* compared with *best supportive care* alone for health-related quality of life.

The evaluation of the results of the SGRQ and WHO QoL corresponds to that of the company. The company's dossier also describes a responder analysis which combines a deterioration in an adapted version of the SGRQ and death. From these data, the company derives an indication of a slower deterioration in the quality of life under pirfenidone. The Institute does not concur with this assessment (see Section 2.7.2.4.3 of the full dossier assessment for a discussion of these data).

Adverse events

The overall rates of adverse events and serious adverse events were comparable between the two treatment options investigated. The meta-analyses of these outcomes showed no statistically significant group difference.

However, adverse events that led to discontinuation of treatment occurred statistically significantly more often in the pirfenidone/BSC group than in the placebo/BSC group. Adverse events affecting the gastrointestinal tract or skin and subcutaneous tissue were also observed statistically significantly more frequently under pirfenidone/BSC than under placebo/BSC.

Thus for the outcomes "discontinuation due to adverse events", "adverse gastrointestinal events" and "adverse events of the skin and subcutaneous tissue" there is proof of greater harm from pirfenidone combined with *best supportive care* compared with *best supportive care* alone.

The pharmaceutical company derives no conclusion about harm from the above outcomes, but classes a non-statistically significant reduction in hospital admissions due to respiratory problems under pirfenidone/BSC as an indication of a relevant prevention of serious adverse events. The Institute does not concur with this assessment (see Section 2.7.2.4.3 of the full dossier assessment for a discussion of these data).

Further information about the outcome results can be found in Module 4, Section 4.4.4 of the dossier and in Section 2.7.2.4.3 of the full dossier assessment.

2.5 Extent and probability of the added benefit

Derivation of the extent and probability of added benefit is discussed below at outcome level, taking into account outcome categories and effect sizes. The methodology used is explained in Appendix A of Benefit Assessment A11-02 [2].

The procedure for formulating an overall conclusion regarding the extent of added benefit based on the aggregation of the conclusions derived at outcome level is a proposal from IQWiG. The decision regarding added benefit is made by the G-BA.

2.5.1 Evaluation of added benefit at outcome level

The data presented in Section 2.4 provided an indication of added benefit and proof of greater harm of pirfenidone combined with *best supportive care* compared with *best supportive care* alone. An assessment of the extent of the respective added benefit at outcome level was made and is shown in Table 11.

Table 11: Extent of added benefit at outcome level – pirfenidone/BSC vs. placebo/BSC

	Effect estimator [95 % CI] / Proportion of event pirfenidone/BSC vs. placebo/BSC / p-value / Probability[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	HR 0.78 [0.47; 1.30] 7.8 % vs. 9.8 % p=0.340	Lesser benefit / added benefit not proven
Morbidity		
Dyspnoea (as per UCSB Shortness of Breath Questionnaire)	Mean difference: -3 [-6; 1] points p=0.195	Lesser benefit / added benefit not proven
Exercise tolerance (6-minute walk test; responder analysis: deterioration of ≥50 m)	RR 0.74 [0.62; 0.89] 35 % vs. 47 % p=0,001 Probability: indication	Outcome category: non-serious symptoms / late complications $0.80 \leq CI_0 < 0.90$ Added benefit, extent: minor
Need for supplemental oxygen	0.98 [0.68; 1.42] 21 % vs. 21 % p=0.928	Lesser benefit / added benefit not proven
Health-related quality of life		
SGRQ	Mean difference: -1 [-4; 2] point p=0.611	Lesser benefit / added benefit not proven
WHO QoL	Mean difference: 0 [0; 1] points p=0.554	Lesser benefit / added benefit not proven

(continued on next page)

Table 11: Extent of added benefit at outcome level – pirfenidone/BSC vs. placebo/BSC (Continuation)

	Effect estimator [95 % CI] / Proportion of event pirfenidone/BSC vs. placebo/BSC / p-value / Probability[a]	**Derivation of extent**[b]
Adverse events		
Adverse events	RR 1.01 [0.99; 1.03] 99 % vs. 98 % p=0.431	Lesser / greater harm not proven
Serious adverse events	RR 1.04 [0.84; 1.29] 33 % vs. 31 % p=0.709	Lesser / greater harm not proven
Discontinuation due to adverse events	RR 1.71 [1.12; 2.62] RR[c] 0.58 [0.38; 0.895] 15 % vs. 9 % p=0.014 Probability: proof	Outcome category: non-serious / non-severe adverse events CI_0 <0.90 Greater harm, extent: minor
Adverse events affecting the gastrointestinal tract	RR 1.34 [1.20; 1.48] RR[c] 0.75 [0.68; 0.83] 78 % vs. 59 % p<0.001 Probability: proof	Outcome category: non-serious / non-severe adverse events 0.80≤CI_0 <0.90 Greater harm, extent: minor
Adverse events affecting the skin and subcutaneous tissue	RR 1.63 [1.38; 1.92] RR[c] 0.61 [0.52; 0.72] 60 % vs. 37 % p<0.001 Probability: proof	Outcome category: non-serious / non-severe adverse events CI_0<0.80 Greater harm, extent: considerable

a: Probability, if statistically significant differences are present.

b: Estimations of effect size are made depending on outcome category with different limits based on upper limit of the confidence interval (CI_0).

c: Institute calculations, event proportion placebo / pirfenidone (effect direction reversed to enable immediate use of limits).

CI: confidence interval; CI_o: upper limit of confidence interval; HR: hazard ratio; RR: relative risk; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 12 summarizes the results on which the overall conclusion about the extent of added benefit is based.

Table 12: Results accompanying the overall conclusion about the extent of added benefit – pirfenidone/BSC vs. placebo/BSC

Positive Effects	Negative Effects
Indication of a minor added benefit (non-serious symptoms / late complications: exercise tolerance [walking distance])	Proof of greater harm – extent: minor (non-serious / non-severe adverse events: discontinuation due to adverse events)
	Proof of greater harm – extent: minor (non-serious / non-severe adverse events: adverse events affecting the gastrointestinal tract)
	Proof of greater harm – extent: considerable (non-serious / non-severe adverse events: adverse events affecting the skin and subcutaneous tissue)

The overall conclusion about the extent of added benefit must balance the indication of added benefit for the outcome “exercise tolerance” against proof of greater harm for the outcome “discontinuation due to adverse events”, “adverse events affecting the gastrointestinal tract” and “adverse events affecting the skin and subcutaneous tissue”. The aspects to be weighed up against each other have a comparable outcome quality (non-serious / non-severe symptoms and non-serious / non-severe adverse events). The extent of the effect is classed as “minor” for the positive effect and in two cases as “minor” and in one case as “considerable” for the negative effects.

In accordance with § 35a SGB V, an added benefit of orphan drugs is deemed as proven by the fact that they have been approved.

The dossier assessment was undertaken to classify the extent of the added benefit. Since, taken as a whole, the submitted data do not provide an indication of an added benefit of pirfenidone, then on the basis of these data and in accordance with the legal regulations, the extent of the added benefit of pirfenidone is classed as “no proven added benefit”.

2.6 List of studies included

Study PIPF-004

Intermune. A randomized, double-blind, placebo-controlled, phase 3, three-arm study of the safety and efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis: study PIPF-004; clinical study report [unpublished]. 2009.

Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011; 377(9779): 1760-1769.

Study PIPF-006

Intermune. A randomized, double-blind, placebo-controlled, phase 3 study of the safety and efficacy of pirfenidone in patients with idiopathic pulmonary fibrosis; study PIPF-006; clinical study report [unpublished]. 2009.

Noble PW, Albera C, Bradford WZ, Costabel U, Glassberg MK, Kardatzke D et al. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomised trials. Lancet 2011; 377(9779): 1760-1769.

References for English extract (please see full dossier assessment for full reference list)

1) Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computational Statistics and Data Analysis 1994; 17(5): 555-574

2) Institute for Quality and Efficiency in Health Care. Ticagrelor: Benefit assessment according to § 35a Social Code Book V; extract of dossier assessment; Commission No. A11-02 [online]. 29.09.2011 [Accessed on: 14.05.2012]. URL: https://www.iqwig.de/download/A11-02_Extract_of_dossier_assessment_Ticagrelor.pdf

The full report (German version) is published under www.iqwig.de