## TECHNOLOGY REVIEW (MINI-HTA)

# ANTIFIBROTIC FOR TREATMENT OF IDIOPATHIC PULMONARY FIBROSIS

**Malaysian Health Technology Assessment Section (MaHTAS)**
**Medical Development Division**
**Ministry of Health Malaysia**
**006/2020**

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Mini-HTA
INAHTA

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Available online via the official Ministry of Health Malaysia website: http://www.moh.gov.my

**eISSN:**

**SUGGESTED CITATION:** Roza S and Izzuna MMG. Antifibrotic for treatment of Idiopathic Pulmonary Fibrosis. Technology Review. Ministry of Health Malaysia: Malaysian Health Technology Assessment Section (MaHTAS); 2020. 55p. Report No.: 006/2020. eISSN:

**DISCLOSURE:** The author of this report has no competing interest in this subject and the preparation of this report is entirely funded by the Ministry of Health Malaysia.

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## EXECUTIVE SUMMARY

### Background

Idiopathic pulmonary fibrosis (IPF) is a devastating, rapidly fatal lung disease with considerable impact on patients and carers as the disease progresses, characterised by progressive fibrosis of lung interstitium, decreased lung volume and pulmonary insufficiency, with a median survival of three to five years from diagnosis. The condition is more common in males with advancing age. Idiopathic pulmonary fibrosis is classified as a rare disease, designated as an orphan indication by the European Medicines Agency. An annual incidence of three to nine cases per 100,000 population for Europe were reported. In Malaysia, 54 IPF cases were reported from January 2017 to June 2019 in a single centre. A total of 124 patients with IPF were reported from three centers from 2017 to September 2020.Out of this, 80 patients were classified as having mild or moderate IPR (64.5%) with the remaining were having severe IPF. Early and accurate diagnosis is important for a better outcome. While IPF is ultimately fatal, its clinical course is variable and unpredictable, with some patients experiencing a rapid decline in lung function while others progress much more slowly. Prompt treatment of IPF is crucial to preserve individuals' lung function, reducing the risk of acute exacerbations and improving outcomes.

Conventional medication for patients with IPF included glucocorticosteroids or immunosuppressants. N-acetylcysteine and triple therapy (N-acetylcysteine, prednisolone and azathioprine) are not recommended but still being used in clinical practice. The triple therapy was shown to increase the rate of mortality and hospitalisation compared with placebo. Advances in the management of this disease has been transformed with two disease-modifying therapies have been approved in the US, Europe and many other countries, nintedanib and pirfenidone. Nintedanib and pirfenidone were granted orphan drug designation for treatment of rare disease. However, it has been reported that high treatment cost was involved in the use of antifibrotic for treating IPF. No prescription criteria available in selecting different type of antifibrotic to these patients. Earlier, pirfenidone and nintedanib were reported as not registered in the Ministry of Health (MOH) formulary, and needed Director General (DG) of Health approval on a case by case basis. However, recently in November 2019 Nintedanib was listed in the MOH drug formulary leaving Pirfenidone that still requiring DG's approval on a case by case basis. The choice of antifibrotic for IPF patient is as what listed in the formulary. In the case of patients who have contraindication to Nintedanib, or not keen on taking Nintedanib (porcine based element) in Muslim patient, they can opt for Pirfenidone. Hence, this technology review was conducted following a request from the former head of Respiratory Services, Ministry of Health Malaysia to provide the current best scientific evidence on antifibrotic therapy as an available option for patients with IPF in Malaysia.

### Objective/ aim

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of antifibrotic therapy for the treatment of patients with idiopathic pulmonary fibrosis.

**Results and conclusion**

The review included fourteen studies which were consisted of Health Technology Assessment report (one), systematic reviews with network meta-analysis (three), systematic review with meta-anaysis (three), randomised controlled trials (three), cohort studies (two) and cost-effectiveness analysis (one).The included articles were published between 2014 and 2018. Most of the studies were multinational studies, conducted in countries such as France, Italy, US, UK, Germany, Japan followed by studies conducted in China, US, as well as UK for cost-effectiveness analysis. This review included a total of 9,147 participants enrolled from all the studies. Sample size for each of the included studies ranged from 66 to 1,247 participants. The longest follow-up of the included study was up to seven years. Most of the study participants were patients with mild to moderate IPF with baseline FVC predicted of at least 50%.

**Effectiveness**

Based on the above review, there was sufficient good level of evidences on pirfenidone and nintedanib to be used in the treatment of patients with IPF. Evidence demonstrated that pirfenidone and nintedanib were effective in improving FVC from baseline and slowing rate of FVC decline, compared to placebo in adult patients with IPF. Pirfenidone was effective in lowering risk of decline in percent predicted FVC of ≥10% over one year, compared to placebo in these patients.

- In patients with IPF, pirfenidone and nintedanib showed improvement in FVC from baseline, compared to placebo after one year [pirfenidone versus placebo, mean difference (MD) was 0.12 litre (L) (95%credible interval (CrI) 0.03, 0.22 L), and nintedanib versus placebo, MD was 0.11 L (95%CrI 0.00, 0.22L).
- Both pirfenidone and nintedanib significantly slowed the rate of FVC decline compared to placebo (OR 0.62, 95%CrI 0.52, 0.74) and OR 0.4 (95%CrI 0.34, 0.51) respectively.
- Patients treated with pirfenidone had lower risk of experiencing a decline in percent predicted FVC of ≥10% over one year (OR=0.58, 95%CrI 0.40, 0.88) whereas there was no significant difference between nintedanib and placebo (OR=0.65, 95%CrI 0.42, 1.02).

Pirfenidone demonstrated treatment benefit for mortality outcomes (all-cause and other mortality outcomes; IPF-related mortality, treatment-emergent all-cause mortality, and treatment-emergent IPF-related mortality), progression free survival (reduce risk of disease progression at one year), change from baseline to one year in six-minute walk distance(6MWD)(reducing proportion of patients with a ≥ 50m decline in 6MWD) and dyspnoea (fewer patients in the pirfenidone group experienced a ≥ 20-point increase in the UCSD SOBQ score or death at one year), compared with placebo.

Nintedanib demonstrated benefit in reducing rate of acute exacerbation compared to placebo.

**Safety**

Pirfenidone was approved by the European Medicines Agency for the treatment of mild-to-moderate idiopathic pulmonary fibrosis, approved in several countries (Japan,India, China, United States). Nintedanib was approved by the United States Food and Drug Administration for use in IPF, and approved in the EU, Canada, Japan, Switzerland, and few other countries. Long term treatment with pirfenidone or nintedanib was reported as safe and generally well tolerated with gastrointestinal and skin related events were commonly reported adverse

events following pirfenidone, of which were mostly mild to moderate, while diarrhoea is the most common adverse event reported following nintedanib use.

**Economic evaluation/cost-effectiveness analysis**

In a cost-effectiveness analysis conducted in UK, the ICER ranged from £132,658 to £145,310 per QALY gained for nintedanib and £172,198 to £190,146 per QALY gained for pirfenidone, compared with BSC. In the base case deterministic pairwise comparison with pirfenidone, nintedanib was found to have fewer acute exacerbations and resulted in less cost and more QALY gained. The cost effectiveness acceptability curve showed nintedanib dominates pirfenidone at any threshold level. Adequate informed consent should be obtained prior pirfenidone or nintedanib administration, and sufficient education to patients is required.

In Malaysia, a total of 124 patients with IPF were reported since 2017 to September 2020 from three centers (National Respiratory Institute, Hospital Serdang and Hospital Taiping). Out of this, 80 patients were classified as having mild or moderate IPR (64.5%) with the remaining were having severe IPF. The number of mild or moderate IPR cases by year reported from these centers were 18(2017), 22(2018), 24(2019) and 16(2020), respectively with average of 20 cases reported per year. Estimated annual treatment cost of patients with IPF using pirfenidone is RM 50,880, and using nintedanib is RM42,000. Hence, considering this figures, estimated annual treatment cost of using nintedanib or pirfenidone is between RM840,000 to RM1,017,600 for mild or moderate IPF patients in Malaysia. However this estimation is limited by the unavailability of data on number of patients requiring pirfenidone such as those contraindicated to nintedanib

**Methods**

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2020), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2020), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2020), EBM Reviews-Health Technology Assessment (1st Quarter 2020), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2020). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits were applied to the search. The last search was run on 31 March 2020. Additional articles were identified from reviewing the references of retrieved articles. One of the tools used to assess the risk of bias and methodological quality of all the articles retrieved is the Critical Appraisal Skills Programme (CASP) checklist. All full text articles were then graded based on guidelines from the U.S./Canadian Preventive Services Task Force.

## TABLE OF CONTENTS

## ABBREVIATION

| | |
|---|---|
| ADR | Adverse dug reaction |
| ATP | Adenosine Triphospate |
| CI | Confidence Interval |
| CrI | Credible Interval |
| CT | Computed Tomography |
| DLCO | diffusing capacity of lung for carbon monoxide |
| FVC | Forced Vital Capacity |
| HR | Hazard Ratio |
| HRCT | High Resolution Computed Tomography |
| HRQOL | Health related quality of life |
| IPF | Idiopathic Pulmonary Fibrosis |
| IQR | Interquartile Range |
| MOH | Ministry of Health |
| NAC | N-Acetylcysteine |
| nMA | network meta-analysis |
| nRTK | non Receptor Tyrosine Kinases |
| PCA | Percutaneous cryoablation |
| PEY | person exposure years |
| PFS | Progression Free Survival |
| PGDF | Platelet Derived Growth Factor |
| QOL | Quality of Life |
| RCT | Randomised controlled trial |
| RR | Relative risk |
| RTK | Receptor Tyrosine Kinases |
| SADR | Serious Adverse Drug Reaction |
| SE | Standard Error |
| SR | Systematic review |
| TE-IPF | Treatment-Emergent Idiopathic Pulmonary Fibrosis |
| TGF | Transforming Growth Factor |
| TNF | Tumour necrosis factor |
| UCSD SOBQ | University of California San Diego Shortness of Breath Questionnaire |
| VC | Vital capacity |
| VEGF | Vascular Endothelial Growth Factor |
| vs | versus |
| WMD | Weighted mean difference |
| 6MWD | Six Minute Walking Distance |

## 1.0 BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a devastating, rapidly fatal lung disease with considerable impact on patients and carers as the disease progresses. [1] It is characterised by progressive fibrosis of lung interstitium, decreased lung volume and pulmonary insufficiency, occurring primarily in older adults, with a median survival of three to five years from diagnosis.[2] Idiopathic pulmonary fibrosis (IPF) is the most common of idiopathic interstitial pneumonia, distinguished from other interstitial lung disease by combination of clinical, radiological and histological finding.[3] Healthy tissue is replaced by altered extracellular matrix and alveolar architecture is destroyed, which leads to decrease lung compliance, disrupted gas exchange, and ultimately respiratory failure and death.[4]

The epidemiology of IPF shows the condition to be more common in males and with advancing age.[5] An annual incidence of three to nine cases per 100,000 population for Europe were reported.[6] In Malaysia, 54 IPF cases were reported from January 2017 to June 2019 in a single centre. A total of 124 patients with IPF were reported from three centers from 2017 to September 2020.Out of this, 80 patients were classified as having mild or moderate IPR (64.5%) with the remaining were having severe IPF. Mean age of diagnosis was 67 years of which 46% and 50% were former and never smokers respectively. The country needs to prepare for the emerging of IPF as the country reach ageing nation in the next ten years.[7] Idiopathic pulmonary fibrosis (IPF) is classified as a rare disease, designated as an orphan indication by the European Medicines Agency.[8] However, the annual per capita cost of patients with IPF in North America was estimated around US$20,000, 2.5 to 3.5 higher than the national healthcare expenditure.[9]

The diagnosis of IPF requires the following: (i) Exclusion of other known causes of Interstitial Lung Disease (e.g., domestic and occupational environmental exposures, connective tissue disease, and drug toxicity). (ii)The presence of a usual interstitial pneumonia (UIP) pattern on high-resolution computed tomography (HRCT) in patients not subjected to surgical lung biopsy. (iii) Specific combinations of HRCT and surgical lung biopsy pattern in patients subjected to surgical lung biopsy.[10] Early and accurate diagnosis is important to maximise the potential for a better outcome. Idiopathic pulmonary fibrosis (IPF) is a difficult condition to manage particularly in the latter stage.[11] While IPF is ultimately fatal, its clinical course is variable and unpredictable, with some patients experiencing a rapid decline in lung function while others progress much more slowly. [10] Prompt treatment of IPF is crucial to preserving individuals' lung function, reducing the risk of acute exacerbations and improving outcomes.[12]

In addition to antifibrotic therapies, patients may benefit from holistic approach of care including pulmonary rehabilitation, symptom management, education and support, management of co-morbidities, supplemental oxygen for those with hypoxaemia, tailored palliative care, and lung transplantation for minority of patients. [12,13]

Conventional medication for patient with IPF included glucocorticosteroids or immunosuppressants. N-acetylcysteine and triple therapy (N-acetylcysteine, prednisolone and azathioprine) are not recommended but still being used in clinical practice.[14] The triple therapy was shown to increase the rate of mortality and hospitalisation compared with placebo.[15] Advances in the understanding of its pathogenesis and management of this disease has been transformed with two disease-modifying therapies have been approved in

the US, Europe and many other countries, nintedanib and pirfenidone.[4,12] Nintedanib and pirfenidone were granted orphan drug designation for treatment of rare disease (IPF).[16] The new treatments offer new hope for patients and carers.

However, it has been reported that high treatment cost was involved in the use of antifibrotic for treating IPF. No prescription criteria available in selecting different type of antifibrotic to these patients. Earlier, pirfenidone and nintedanib were reported as not registered in the Ministry of Health (MOH) formulary, and needed the Director General (DG) of Health approval on a case by case basis. However, recently in November 2019 Nintedanib was listed in the MOH drug formulary leaving Pirfenidone that still requiring DG's approval on a case by case basis. The choice of antifibrotic for IPF patient is as what listed in the formulary. In the case of patients who have contraindication to Nintedanib, or not keen on taking Nintedanib (porcine based element) especially among Muslim patient, they can opt for Pirfenidone. Hence, this technology review was conducted following a request from the former head of Respiratory Services, Ministry of Health Malaysia to provide the current best scientific evidence on antifibrotic therapy as an available option for patients with IPF in Malaysia.

## 2.0 OBJECTIVE / AIM

The objective of this technology review is to assess the effectiveness, safety and cost-effectiveness of antifibrotic therapy in the treatment of IPF.

## 3.0 TECHNICAL FEATURES

### 3.1 Pirfenidone

Pirfenidone or Esbriet, Pirespa, Etuary (trade names) is a medication used for the treatment of idiopathic pulmonary fibrosis. It works by reducing lung fibrosis through downregulation of the production of growth factors and procollagens I and II. In Europe, pirfenidone is indicated for the treatment of mild-to-moderate IPF. It was approved by the European Medicines Agency in 2011. In October 2008, it was approved for use in Japan, in India in 2010, and in China in 2011 (commercial launch in 2014). In October 2014, it was approved for sale in the United States. In Mexico it has been approved on a gel form for the treatment of scars and fibrotic tissue and has proven to be effective in the treatment of skin ulcers.[17]

#### Pharmacodynamic / Mechanism of action

Pirfenidone belongs to immunosuppressants or other immunosuppressants in pharmacotherapeutic group according to EMA. The mechanism of action of pirfenidone has not been fully established. However, existing data suggest that pirfenidone exerts both antifibrotic and anti-inflammatory properties in a variety of in vitro systems and animal models of pulmonary fibrosis (bleomycin- and transplant-induced fibrosis).[18]

Idiopathic Pulmonary Fibrosis (IPF) is a chronic fibrotic and inflammatory pulmonary disease affected by the synthesis and release of pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α) and interleukin-1-beta (IL-1β) and pirfenidone has been shown to reduce the accumulation of inflammatory cells in response to various stimuli.[18]

Pirfenidone attenuate fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and increase biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as, transforming growth factor-beta (TGF-β) and platelet-derived growth factor (PDGF).[18]

A number of cell-based studies have shown that pirfenidone reduces fibroblast proliferation, inhibits transforming growth factor beta stimulated collagen production and reduces the production of fibrogenic mediators such as transforming growth factor beta.[19] Pirfenidone has also been shown to reduce production of inflammatory mediators such as tumor necrosis factor alpha and IL-1β in both cultured cells and isolated human peripheral blood mononuclear cells.[20]

## Pharmacokinetics

Chemical formula for pirfenidone is C12H11NO (Figure 1). Pirfenidone or Esbriet, Pirespa, Etuary (trade names) is available as Esbriet 267 mg film-coated tablets, Esbriet 534 mg film-coated tablets Esbriet and 801 mg film-coated tablet in pharmaceutical form. Treatment with Esbriet should be initiated and supervised by specialist physicians experienced in the diagnosis and treatment of IPF. Upon initiating treatment, the dose should be titrated to the recommended daily dose of 2403 mg/day over a 14 days period as follows:

- Days 1 to 7: a dose of 267 mg administered three times a day (801 mg/day)
- Days 8 to 14: a dose of 534 mg administered three times a day (1602 mg/day)
- Day 15 onward: a dose of 801 mg administered three times a day (2403 mg/day)

According to EMA, the recommended maintenance daily dose of Esbriet is 801 mg three times a day with food for a total of 2403 mg/day

Pirfenidone is administered orally. Though the presence of food significantly reduces the extent of absorption, the drug is to be taken after food, to reduce the nausea and dizziness associated with the drug. The drug is around 60% bound to plasma proteins, especially to albumin. Elimination half life of pirfenidone is 2.4 hours. Up to 50% of the drug is metabolised by hepatic CYP1A2 enzyme system to yield 5-carboxypirfenidone, the inactive metabolite. Almost 80% of the administered dose is excreted in the urine within 24 hours of intake.[18]


Figure 1: Pirfenidone chemical formula (left) and physical form (right)

## 3.2 Nintedanib

Nintedanib is marketed under the brand names Ofev and Vargatef. Ofev is an oral medication used as a treatment for IPF whereas Vargatef is used in combination with docetaxel for the treatment of adult patients with locally advanced, metastatic or locally recurrent non-small cell lung cancer (NSCLC) of adenocarcinoma tumour histology after first-line chemotherapy. The brand name Ofev is used for marketing in IPF. [21]

### Pharmacodynamic / Mechanism of action

It is a small molecule that inhibits multiple receptor tyrosine-kinases (RTK) and non-receptor tyrosine kinases (nRTK). Nintedanib inhibits the following RTK; vascular endothelial growth factor (VEGF) receptor 1-3, fibroblast growth factor (FGF) receptor 1-3, platelet derived growth factor (PDGF) receptor ά and ß and fms-like tyrosine kinase-3(FLT3). Among them, FGF, PDGF and VEGF have been implicated in the pathogenesis of IPF. It binds competitively to the Adenosine Triphospate (ATP) binding pocket of these receptors, block intracellular signalling crucial for processes like fibroblast proliferation, migration and transformation of fibroblast.[22]

Nintedanib competitively inhibits both nonreceptor tyrosine kinases (nRTKs) and receptor tyrosine kinases (RTKs). The nRTK targets of nintedanib include Lck, Lyn, and Src kinases.[23]

### Pharmacokinetic

The chemical formula of nintedanib is C31H33N5O4 (Figure 2). Only a small percentage of orally taken nintedanib is absorbed in the gut, partially due to transport proteins (such as P-glycoprotein) moving the substance back into the lumen. Combined with a high first-pass effect, this results in an oral bioavailability of about 4.7% with a 100mg tablet.The drug reaches peak plasma levels in 2 to 4 hours after oral intake in the form of a soft gelatin capsule. Elimination half-life is ten to 15 hours.(Product monograph) Nintedanib (ofev) for oral administration are available in 150mg and 100mg capsules. The recommended dosage is 150mg twice daily. [24]

Nintedanib is mainly inactivated by esterases that cleave the methyl ester, resulting in the free carboxylic acid form, which is then glucuronidated by uridinediphosphate-glucuronosyltransferases and excreted mostly via the bile and faeces. No relevant cytochrome P450 mediated metabolism has been observed.[21]

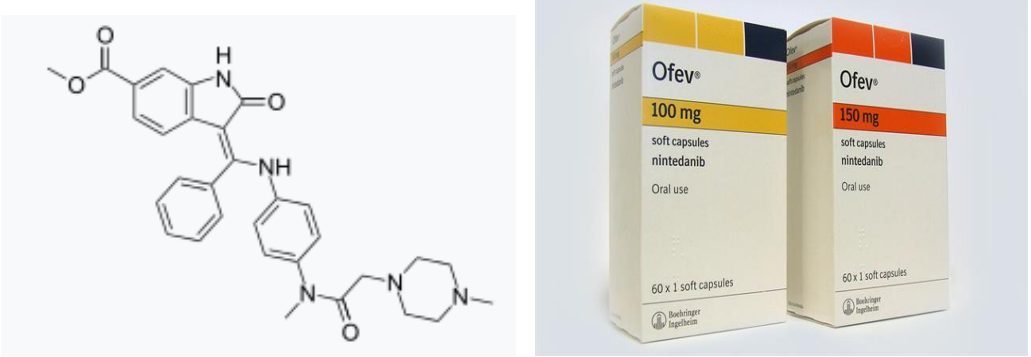


Figure 2: Nintedanib structural formula (left) and physical form (right)

## 4.0 METHODS

### 4.1 SEARCHING

Electronic databases searched through the Ovid interface:

- MEDLINE(R) In-Process and Other Non-Indexed Citations and Ovid MEDLINE (R) 1946 to present
- EBM Reviews – Cochrane Central Registered of Controlled Trials – March 2020
- EBM Reviews – Database of Abstracts of Review of Effects – 1st Quarter 2020
- EBM Reviews – Cochrane Database of Systematic Reviews – 2005 to March 2020
- EBM Reviews – Health Technology Assessment – 1st Quarter 2020
- EBM Reviews - NHS Economic Evaluation Database - 1st Quarter 2020

Other databases:

- PubMed
- Horizon Scanning database (National Instutute of Health research (NIHR) Innovation Observatory, Euroscan International Network)
- Other websites: US FDA, INAHTA, MHRA

General databases such as Google and Yahoo were used to search for additional web-based materials and information. Additional articles retrieved from reviewing the bibliographies of retrieved articles or contacting the authors. The search was limited to articles on human, and systematic review and randomized controlled trial in the design. There was no language limitation in the search. Appendix 1 showed the detailed search strategies. The last search was conducted on the 31 March 2020.

### 4.2 SELECTION

A reviewer screened the titles and abstracts against the inclusion and exclusion criteria and then evaluated the selected full-text articles for final article selection. The inclusion and exclusion criteria were:

**Inclusion criteria**

| | |
|---|---|
| Population | Patients with idiopathic pulmonary fibrosis, idiopathic lung fibrosis |
| Interventions | antifibrotic, antifibrotic therapy, pirfenidone, nintedanib, ofev |
| Comparators | N-acetylcysteine, conventional therapy, best supportive care, placebo |
| Outcomes | forced vital capacity (FVC), decline in percent predicted FVC, change in six minutes walking distance (6MWD), (change in health related quality of life (QoL), mortality (all cause mortality, IPF related mortality), progression free survival (PFS), acute exacerbation, adverse events, complications |
| Study design | Systematic reviews (SR), randomised control trials (RCTs), observational studies |
| Type of publication | English, full text articles |

**Exclusion criteria**

| | |
|---|---|
| Study design | Case report, survey, anecdotal, animal studies |
| Type of publication | Non-English |
| Intervention | Other pharmacological antifibrotic therapy such as N-acetylcysteine, azathioprine, prednisolone, thalidomide |

Relevant articles were critically appraised using Critical Appraisal Skills Programme (CASP) checklist and evidence graded according to the US/Canadian Preventive Services Task Force (See Appendix 2). Data were extracted from included studies using a pre-designed data extraction form (evidence table as shown in Appendix 6) and presented qualitatively in narrative summaries. No meta-analysis was conducted for this review.

## 5.0 RESULTS

A total of 822 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2020), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2020), EBM Reviews-Database of Abstracts of Review of Effects (1st Quarter 2020), EBM Reviews-Health Technology Assessment (1st Quarter 2020), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2020) and PubMed.

Thirty-eight articles were identified from references of retrieved articles. After removal of 38 duplicates, 784 titles were screened. A total of 232 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 552 abstracts were found to be irrelevant. Fifty-eight potentially relevant abstracts were retrieved in full text. After applying the inclusion and exclusion criteria and critical appraisal to the 22 full text articles, 14 full text articles were included and 8 full text articles were excluded. (Figure 3). The review included fourteen studies which were consisted of Health Technology Assessment report (one), systematic reviews with network meta-analysis (three), systematic review with meta-analysis (three), RCT (three), cohort studies (three) and cost-effectiveness analysis (one).

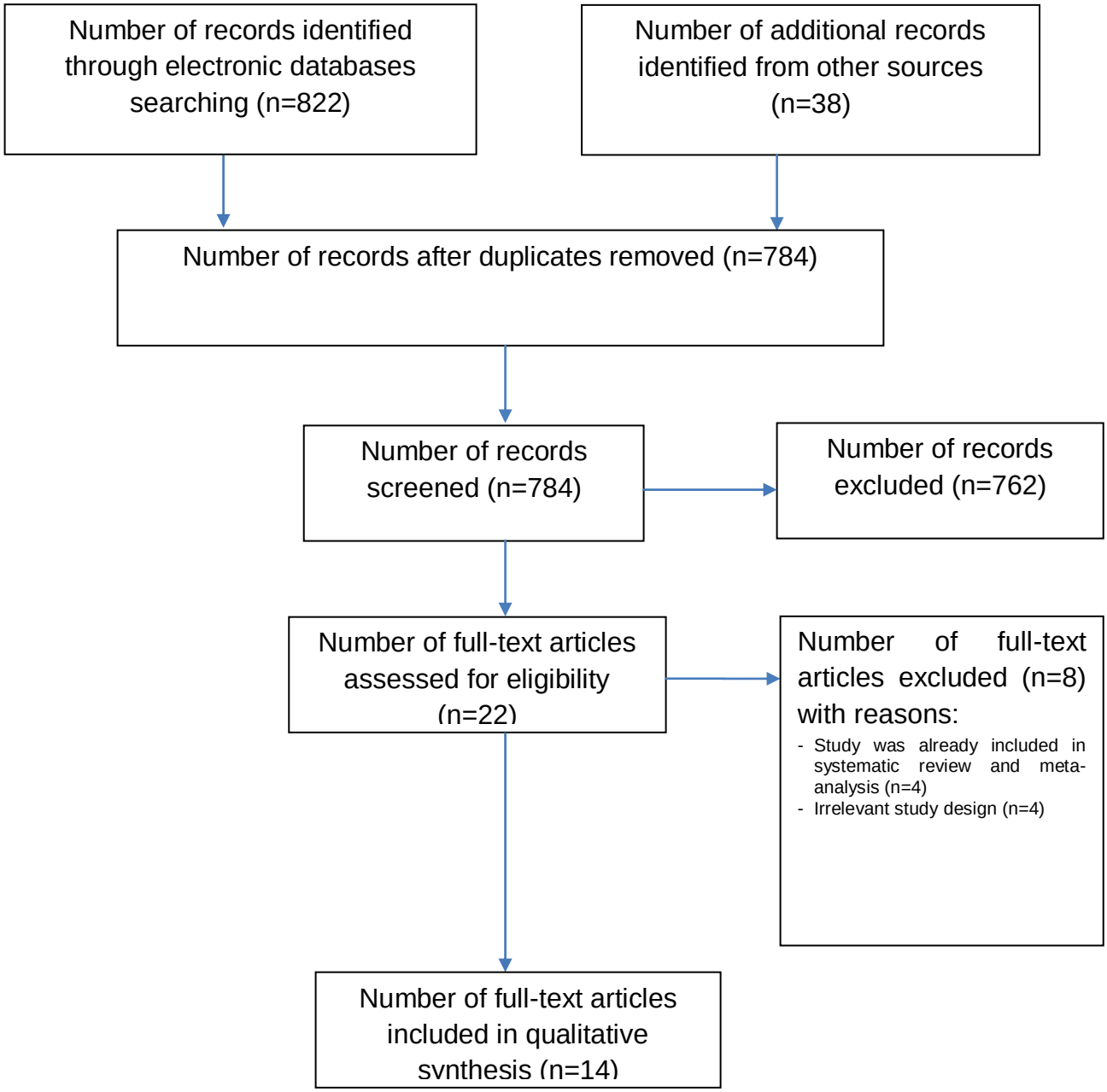


Figure 3: Flow chart of study selection

Of the 14 included articles in this review, ten studies were included in the effectiveness section, five studies were in the safety and one study was in the cost-effectiveness section.

The included articles were published between 2014 and 2018. Most of the studies were multicountry studies, conducted in countries such as France, Italy, US, UK, Germany, South Korea, Japan followed by studies conducted in China, US, as well as UK for cost-effectiveness analysis.

This review included a total of 9,147 participants enrolled from all the studies. Sample size for each of the included studies ranged from 66 to 1,247 participants. The longest follow-up of the included study was up to seven years. Most of the study participants were patients with mild to moderate IPF with baseline FVC predicted of at least 50%.

## 5.1 RISK OF BIAS / QUALITY ASSESSMENT OF INCLUDED STUDIES

The quality of the studies included in this review was assessed using selected domain based on CASP checklist, except for RCT where Cochrane Risk of Bias 2.0 was used. The results were illustrated in the figure as below.(Figure 4).

| Criteria assessed | Authors look for the right type of papers? | Selection of studies (all relevant studies included?) | Assessment of quality of included studies? | If the results of the review have been combined, is it reasonable to do so (heterogeneity)? |
|---|---|---|---|---|
| Noble et.al.2016 [27] | + | + | ? | ? |
| Nathan et al. 2016 [29] | + | + | ? | + |
| Richeldi et al 2016 [31] | + | + | ? | ? |

Figure 4a: Assessment of risk of bias of systematic review (CASP)

| Criteria assessed | Adequate sequence generation | Allocation concealment | Blinding of participants and personnel | Incomplete outcome data addressed | Free of selective reporting | Free of other bias |
|---|---|---|---|---|---|---|
| Vancheri et al.2017 [33] | + | ? | ? | + | + | ? |
| Crestani et al.2018 [35] | + | ? | - | + | + | ? |
| Huang et al.2015 [28] | + | ? | - | + | + | ? |

Figure 4b: Assessment of risk of bias of RCT (Cochrane)

| Criteria assessed | Selection of cohort | Exposure accurately measured | Outcome accurately measured | Confounding factors | Follow-up of subjects |
|---|---|---|---|---|---|
| Ley et al.2017 [30] | + | + | + | ? | + |
| Cottin et al.2018 [34] | + | + | + | ? | + |
| Valeyre et al.2014 [36] | + | + | + | ? | + |

Figure 4c: Quality assessment of cohort studies (CASP)

| Criteria assessed | Rinciog et al. 2017 |
|---|---|
| A well-define question posed? | + |
| Comprehensive description of competing alternative given? | + |
| Effectiveness established? | + |
| Effects of intervention identified, measured and valued appropriately? | + |
| All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly? | + |
| Costs and consequences adjusted for different times at which they occurred (discounting)? | + |
| Results of the evaluation? | + |
| Incremental analysis of the consequences and costs of alternatives performed? | + |
| Sensitivity analysis performed? | + |

Figure 4d: Assessment of risk of bias of economic evaluation (CASP)

## 5.2 EFFECTIVENESS

There were ten studies retrieved on the effectiveness of antifibrotic (pirfenidone and nintedanib) in the treatment of IPF consisted of six systematic review with meta analysis or network meta-analysis, three RCTs and one HTA report.

### 5.2.1 Disease progression (FVC% predicted, six-minute walking distance, progression free survival)

Fleetwood et al. (2017) conducted a systematic review (SR) and network meta-analysis (nMA) to compare the efficacy of treatments for IPF. The SR was conducted in 2015 including phase II and III RCT in adults with IPF, reporting the effectiveness of pirfenidone, nintedanib, N-acetylcysteine (NAC) or triple therapy. Systematic search was conducted in 2011 and updated in 2015 in these databases (MEDLINE, EMBASE, the Cochrane Library and PubMed), conference proceeding and previous SR. Risk of bias in the RCT was assessed using quality assessment approach suggested in the NICE single technology appraisal guidance, which is almost similar to the Cochrane risk of bias tool. A Bayesian nMA was used to compare pirfenidone, nintedanib and

NAC with respect to forced vital capacity (FVC) and mortality. Two networks were developed, base-case network included phase III trials of pirfenidone, nintedanib and NAC while extended network also included phase II and triple therapy. The nMA included nine studies (seven phase III and two phase II RCT). The network was limited to study arms investigating the approved doses of pirfenidone (1800 or 2403 mg/day) and nintedanib (300 mg/day). The studies varied in study length and time points where outcome were measured, from 32 weeks to 72 weeks, with majority trials reporting at 52 weeks.

They found for change from baseline in FVC, pirfenidone and nintedanib were more effective than placebo after one year [pirfenidone versus placebo, mean difference (MD) was 0.12 litre (L), 95% credible interval (CrI): 0.03, 0.22 L), and nintedanib versus placebo, MD was 0.11 L, (95% CrI 0.00, 0.22 L). There was no significant difference in the mean effect for change from baseline in FVC for NAC compared with placebo (MD was 0.01 L, 95% CrI -0.15, 0.17 L). (Figure 5a)

Patients treated with pirfenidone also had lower risk of experiencing a decline in percent predicted FVC of ≥10% over one year (OR=0.58, 95% CrI: 0.40, 0.88), whereas there was no significant difference between nintedanib and placebo (OR=0.65, 95% CrI: 0.42, 1.02), as shown in Figure 5b. [25 level I]

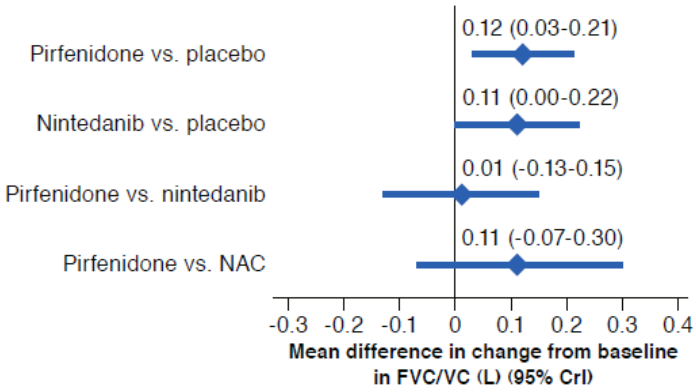


Figure 5a: Result of the principal analyses: forest plot for change from baseline in FVC/VC (L)

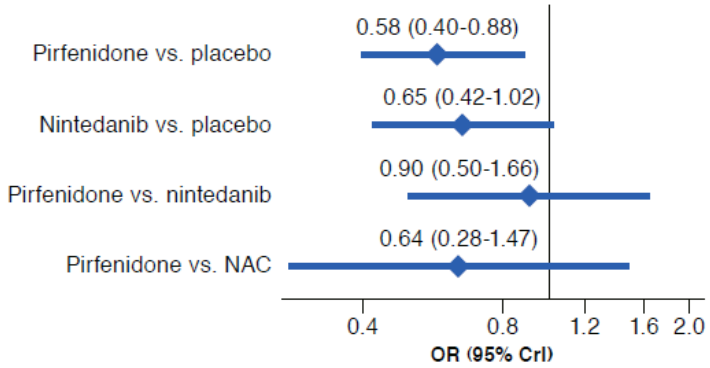


Figure 5b: Forest plot for 10% reduction in FVC/VC

Loveman E et al. (2015) also conducted a SR with network meta analysis (nMA) and indirect comparison to investigate the effectiveness of treatments for IPF. They searched MEDLINE, EMBASE and the Cochrane library for relevant studies until May 2014. This is an update of HTA assessing clinical and cost effectiveness of treatments for IPF, published in 2015. They identified RCTs that included participants with confirmed diagnosis of IPF. Interventions were NAC alone or in combination, pirfenidone or nintedanib, assessing outcomes measuring indices of lung function/capacity, exercise performance, quality of life and adverse events. Data was synthesised narratively and using a Bayesian nMA. Predefined process for selecting references, extracting data and assessing study quality were applied. The nMA included 11 studies (five on pirfenidone, three on NAC, and three on nintedanib).The nMA combines evidence from trials comparing different sets of treatment that form a connected evidence network through common comparators (placebo), where randomised evidence between all relevant comparators is unavailable. The nMA was performed in WinBUGS using adapted code, and fixed effect model was used. For FVC measures, a standardised mean difference (SMD) approach was used and converted to OR for interpretation. They included 11 studies of similar population and good overall quality. Participants were patients with mild to moderate IPF, with baseline FVC ranging from 68% to 89% of predicted values, around 64 to 68 years old and mostly men. Ratio of forced expiratory volume (FEV) was not consistently reported across the studies. Treatment duration ranged from eight to 16 months, with majority follow up was until 12 months. The result demonstrated only two treatments, pirfenidone (OR 0.62, 95% CrI: 0.52, 0.74) and nintedanib (OR 0.41, 95% CrI: 0.34, 0.51) produced a statistically significant slowing in the rate of FVC decline compared with placebo.(Figure 6a). In an indirect comparison, nintedanib is significantly better than pirfenidone in slowing FVC decline (OR 0.67, 95% CrI: 0.51, 0.88). For acute exacerbation, both nintedanib and pirfenidone have favourable point estimates however only the OR for nintedanib achieve significance (OR 0.50, 95% CrI: 0.31, 0.79).(Figure 6b) The nMA OR for all-cause mortality compared with placebo showed that both pirfenidone and nintedanib had favourable point estimates, however only pirfenidone was statistically significant (OR 0.50, 95% CrI: 0.29, 0.84) as shown in Figure 6c. In indirect comparison pirfenidone is associated with lower odds of all-cause mortality, compared to nintedanib but was not statistically significant (OR 1.39, 95% CrI: 0.70, 2.82). They concluded two treatments show beneficial effect, and when compared indirectly nintedanib appears to have superior benefit on FVC. Limitation to indirect comparison should be considered when interpreting these results. [26 level I]

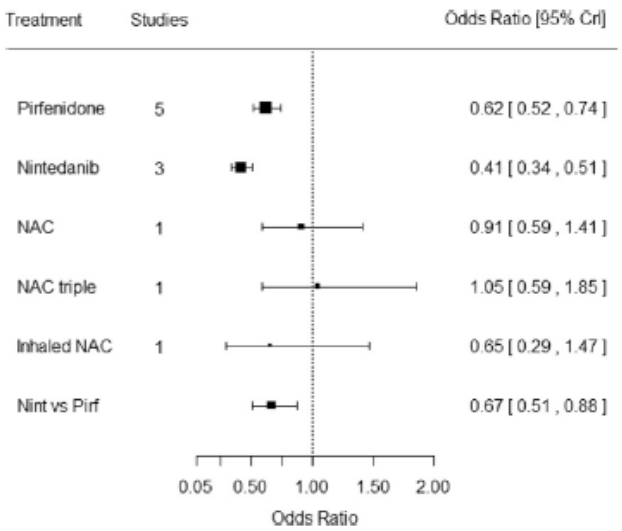


Figure 6a: Result of the nMA for FVC decline

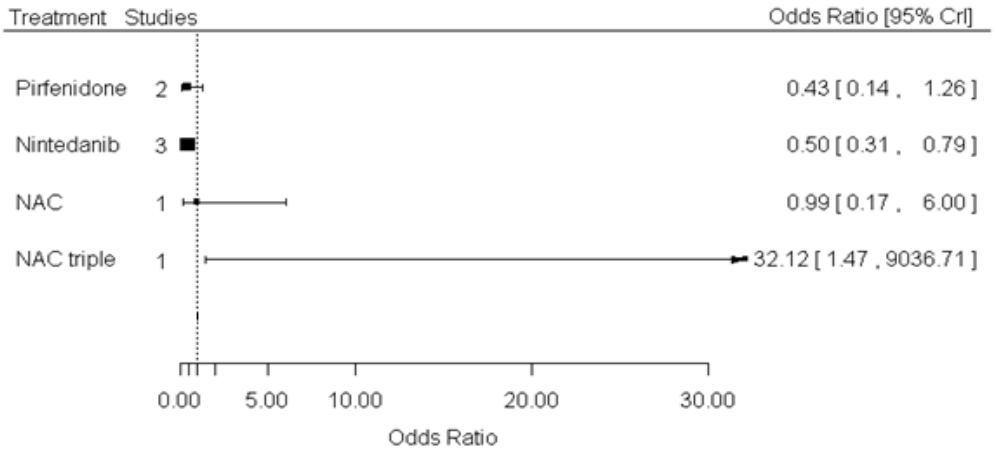


Figure 6b: Result of the nMA for acute exacerbation

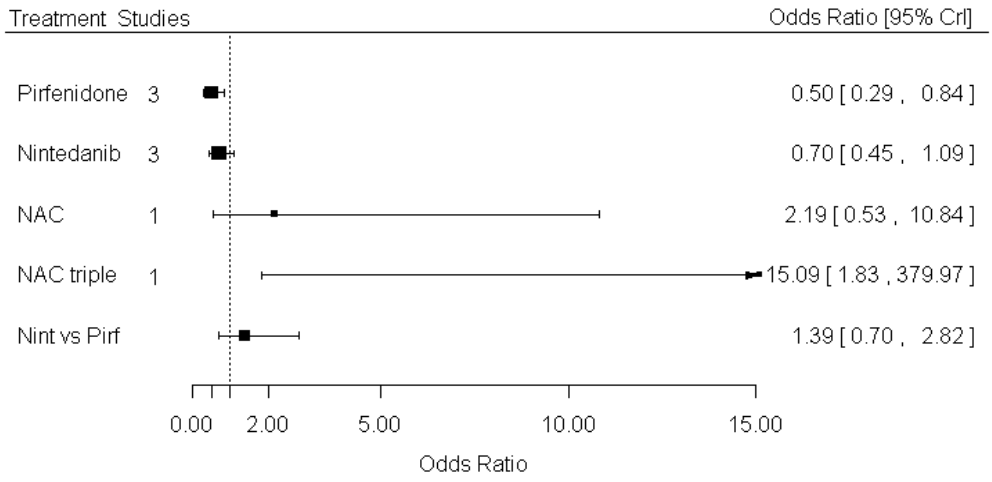


Figure 6c: Result of the nMA for all-cause mortality

Loveman E et al. (2014) earlier had conducted SR, nMA and economic evaluation on the effectiveness and cost-effectiveness of treatments for IPF. This SR included RCT, controlled clinical trials, economic evaluation and health related quality of life (HRQOL) studies assessing clinical effectiveness, quality of life and cost-effectiveness of pharmacological and non-pharmacological treatments of IPF. Patients with IPF were eligible participants. Best supportive care, placebo or any of the intervention was eligible as comparator. Outcomes of relevant include measures of survival, measures of symptom (cough, breathlessness), HRQOL, lung function, exercise performance, adverse events, and measure of cost and cost-effectiveness. Quality assessment of the studies followed Cochrane risk of bias tool (clinical effectiveness) and Drummond and colleagues (cost-effectiveness). Systematic search was done from bibliographic databases to July 2013. An advisory group was consulted about the choice of intervention. Two reviewers screened references, extracted data and appraised the study quality. A narrative review was undertaken, and where feasible fixed-effect and random-effect meta-analysis were undertaken including nMA. A decision-analytic Markov model was developed to estimate cost-effectiveness of pharmacological treatment for IPF. The model structure used four distinct health states; unprogressed IPF, progressed IPF, lung transplant, and dead. They included 14 studies in the review (13 RCTs and one CCT), comprised of one on azathioprine, three on NAC (alone or combination), four pirfenidone, one nintedanib, one sildenafil, one thalidomide, two pulmonary rehabilitation and one disease management programme. In ten studies, population was classified as mild to moderate IPF with baseline FVC ranged between 65 and 90%, while four studies included moderate to severe IPF (baseline FVC ranged from 55 to 70%) whereby three out of the four were non-pharmacological intervention studies. Evidence suggested that some effective treatments were available. In nMA only nintedanib and pirfenidone showed statistically significant improvements for slowing the rate of decline in FVC compared to placebo, with OR of 0.68, 95% CrI 0.54, 0.85 (pirfenidone) and OR of 0.38 (95% CrI 0.22, 0.66), respectively. (Table 1)

They concluded pirfenidone and nintedanib offer potential hope for IPF treatment, however their cost-effectiveness is likely to be prohibitive. Few interventions have statistically significant effect, such as nintedanib and pirfenidone, and cost-effective of

treatments is uncertain. Lack of studies on palliative care approaches was identified. Further research on intervention to alleviate symptom of debilitating condition in particular pulmonary rehabilitation and thalidomide, as well as a well conducted RCT on inhaled NAC was suggested.[1 level I]

Table 1: nMA fixed effect results, for slowing the decline in FVC

| Treatment (vs placebo) | No. of studies (n) | Total participants (n) | OR (95%CrI) |
|---|---|---|---|
| Azathioprine | 1 | 19 | 1.56 (0.74 to 3.29) |
| **Nintedanib** | **1** | **170** | 0.38 (0.22 to 0.66) |
| NAC triple therapy | 2 | 294 | 0.94 (0.55 to 1.62) |
| Inhaled NAC | 1 | 76 | 0.66 (0.29 to 1.49) |
| **Pirfenidone** | **4** | **1006** | 0.68 (0.54 to 0.85) |
| Sildenafil | 1 | 180 | 0.89 (0.52 to 1.51) |

Noble et al. (2016) conducted meta analysis on data from three multinational phase III trials to obtain the most precise estimate of magnitude of treatment effect on measures of pirfenidone in disease progression of patients with IPF. All patients randomised to pirfenidone 2403 mg/day or placebo in the CAPACITY or ASCEND studies were included. Study drug was administered in three equally divided doses and escalated to the full dose over two weeks. The CAPACITY trials (study 006 and 004) evaluated efficacy and safety of treatment with pirfenidone for a minimum of 72 weeks, while the ASCEND study (study 016) evaluated pirfenidone for 52 weeks. The pre-specified end-point in all the three trials were change from baseline in percent predicted FVC. Pooled analysis of outcomes were based on the pre-specified endpoints and analytic methods described in the ASCEND study protocol. Primary efficacy outcome was change from baseline to week 52 in FVC% predicted. Secondary efficacy outcome included change from baseline to month 12 in 6MWD, change from baseline to month 12 in dyspnoea and progression-free survival (time to the first occurrence of death or disease progression, defined as a confirmed ≥10% decline in FVC% predicted or confirmed ≥ 50m decline in 6MWD). Safety outcomes were reported as treatment-emergent events, defined as events occurring between baseline and 28 days after the last dose of study drug up to one year. In this study, they analysed a total of 1247 participants (624 randomised to pirfenidone 2403 mg/day and 624 to placebo). Baseline value for FVC% predicted for pooled pirfenidone group and placebo were 71.1% (range 48 to 124) and 70.3% (range 48 to 136), and value for diffusing capacity of the lung for carbon monoxide (DLCO) % predicted were 44.0% (27 to 81) and 44.1% (27 to 170) respectively. They found at one year, pirfenidone reduced the proportion of patients with a ≥10% decline in percent predicted FVC or death by 43.8% (95% CI: 29.3, 55.4%) and increased the proportion of patients with no decline by 59.3% (95% CI: 29.0, 96.8), compared with placebo ($p<0.0001$). The significant treatment benefit was demonstrated at each time point beginning at three months up to 52 weeks. (Figure 5a). The mean change from baseline to one year in FVC was -216ml (pirfenidone) and -363ml (placebo), hence resulting in absolute difference of 148ml, $p<0.001$.

A treatment benefit was also observed for progression free survival, six-minute walk distance (6MWD) and dyspnoea.

In the pooled analysis of change from baseline to one year in 6MWD, pirfenidone reduced the proportion of patients with a ≥50m decline or death by 28.7% (95% CI: 15.1, 40.2) compared with placebo. A total of 153 (24.8%) patients in the pirfenidone group experienced a ≥50m decline in 6MWD or death compared with 214 (34.8%) patients in the placebo group (p<0.001).

Pirfenidone reduced the risk of death or disease progression at one year by 38% compared with placebo (HR 0.62, 95%CI 0.51 to 0.75), as illustrated in Figure 7a.

For dyspnoea outcome, pooled analysis showed that fewer patients in the pirfenidone group compared with placebo experienced a ≥20-point increase in the University of California San Diego Shortness of Breath Questionnaire (UCSD SOBQ) score or death at month 12, a total of 148 (24.0%) patients in the pirfenidone versus 194 (31.4%) patients in the placebo group, relative difference of 23.7% (95% CI: 8.4, 36.4). Figure 7b summarises the overall efficacy results for the measured outcomes. [27 level I]

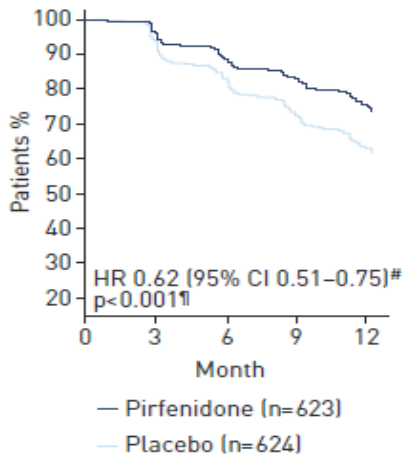


Figure 7a: Progression-free survival for one year. Time to death or disease progression (confirmed ≥10% decline in FVC% predicted or ≥50m decline in 6MWD) [27]

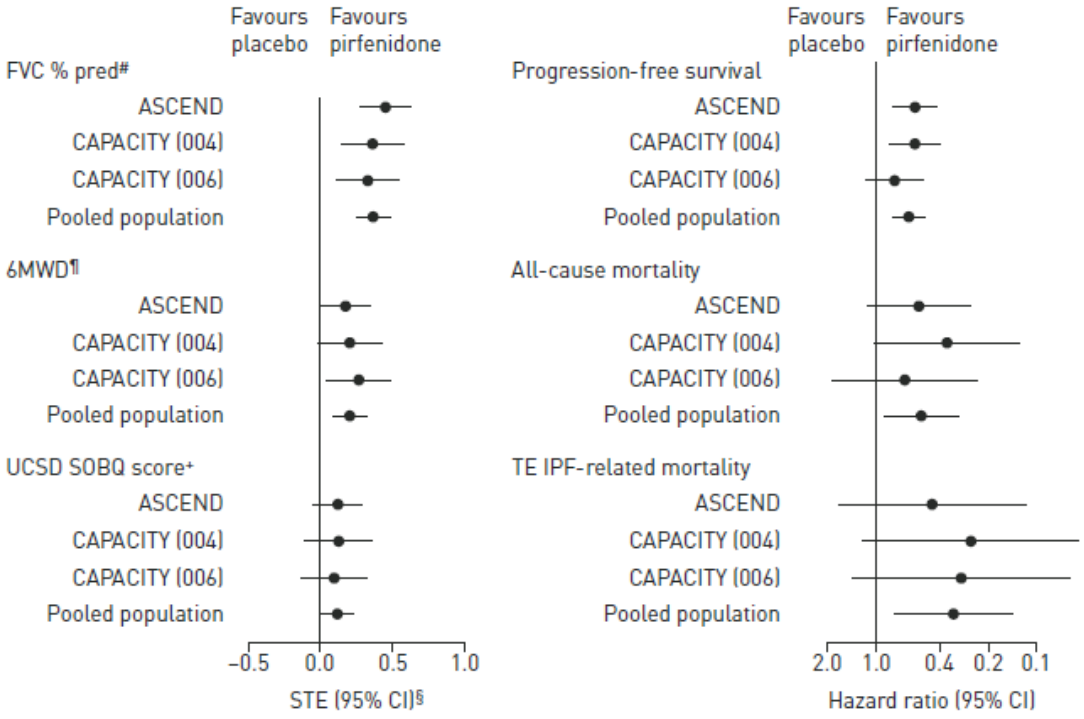


Figure 7b: Summary of clinical efficacy outcomes at one year [27]

FVC: force vital capacity, 6MWD: 6 minute walk distance; UCSD SOBQ: University of California San Diego Shortness of Breath Questionnaire; TE-IPF:Treatment emergent idiopathic pulmonary fibrosis

Assessment of outcomes at the time of the study end point in the respective studies showed magnitude of treatment effect following treatment up to 72 weeks was consistent with magnitude over one year. (Figure 7c, Table 2). [27 level I]

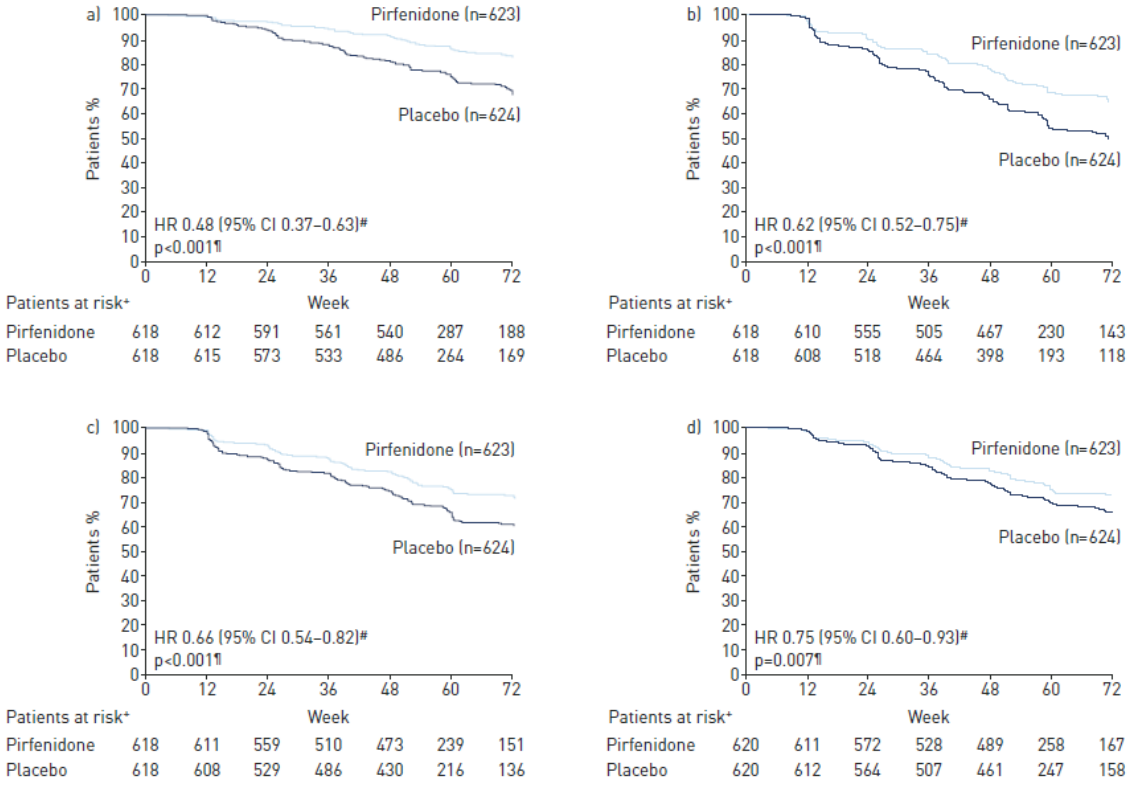


Figure 7c: Kaplan-Meier distribution of measured outcomes in the pooled population up to 72-weeks of treatment [27]

(a) Time to confirmed ≥10% decline in FVC% predicted or death (b) progression free survival (c) Time to confirmed ≥50m decline in 6MWD or death (d) Time to worsening dyspnoea or death

Table 2: Magnitude of treatment effect for measured outcomes following treatment up to 72 weeks compared to placebo [27]

| **Outcome** | **Risk reduction** | **Estimate of effect (HR, 95%CI)** |
|---|---|---|
| ≥10% decline in FVC% predicted or death | 52% | 0.48 (0.37 to 0.63) |
| Risk of death or disease progression | 38% | 0.62(0.52 to 0.75) |
| Risk of a ≥50m decrement in 6MWD or death | 34% | 0.66(0.54 to 0.82) |
| Risk of worsening dyspnoea* or death | 25% | 0.75(0.60 to 0.93) |

*measured by a ≥20point increase in UCSD SOBQ score

Huang et al. (2015) conducted a double blind RCT of pirfenidone in Chinese IPF patients. This study involved 18 to 75 years old patients with IPF, with percentage of predicted FVC of at least 45%, percentage of carbon monoxide diffusing capacity (DLCO) of at least 30% and $PaO_2$ of at least 50 mmHg when the patient is at rest and breathing room air. This double blind, randomised, placebo controlled, multicentre trial

was conducted in five sites in northern China including Beijing, Tianjin and Shenyang. This double blind, modified placebo controlled, randomised phase II trial randomly assigned Chinese IPF patients with mild to moderate impairment of pulmonary function to receive either oral pirfenidone (1800 mg per day) and NAC (1800 mg per day); or placebo and NAC (1800 mg per day) for 48 weeks. All patients were treated with 600mg NAC three times daily, as a baseline treatment. Then random assignment to pirfenidone or placebo (1:1) was done using a modified permuted-block centralized dynamic randomisation method with block size of 4. Dose titration schedule arranged for all patients, (pirfenidone/placebo 200 mg three times a day for the first seven days, 400 mg three times daily for second week and 600 mg (target dose) three times daily for third week onward). A complete blood count, urinalysis, ESR, C-reactive protein, liver, kidney and lipid level, auti-antibody panel were tested. All high-resolution CT scan (HRCT), pulmonary function test, six-minute walk test, arterial blood gas, electrocardiography, dyspnoea and St George Respiratory questionnaire were performed at baseline and at 24-week interval. The primary endpoints were changes in FVC (from baseline to week 48) and walking distance and the lowest $SPO_2$ during the 6-minute walk test (6MWT) at week 48. Secondary endpoint was the progression-free survival time. [28 level I]

They screened 86 patients, and 76 cases were enrolled (pirfenidone and NAC: 38 cases, placebo and NAC: 38 cases). Sixty-six cases completed the study. Age at baseline were 59.03 ± 5.94 (pirfenidone) and 61.61 ±6.39 (placebo). Majority were men at baseline (33/38, 86.8% in pirfenidone group) and 100% (n=38) in placebo group. They found the effect of pirfenidone treatment was significant at the 24$^{th}$ week, but this effect did not persist to the 48$^{th}$ week. At the 24$^{th}$ week, the mean decline in both FVC and $SPO_2$ (%) during the 6MWT in the pirfenidone group was lower than that of control (-0.08 ±0.20L vs -0.22 ± 0.29L, p=0.02, and -3.44% ± 4.51% vs -6.29% ± 6.06%, p=-0.03, respectively). However, there was no significant difference between these two groups, at the 48$^{th}$ week (-0.15 ± 0.25L vs -0.25±0.28L, p=0.11) and -4.25% ±7.27% vs -5.31% ± 5.49%, p=-0.51, respectively. [28 level I]

The pirfenidone treatment group did not achieve the maximal distance difference on the 6MWT at either 24$^{th}$ or 48$^{th}$ week. But pirfenidone treatment prolonged the progression free survival (PFS) time in the IPF patients (HR -1.88, 95% CI: 1.09, 3.24). (Figure 8). They concluded compared with placebo combined with high dose NAC, pirfenidone combined with high dose NAC prolonged the PFS of Chinese IPF patients with mild to moderate impairment of pulmonary function. The percent changes in FVC and $SPO_2$ on the 6MWT were significantly different at 24 week, but did not persist to the 48 week. Further studies involving larger sample size and longer duration are needed to confirm the result regarding the treatment of IPF patients with pirfenidone.[28 level I]

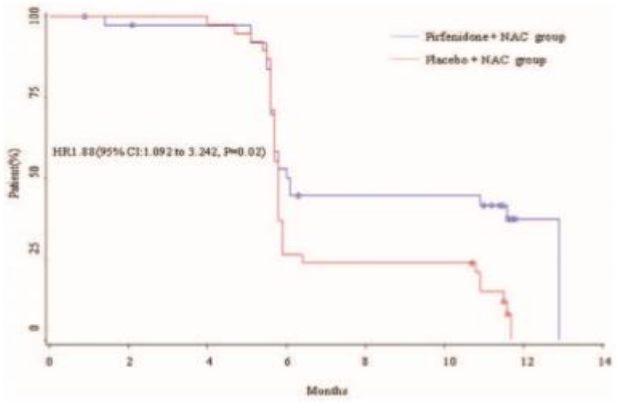


Figure 8: Kaplan-Meier curves for the
duration of progression free survival in the pirfenidone and placebo group

## 5.2.2 Mortality

Fleetwood et al. (2017) in the SR and nMA conducted to compare the efficacy of treatments for IPF found pirfenidone reduced all-cause mortality compared to placebo over one year (Hazard ratio, HR=0.52, 95% CrI 0.28, 0.92). There was no evidence of difference in all-cause mortality between nintedanib and placebo (HR=0.70, 95% CrI: 0.32, 1.55), or NAC and placebo (HR=2.00, 95% CrI: 0.46, 8.62). They concluded that over one year, pirfenidone and nintedanib were effective at reducing lung function decline, and pirfenidone may reduce the odds of experiencing decline in percent predicted FVC of ≥10% compared with placebo in the first year of treatment. The result of their analysis also suggested that pirfenidone improved survival (reduced rate of all-cause mortality, with HR of 0.52) relative to placebo as shown in Figure 9.[25 level I]

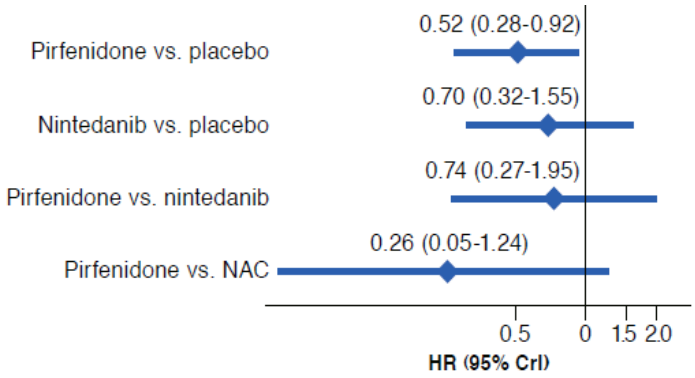


Figure 9: Forest plot for all-cause mortality at 52 weeks [25]

Nathan et al. (2016) conducted a meta analysis of clinical trials in IPF on the effect of pirfenidone on mortality. A meta analysis conducted of the combined patient population of three global phase III RCT of pirfenidone versus placebo; (Clinical Studies Assessing Pirferidone in IPF (CAPACITY 004 and 006, trial duration 72 to 120

weeks)), Assessment of pirfenidone to confirm efficacy and safety in IPF (ASCEND 016,52 weeks). Another meta analysis of these data and data from two Japanese trials [Shionogi phase II (SP2) and Shionogi phase III (SP3)] were also conducted. In earlier meta analysis (three RCT), patient level data were used to estimate treatment effect, whereas meta-analysis of five RCTs used group level data allowing assessment of heterogeneity between studies. Study population of this meta analysis of three RCTs were patients with IPF who were randomly assigned to receive either 2403mg pirfenidone a day or placebo in CAPACITY 004 and 006, and ASCEND 016 trials, as well as the Japanese SP2 and SP3 trials who received 1800mg pirfenidone a day (equivalent to 2403mg per day when average lighter weight of Japanese patient adjusted for). Mortality outcomes assessed were all-cause mortality, treatment-emergent deaths, IPF-related mortality and all-cause mortality and treatment-emergent IPF-related mortality. All-cause mortality was defined as death from any cause at any time during the study, irrespective of whether the patient received pirfenidone. Treatment-emergent deaths were defined as those that occurred while patients were still receiving pirfenidone or placebo, or within 28days of the last dose. For IPF-related mortality, the primary cause of death and its relation to IPF were determined by the site investigators in CAPACITY trials and assessed by a blinded independent mortality assessment committee in ASCEND trial. All-cause mortality and treatment-emergent IPF related mortality were prespecified secondary endpoints and treatment-emergent all-cause mortality and IPF-related mortality were prespecified exploratory endpoints in ASCEND. For pooled analysis, the total number of events for each mortality outcome was determined from the combined patient population. Cox proportional hazard model was used to estimate hazard ratio.

They found at week 52, the relative risk (RR) of death for all four mortality outcomes were significantly lower in pirfenidone compared with placebo in the pooled population (all cause mortality, HR=0.52,95%CI 0.31, 0.87; treatment-emergent all-cause mortality, HR=0.45, 95%CI 0.24, 0.83; IPF-related mortality, HR=0.35, 95%CI 0.17, 0.72; and treatment-emergent IPF-related mortality, HR=0.32, 95%CI 0.14,0.76). (Table 3).

Consistent with pooled analysis, meta analysis for all-cause mortality at 52 weeks showed significant risk reduction in pirfenidone compared with placebo group. Treatment benefit of pirfenidone over placebo in IPF across four complementary mortality outcomes was reported, as shown in Table 4. Further work to analyse reduction in the risk of mortality in patients after longer term exposure to pirfenidone is encouraged to inform future clinical decision making. [29 level I]

Table 3: All-cause mortality outcomes following pirfenidone compared with placebo over 120 weeks

| Timepoint | Meta analysis (3 trials:004*,006** & 016#) | | Meta analysis (all 5 trials) | |
|---|---|---|---|---|
| | **Pirfenidone (n=623)** | **Placebo (n=624)** | **Pirfenidone (n=806)** | **Placebo (n=769)** |
| Week 52 | | | | |
| **Death,n(%)** | 22(3.5%) | 42(6.7%) | 25(3.1%) | 50(6.5%) |
| **HR** | 0.52 | | 0.50 | |
| **95%CI** | 0.31 to 0.87 | | 0.31 to 0.80 | |
| **p** | 0.0107 | | 0.0042 | |
| Week 72 | | | | |
| **Death,n(%)** | 32(5.1%) | 50(8.0%) | 35(4.3%) | 58(7.5%) |
| **HR** | 0.63 | | 0.60 | |
| **95%CI** | 0.41 to 0.98 | | 0.39 to 0.91 | |
| **p** | 0.0404 | | 0.0166 | |
| End of study | | | | |
| **Death,n(%)** | 38(6.1%) | 54(8.7%) | 41(5.1%) | 62(8.1%) |
| **HR** | 0.69 | | 0.65 | |
| **95%CI** | 0.46 to 1.05 | | 0.44 to 0.97 | |
| **p** | 0.0789 | | 0.0346 | |

*=CAPACITY 004 study (pirfenidone vs placebo,n=174 vs n=174)

**=CAPACITY 006 study (pirfenidone vs placebo, n=171 vs n=173)

# =ASCEND 016 study (pirfenidone vs placebo, n=278 vs n=277)

Table 4: Other mortality outcomes following pirfenidone compared with placebo over 120 weeks

| Timepoint/ Meta analysis (**004,006 & 016**) | Treatment emergent all-cause mortality | | IPF-related all cause mortality | | Treatment-emergent IPF-related mortality | |
|---|---|---|---|---|---|---|
| | **Pirfenidone (n=623)** | **Placebo (n=624)** | **Pirfenidone (n=806)** | **Placebo (n=769)** | **Pirfenidone (n=806)** | **Placebo (n=769)** |
| Week 52 | | | | | | |
| **Death,n(%)** | 14(2.2%) | 32(5.1%) | 10(1.6%) | 28(4.5%) | 7(1.1%) | 22(3.5%) |
| **HR** | 0.45 | | 0.35 | | 0.32 | |
| **95%CI** | 0.24 to 0.83 | | 0.17 to 0.72 | | 0.14 to 0.76 | |
| **p** | 0.0094 | | 0.0029 | | 0.0061 | |
| Week 72 | | | | | | |
| **Death,n(%)** | 20(3.2%) | 39(6.3%) | 17(2.7%) | 35(5.6%) | 11(1.8%) | 28(4.5%) |
| **HR** | 0.52 | | 0.48 | | 0.40 | |
| **95%CI** | 0.30 to 0.89 | | 0.27 to 0.85 | | 0.20 to 0.80 | |
| **p** | 0.0154 | | 0.0107 | | 0.0072 | |
| End of study | | | | | | |
| **Death,n(%)** | 26(4.2%) | 43 (6.9%) | 22(3.5%) | 39(6.3%) | 15(2.4%) | 32(5.1%) |
| **HR** | 0.61 | | 0.55 | | 0.47 | |
| **95%CI** | **0.37 to 0.99** | | **0.33 to 0.93** | | **0.25 to 0.87** | |
| **p** | **0.0420** | | **0.0237** | | **0.0132** | |

### 5.2.3 Hospitalisation

Ley B et al. (2017) conducted a retrospective review of individual patient data from three phase III trials of pirfenidone for IPF.This study compared the risk of non-elective hospitalization by type, (namely all-cause, respiratory related and non-respiratory related) and death after hospitalisation, with use of pirfenidone versus placebo over 52 weeks. All patients were required to have a diagnosis of IPF, FVC percent predicted of at least 50% and a 6MWD of at least 150 m. Patients were followed up for 72 to 120 weeks and 52 weeks from time of randomisation in CAPACITY and ASCEND trials, respectively. In this study, the individual patient data was pooled from two CAPACITY trials (Clinical Studies Assessing Pirfenidone in IPF: Research of Efficacy and Safety Outcomes) and the ASCEND (Assessment of Pirfenidone to confirm efficacy and safety in IPF) trial including all patients randomised to pirfenidone 2,403 mg/d (n=623) or placebo (n=624), and analysed according to treatment assignment at randomisation (intention to treat).

Follow-up was censored at the time of loss to follow-up, death or administratively at 52 weeks. Cox proportional hazard model stratified by trials, Kaplan-Meier curves and the log rank test were used to compare time to first non-elective hospitalisation in pirfenidone vs placebo treated patients. The risk of hospitalisation over 52 weeks was compared using standard time-to-event methods. Among those hospitalised, the risk of death after hospitalisation was compared with adjustment for treatment group propensity.

A total of 1,247 patients (692 from CAPACITY trials and 555 from the ASCEND trial) were included in the analysis. They found pirfenidone was associated with lower risk of respiratory-related hospitalisation than placebo (7% vs 12%; HR 0.52, 95% CI: 0.36, 0.77), but all-cause (HR 0.91, 95% CI: 0.70, 1.19), or non-respiratory-related hospitalisation (HR 1.32, 95% CI: 0.92 , 1.88) was not (Figure 10). Among those hospitalised for any reason, treatment with pirfenidone was associated with lower risk of death after hospitalisation up to 52 weeks after randomisation, but no longer significant with longer follow-up.

Non-elective hospitalization events by type per 100 person-years were lower in pirfenidone vs placebo for all-cause hospitalisation (23.1 vs 25.3) and respiratory hospitalisation (9.0 vs 14.6).

They concluded in a pooled analysis of three phase III pirfenidone trials, patients receiving pirfenidone had a lower risk of respiratory-related hospitalization over the course of one year. The effect of pirfenidone on death after hospitalization is uncertain. Future studies to examine long term effects of pirfenidone on hospitalisation rates, outcome of hospitalisation and healthcare cost in IPF were suggested. [27 level II-2]

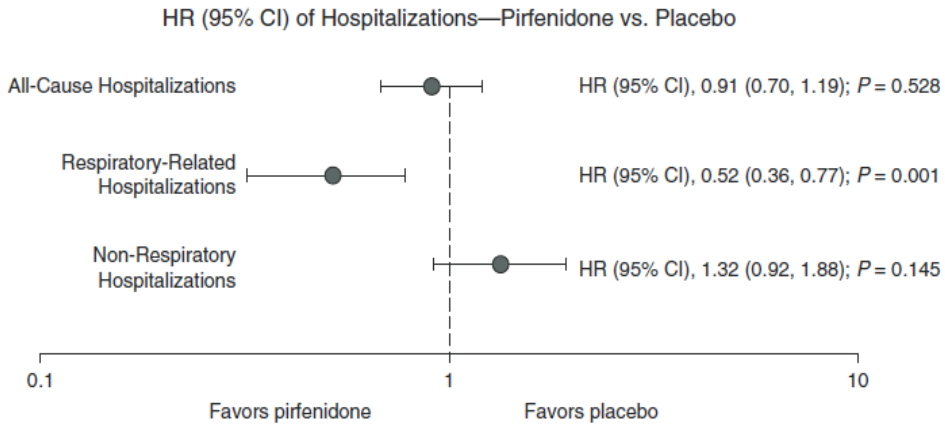


Figure 10: First nonelective hospitalisation by type (all-cause, respiratory related and non-respiratory related) in pirfenidone compared to placebo

### 5.2.4 Acute exacerbation (Nintedanib)

Richeldi et al. (2016) conducted a meta-analysis on nintedanib in patients with IPF, combining evidence from the TOMORROW and INPULSIS trials. All the studies investigated efficacy and safety of nintedanib versus placebo in patients with IPF. The TOMORROW trial was a phase II randomised, placebo controlled, 52 week in dose finding trial of nintedanib in 428 patients with IPF. This study pooled data from these three trials to obtain an overall estimate of the treatment effect of nintedanib 150 mg twice daily. The meta-analysis were conducted for annual rate of decline in FVC, time to first acute exacerbation, change from baseline in St George Respiratory Questionnaire (SGRQ) total score and all cause and respiratory mortality over 52 weeks.

They included 1231 patients (nintedanib=723, placebo=508) in the pooled analysis. Baseline characteristics were similar across the trials, mean age was 66.5 (8.1) years (nintedanib) and 66.6 (8.0) years (placebo). Baseline mean (SD) of FVC was 2714(762) ml and 2738(803) ml for nintedanib and placebo group respectively.

Adjusted annual rate of decline in FVC was -112.4 ml/year with nintedanib and -223.3 ml/year with placebo (difference: 110.9 ml/year (95% CI: 78.5, 143.3), p<0.0001). The hazard ratio for time to first acute exacerbation was 0.53 (95% CI: 0.34, 0.83), p=0.0047. Adjusted mean change from baseline in SGRQ score at week 52 was 2.92 with nintedanib and 4.97 with placebo [difference = -2.05 (95% CI: -3.59, -0.50), p=0.0095]. (Figure 11).

Hazard ratio for time to all-cause and on-treatment mortality were 0.70 (95% CI: 0.46, 1.08, p=0.0954), and 0.57 (95% CI: 0.34, 0.97, p=0.0274), respectively in favour of nintedanib. (Figure 12). Diarrhoea was the most frequent adverse event in the nintedanib group (61.5% of patient treated with nintedanib versus 17.9% treated with placebo). They concluded nintedanib has a beneficial effect on slowing disease progression in patients with IPF. [31] level I

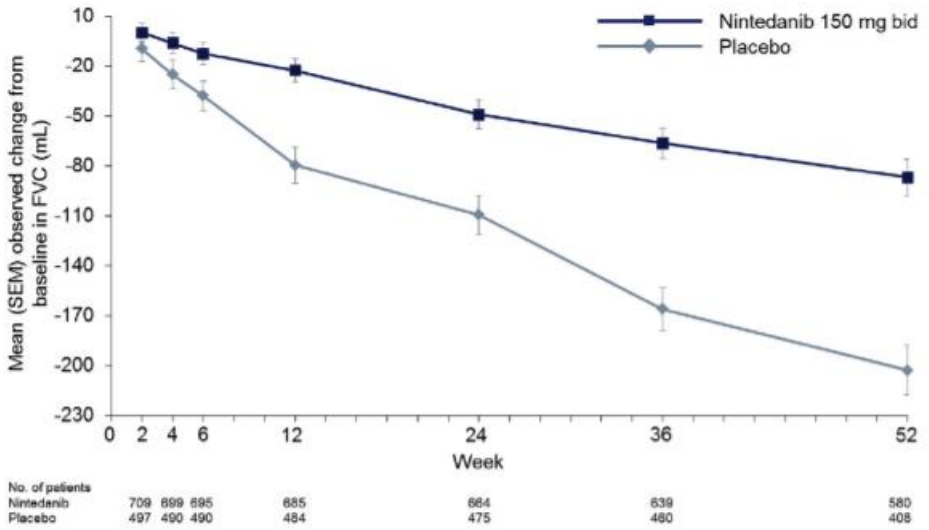


Figure 11: Changes in FVC over time pooled data; from the TOMORROW and INPULSIS trials [31]

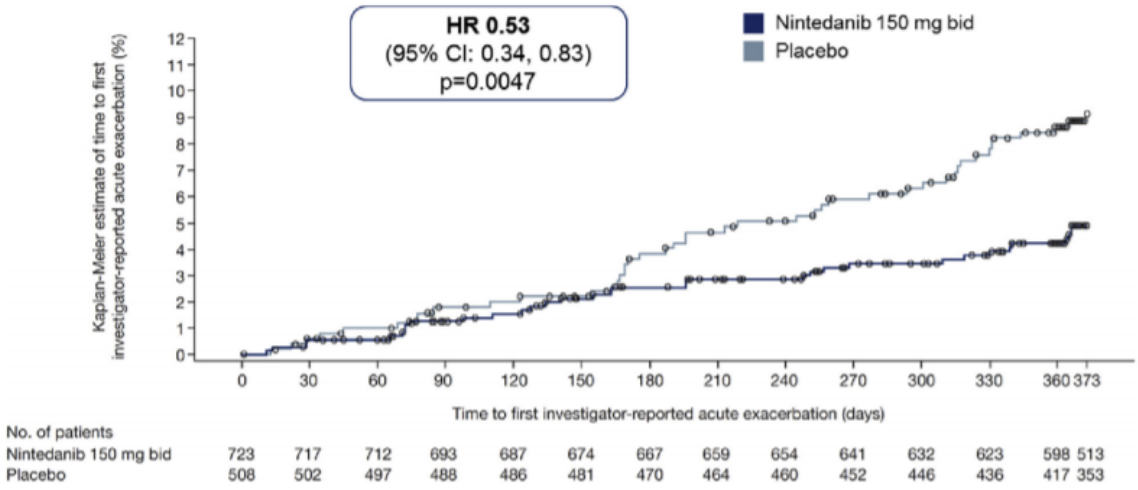


Figure 12: Time to first investigator reported acute exacerbation; pooled data from the TOMORROW and INPULSIS trials [31]

Loveman et al. (2015) conducted Health Technology Assessment to assess clinical effectiveness and an analysis of cost-effectiveness of treatments for IPF based on an economic model informed by systematic reviews of cost-effectiveness and quality of life. Systematic search was done from eleven electronic bibliographic databases, including MEDLINE, EMBASE, Web of Science, and The Cochrane Library and the Centre for Reviews and Dissemination databases, from database inception to July 2013. Reference lists of relevant publications were also checked and experts consulted. Two reviewers independently screened references for the systematic reviews, extracted and checked data from the included studies and appraised their risk

of bias. An advisory group was consulted about the choice of interventions until consensus was reached about eligibility. Interventions assessed were pharmacological interventions for mild to moderate IPF (Azathioprine, BIBF 1120 [nintedanib]), NAC (alone or in combination), pirfenidone, thalidomide; pharmacological interventions for severe IPF (Sildenafil) and non-pharmacological interventions (disease management programmes, pulmonary rehabilitation).

A network meta-analysis (NMA) was performed. A decision-analytic Markov model was developed to estimate cost-effectiveness of pharmacological treatments for IPF.

The review included fourteen studies in the review of clinical effectiveness, of which one evaluated azathioprine, three N-acetylcysteine (NAC) (alone or in combination), four pirfenidone, one BIBF 1120 [nintedanib]), one sildenafil, one thalidomide, two pulmonary rehabilitation, and one a disease management programme. In patients with mild to moderate IPF, ten studies evaluating five pharmacological interventions (azathioprine, BIBF 1120, NAC, pirfenidone and thalidomide) were included. Nintedanib 300mg/day was more favourable than placebo on some measures of lung function, rates of acute exacerbations and the number of deaths; however, the primary outcome of annual rate of decline in FVC was not statistically significantly different between groups in this 54-month study. Pirfenidone was studied in four RCTs, and meta-analysis of FVC showed pirfenidone and nintedanib appear to be clinically effective, compared to placebo. (Figure 11).

Study quality was generally good, with low risk of bias. The current evidence suggests that some treatments appear to be clinically effective. The fixed-effects NMA found only nintedanib and pirfenidone to have a statistically significant improvement in FVC over placebo. A head-to-head comparison of nintedanib versus pirfenidone showed a trend favouring nintedanib, but this was not statistically significant.

They concluded the review has identified limited evidence on the effectiveness of a number of available treatments for IPF. Pirfenidone and nintedanib appear to be clinically effective (Figure 13); however, general recommendations cannot be made in terms of their cost-effectiveness owing to limitations in the evidence base. Research is required on the effects of symptom control interventions, in particular pulmonary rehabilitation and thalidomide. Other research priorities include a well-conducted randomised controlled trial on inhaled NAC therapy and an updated evidence synthesis once the results of ongoing studies are reported.[32 level I]

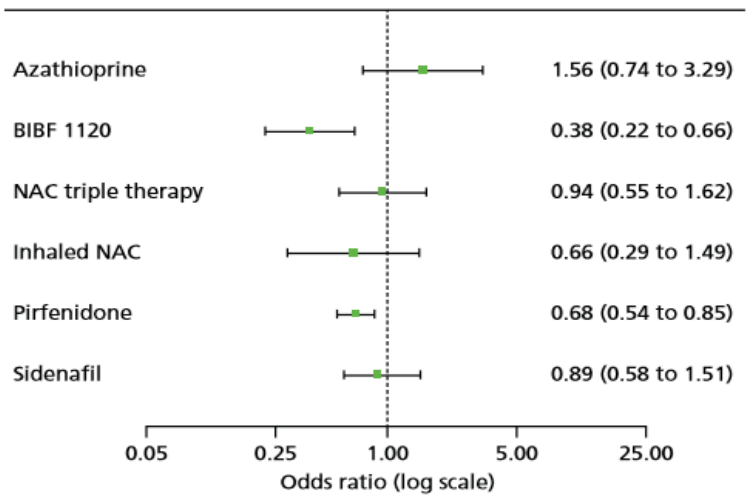


Figure 13: Forest plot of odds ratios on slowing the decline in FVC (various treatment vs placebo)

### 5.2.5 Combination of Nintedanib and pirfenidone

Vancheri et al. (2018) in an open label RCT investigated safety, tolerability, pharmacokinetic and exploratory efficacy endpoints in patients treated with nintedanib and add-on pirfenidone versus nintedanib alone. The INJOURNEY trial involved patients with IPF and FVC greater than or equal to 50% predicted at screening. These batch completed a four to five week run in with interruption were randomized (1:1) to receive nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801mg three times daily) or nintedanib 150 mg twice daily alone in an open-label manner for 12 weeks. The diagnosis of IPF follows the American Thoracic Society/Japanese Thoracic Society/Latin American Thoracic Association guidelines. Mean age of patients were 68.9 years, mean FVC was 84.0% predicted, and mean diffusing capacity of the lung for carbon monoxide was 47% predicted. Predose plasma through concentration (pharmacokinetic) of nintedanib were similar when it was administered alone or with add-on pirfenidone. Mean (SE) changes from baseline in FVC at week 12 were -13.3(17.4) ml and -40.9(31.4) ml in patients treated with nintedanib with add-on pirfenidone (n=48) and nintedanib alone (n=44), respectively. Mean (SE) absolute change from baseline in EQ-5D total score at week-12 were -1.1(2.7) in patients treated with nintedanib with add-on pirfenidone and -1.0(1.7) in patients treated with nintedanib alone. They concluded nintedanib with add-on pirfenidone had a manageable safety and tolerability profile in patients with IPF. These data support further research into combination regimen of these treatments in the treatment of IPF. Further large controlled studies are warranted to confirm the benefit/risk ratio of combination antifibrotic therapy in IPF patients. [33 level I]

## 5.3 SAFETY

There were six studies retrieved on the safety of antifibrotics (pirfenidone) in the treatment of IPF, consisted of one meta-analysis of RCT, three RCTs and two cohort studies.

Cottin V et al. (2018) in a multicentre prospective observational PASSPORT study assessed the long term safety of pirfenidone among patients who were newly prescribed pirfenidone and followed up for two years. Physicians collected data at baseline and at every three months. Post-hoc stepwise logistic regression models were used to identify baseline characteristics associated with discontinuing treatment due to an adverse drug reactions (ADR).The study involved 1009 participants, 99.7% with IPF with median exposure of pirfenidone of 442.0 days for all patients in PASSPORT study. A total of 354 (35.1%) participants completed follow up. Among the 354 patients who completed the two year study, the median (IQR) pirfenidone exposure was 741.5 (722.0 to 767.0) days.

Overall, 741 (73.4%) patients experienced ADR, most commonly nausea (20.6%), fatigue (18.5%),decreased appetite (16.2%), decreased weight (16.0%), rash (12.2%) and others. Adverse drug reaction (ADR) led to treatment discontinuation in 290 (28.7%) patients after a median of 99.5 days. Of the 741 patients with ADR, 358 underwent dose adjustment (48.3%), and 383 (51.7%) did not experience dose adjustment. A total of 55 (5.5%) patients experienced serious ADR (SADR), with six patients experienced SADR that led to a fatal outcome. Serious ADR was defined as ADR at any dose that resulted in death, disability, or a congenital anomaly/birth defect, was life-threatening, required in-patient hospitalization or prolonged an existing hospitalization. Adverse drug reactions of special interest were reported in 693 patients, most commonly gastrointestinal symptoms (38.3%) and photosensitivity reaction or skin rash (29.0%). Older age and female sex were associated with early treatment discontinuation due to ADR. Findings were consistent with safety profile of pirfenidone, with no new safety signals observed.[34 level II-2]

Crestani et al. (2018) in another open-label extension study, INPULSIS-ON assessed long term safety and tolerability of nintedanib in patients with IPF. The efficacy and safety of nintedanib was assessed in two phase III placebo controlled INPULSIS trial. Patients who completed the 52 week treatment period in INPULSIS trial could receive open label nintedanib in this extension trial, INPULSIS-ON. The off-treatment period between INPULSIS and INPULSIS-ON could be four to 12 weeks. Patients receiving nintedanib 150 mg twice daily or placebo at the end of INPULSIS trial received 150 mg twice daily in INPULSIS-ON. Patients receiving nintedanib 100 mg twice daily or placebo at the end of an INPULSIS trial could receive 100 mg twice daily or 150 mg twice daily in INPULSIS-ON. Spirometric tests were done at baseline, weeks two, four, six, 12,24,36,48 and then every 16 weeks. The primary outcome of INPULSIS-ON was to characterize the long-term safety and tolerability of nintedanib in patients with IPF, and this was analysed in patients who received at least one dose of nintedanib in INPULSIS-ON. Of 807 patients who completed the INPULSIS trial, 734 (91%) were treated in INPULSIS-ON. A total of 430 (59%) patients received nintedanib in INPULSIS and continued nintedanib in INPULSIS-ON, and 304 (41%) had received placebo in INPULSIS and initiated nintedanib in INPULSIS-ON. Median exposure time

for patients treated with nintedanib in both INPULSIS and INPULSIS-ON trial was 44.7 months (range 11.9 to 68.3). The safety profile of nintedanib in INPULSIS-ON was consistent with that observed in INPULSIS. Diarrhoea is the most common adverse event (AE) in INPULSIS-ON (60.1 events per 100 patient exposure years in patients who continued nintedanib, 71.2 events per 100 patient exposure-years in patients who initiated nintedanib).The AE that most frequently led to permanent discontinuation of nintedanib was progression of IPF (51 patients continuing nintedanib and 43 patients initiating nintedanib).The event rate of bleeding was 8.4 versus 6.7 events per 100 patient exposure-years in patients continuing nintedanib vs patients initiated nintedanib. These findings suggest nintedanib has a manageable safety and tolerability profile over long term use, with new safety signal. Patients with IPF could use nintedanib over the long term to slow disease progression.[35 level I]

Valeyre et al. (2014) conducted comprehensive assessment of the long term safety of pirfenidone in patients with IPF. They performed a comprehensive analysis of safety across four clinical trials evaluating pirfenidone in patients with IPF. In this study, all patients receiving pirfenidone 2403 mg/day in the phase III CAPACITY studies (study 004 & 006) and all patients receiving at least one dose of pirfenidone in one of two ongoing open-label studies in patients with IPF (studies 002 & 012) were selected for inclusion. In study 004, patients were randomly assigned to (2:1:2) to one of three arms, pirfenidone 2403 mg/day, pirfenidone 1197 mg/day or placebo. In study 006, patients were randomly assigned to (1:1) to treatment with pirfenidone 2403 mg/day or placebo. Study drug was administered orally in three divided doses and escalated to full dose over two-week period.[36 level II-2]

The total duration of study drug exposure, total person exposure years and mean daily dose of study treatment were summarised. Safety outcomes were evaluated from baseline until 28 days after the last dose of study drug. A total of 789 patients were included in the analysis. The median duration of exposure to pirfenidone was 2.6 years (range 1 week to 7.7 years), and the cumulative total exposure was 2059 person exposure years (PEY). Gastrointestinal and skin related events were the most commonly reported adverse events, these were almost always mild to moderate in severity, and rarely led to treatment discontinuation. Elevations (more than three times upper limit of normal) in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) occurred in 21/789 (2.7%) patients, the adjusted incidence of AST/ALT elevations was 1.7 per 100 PEY. They concluded the analysis of safety in a large cohort of IPF patients receiving pirfenidone for a total of 2059 PEY up to 7.7 years (median 2.6 years, range 1week to 7.7 years) demonstrates that long term treatment with pirfenidone is safe and generally well tolerated. [36 level II-2]

Huang et al. (2015) in their double blind placebo controlled, multicentre trial of pirfenidone in Chinese IPF patients studied 18 to 75 years old patients with IPF, with percentage of predicted FVC of at least 45%, percentage of carbon monoxide diffusing capacity (DLCO) of at least 30% and $PaO_2$ of at least 50 mmHg when the patient is at rest and breathing room air. This double blind, modified placebo controlled, randomised phase II trial randomly assigned Chinese IPF patients with mild to moderate impairment of pulmonary function to receive either oral pirfenidone (1800mg per day) and NAC (1800 mg per day); or placebo and NAC (1800 mg per day) for 48 weeks. All patients were treated with 600 mg NAC three times daily, as a baseline

treatment. The primary endpoints were changes in FVC (from baseline to week 48) and walking distance and the lowest $SPO_2$ during the 6MWT at week 48. Secondary endpoint was the progression-free survival time.

They screened 86 patients, and 76 cases were enrolled (pirfenidone and NAC: 38 cases, placebo and NAC: 38 cases). Sixty-six cases completed the study. In the pirfenidone group, the adverse event rate was higher than the control group (52.6% vs 26.3%, p=-0.03). Rash was more common in the pirfenidone group (39.5% vs 13.25, p=-0.02). Rash, pruritus and allergic dermatitis were the skin related adverse events. Three cases withdrew due to back pain (one), rash (one), and elevation of liver enzyme (one). Serious adverse events occurred in four cases, (two cases died of AE-IPF in both groups). Although AE were more common in pirfenidone group, they were mild to moderate in severity, reversible, and without clinical sequalae. [28 level I]

Noble et al. (2016) in another meta-analysis analysed pooled data from three multinational phase three trials to obtain the most precise estimate of magnitude of treatment effect on measures of pirfenidone in disease progression of patients with IPF. All patients randomised to pirfenidone 2403 mg/day or placebo in the CAPACITY or ASCEND studies were included. Study drug was administered in three equally divided doses and escalated to the full dose over two weeks. The CAPACITY trials (study 006 and 004) evaluated efficacy and safety of treatment with pirfenidone for a minimum of 72 weeks, while the ASCEND study (study 016) evaluated pirfenidone for 52 weeks. Gastrointestinal and skin related adverse events were more common in the pirfenidone group, but rarely led to treatment discontinuation. Among the most common adverse events were nausea (35.5%), rash (29.2%), cough (23.1%), diarrhoea (24.6%), upper respiratory tract infection (22.6%), fatigue (23.0%) and headache (20.5%). Nearly all patients in both treatment groups experienced at least one adverse event during one year observation period (98.7% vs 96.5%) in pirfenidone and placebo group. More patients experienced adverse event that led to discontinuation of treatment in pirfenidone vs placebo group, 74 (11.9%) vs 54(8.7%), however there were fewer serious adverse events (128(20.5%) vs 139(22.3%) and treatment related deaths (14(2.2%) vs 32(5.1%) in pirfenidone compared to placebo. They concluded their findings provide further evidence to support that treatment with pirfenidone for one year resulted in clinically meaningful benefit in reducing disease progression and acceptable safety profile in patients with IPF. [27 level I]

Vancheri et al. (2018) in the RCT investigated safety, tolerability, pharmacokinetic and exploratory efficacy endpoints in patients treated with nintedanib and add-on pirfenidone versus nintedanib alone. The trial involved patients with IPF and FVC greater than or equal to 50% predicted at screening who completed a four to five week run in with interruption. They were randomised (1:1) to receive nintedanib 150 mg twice daily with add-on pirfenidone (titrated to 801 mg three times daily) or nintedanib 150mg twice daily alone in an open-label manner for 12 weeks. They found on-treatment gastrointestinal adverse events were reported in 37 out of 53 patients (69.8%) treated with nintedanib with add-on pirfenidone and 27 of 51 patients (52.9%) treated with nintedanib alone. Serious adverse events were reported in two patients (3.8%) compared to five (9.8%) in combination versus nintedanib alone respectively. Serious adverse events were adverse events that were life threatening, required

hospitalisation, persistent or significant disability, congenital anomaly or deemed serious for any reason.[33 level I]

Loveman E at al. (2015) in the HTA conducted found adverse events from the pharmacological interventions were generally mild to moderate and were reasonably well balanced between the treatments and the placebo arms across the studies, with the exception of thalidomide. Severe adverse events appeared to be more common in one study in those treated with triple therapy. [32 level I]

In Malaysia, National Pharmaceutical Regulatory Agency (NPRA) has received 36 reports with 88 adverse events suspected to be related to nintedanib. The most commonly reported ADR were diarrhoea, vomiting, lost of appetite, decreased weight and transaminitis. No event on ischaemic colitis has been reported locally, as of April 2020 according to the Malaysian Adverse Reactions Database, NPRA.

In Europe, pirfenidone is indicated for the treatment of mild-to-moderate idiopathic pulmonary fibrosis. It was approved by the European Medicines Agency in 2011. It was approved for use in Japan (2008), in India (2010), and in China in 2011 (commercial launch in 2014). In October 2014, it was approved for sale in the United States.[18]

Nintedanib received United States Food and Drug Administration (FDA) approval for use for Idiopathic Pulmonary Fibrosis in 2014, and received a positive opinion from the European Medicines Agency on 20 November 2014, being approved in the EU in January 2015.[24] It is also approved in Canada, Japan, Switzerland, and other countries.[37]

NICE recommends nintedanib in cases of IPF where the FVC is 50 to 80% of predicted. NICE recommends discontinuation of therapy if a person's FVC decreases by 10% or more in a 12-month period, indicating disease progression despite treatment.[38]

## 5.4 ECONOMIC EVALUATION / COST-EFFECTIVENESS ANALYSIS

There were three retrieved studies on the cost-effectiveness of nintedanib for the treatment of patients with IP (cost-effectiveness analysis).

Rinciog et al. (2016) conducted a cost-effectiveness analysis of nintedanib in IPF in the UK. The aim was to assess the cost-effectiveness of nintedanib versus pirfenidone, NAC and best supportive care (BSC) for the treatment of IPF from the UK payers perspective. In this study, a Markov model was designed to capture changes in the condition of adults with IPF. Efficacy outcomes included were mortality, acute exacerbations and disease progression defined as lung function decline. Forced vital capacity was the most commonly reported measure in the literature and was selected as the main factor determining disease progression. Treatment safety (serious adverse events) and tolerability (overall discontinuation) were also considered. The baseline risk of these events was derived from patient level data from the placebo

arms of nintedanib clinical trials (TOMORROW, INPULSIS-1, INPULSIS-2). Data for pirfenidone and NAC were either extracted from the main pirfenidone or NAC studies or obtained from a network meta analysis comparing active comparator treatments. A network meta analysis was conducted to estimate the relative effectiveness of the comparator treatments, based on evidence from nine studies. Quality of life and healthcare resource use data from the clinical trials were also incorporated in the model. Five regression models were assessed for goodness of fit; exponential, Gompertz, log logistic, log-normal and Weibull.

The result demonstrated statistically significant difference against placebo on acute exacerbation events avoided (nintedanib vs placebo; OR 0.56, 95% CI: 0.35, 0.89) and (pirfenidone vs placebo; OR1.10, 95% CI: 0.43, 2.85) and lung function decline (nintedanib vs placebo; OR 0.54, 95% CI: 0.42, 0.69) and pirfenidone vs placebo (OR 0.55, 95% CI: 0.41, 0.72).

In the CEA, the results were split between two treatments with relative low costs and modest effectiveness (BSC and NAC) and two treatments that showed improved effectiveness (lung function) and higher cost (nintedanib and pirfenidone). Compared with BSC, the ICER per QALY gained for nintedanib and pirfenidone was £145,310 for nintedanib and £172,198 for pirfenidone, respectively.(Table 6). For both nintedanib and pirfenidone, the increase in cost was due to the drug acquisition cost. All comparators were assumed to have similar projected survival and the difference in quality adjusted life years (QALY) was driven by acute exacerbations and function estimates.

In the base case deterministic pairwise comparison with pirfenidone, nintedanib was found to have fewer acute exacerbations and resulted in less cost and more QALY gained. The cost effectiveness acceptability curve showed nintedanib dominates pirfenidone at any threshold level. (Figure 14). [39]

Table 6: ICER for pirfenidone and nintedanib vs best supportive care

| Item | BSC (baseline) | Pirfenidone | Nintedanib |
|---|---|---|---|
| Total cost (£) | 20,029.23 | 80,474.37 | 78,350.71 |
| Drug acquisition cost | 0.00 | 59,121.16 | 57,582.92 |
| Treatment related adverse event cost | 589.13 | 1002.64 | 702.54 |
| Patient monitoring (liver panel test) cost | 0.00 | 9.06 | 8.83 |
| Background follow up and oxygen use cost | 9231.78 | 10,026.61 | 10,119.06 |
| Acute exacerbation cost | 1265.38 | 1486.63 | 1127.31 |
| End of life palliative care cost | 8942.94 | 8828.27 | 8810.06 |
| Total QALY | 3.0999 | 3.4509 | 3.5013 |
| ICER | Baseline | Dominated by nintedanib | £145,310 per QALY gained vs BSC |

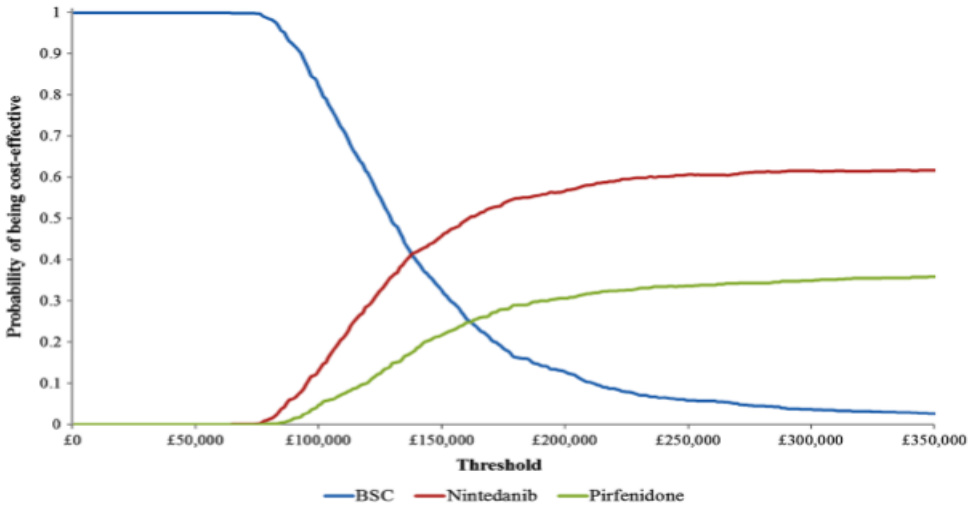


Figure 14: Multiple cost effectiveness acceptability curve
*BSC-best supportive care*

They concluded, compared with placebo (BSC), nintedanib and pirfenidone were the only treatments to show statistical significance in the efficacy parameters. They found substantial uncertainty in the overall cost-effectiveness results between nintedanib and pirfenidone. N-acetylcycteine (NAC) was largely similar to BSC but with a worse survival profile. [39]

Loveman et al. (2014) also conducted a decision-analytic Markov model following nMA to estimate cost-effectiveness of pharmacological treatment for IPF. The model structure used four distinct health states; unprogressed IPF, progressed IPF, lung transplant, and dead. Model cycle length is one month and a lifetime horizon of 30 years was adopted to capture all clinically and economically important events. Following best practice recommendation, the model perspective was the National Health Service and personal social service, a discount rate of 3.5% for cost and health benefits was applied. Costs included were treatment, treatment monitoring, acute exacerbation, lung transplant and adverse event based on the UK health system. Outcomes were expressed as cost per quality adjusted life-years (QALY) gained against the next best alternative treatment using incremental cost effectiveness ratio (ICER). Parameter values were obtained from the nMA and SR.

The model result showed increase survival for five pharmacological treatments (NAC triple therapy, inhaled NAC, nintedanib, pirfenidone, and sildenafil) compared with best supportive care at increased cost, as shown in Table 7. Only inhaled NAC was cost-effective at current willingness to pay threshold but it may not be clinically effective. They stated that pirfenidone and nintedanib could offer potential hope for IPF treatment, however their cost-effectiveness is likely to be prohibitive. [1]

Table 7: Summary of base case results of pharmacological interventions in IPF

| Treatment | Total cost (£) | Total QALYs | ICER vs BSC (£/QALY) | ICER vs next best option (£/QALY) |
|---|---|---|---|---|
| Best supportive care | 3,084 | 2.98 | - | - |
| Azathioprine & prednisolone | 4,313 | 2.66 | Dominated | Dominated |
| NAC triple therapy | 5,021 | 3.03 | 41,811 | Extended dominance |
| Inhaled NAC | 5,029 | 3.37 | 5,037 | 5037 |
| Sildenafil | 12,008 | 3.11 | 68,116 | Dominated |
| Pirfenidone | 70,118 | 3.34 | 190,146 | Dominated |
| Nintedanib | 139,613 | 4.01 | 132,658 | 209,246 |

Loveman et al. (2015) in the HTA conducted to assess clinical effectiveness of treatments for IPF also did an analysis of cost-effectiveness of treatments for IPF based on an economic model informed by systematic reviews of cost-effectiveness and quality of life. A decision-analytic Markov model was developed to estimate cost-effectiveness of pharmacological treatments for IPF. The model uses four distinct health states: unprogressed IPF, progressed IPF, lung-transplant and dead. Parameter values were obtained from NMA and systematic reviews. Univariate and probabilistic sensitivity analyses were undertaken. The model perspective is NHS and Personal Social Services, and discount rate is 3.5% for costs and health benefits. The lifelong costs and benefits associated with each treatment are estimated by the economic model. The base price year for costs is 2012. Future costs and benefits are discounted at 3.5% per annum as recommended by the UK Treasury. The estimates of intervention effectiveness used by the model for reduced rate of decline in FVC per cent predicted are obtained from the NMA. Transition probabilities for IPF progression are taken from the CAPACITY trial where average age at baseline in the pooled population was 66 years, and 73% were men. This is broadly comparable with the UK IPF population. All-cause mortality in the model is defined using these UK data. Mean overall FVC percent predicted at baseline in the CAPACITY trial was 74.7%.

The model base-case results showed increased survival for five pharmacological treatments, compared with best supportive care, at increased cost. Only one treatment, inhaled NAC, is cost-effective at a willingness-to-pay (WTP) threshold of £30,000, but its treatment effect does not achieve statistical significance in either the single primary study or the NMA. The treatment effect of inhaled NAC compared with BSC is associated with an expected value of partial perfect information of £15.8M at a WTP threshold of £20,000, as in Table 8. General recommendations cannot be made of their cost-effectiveness owing to limitations in the evidence base. [32]

Table 8: Summary of base case cost-effectiveness for all treatments

| Treatment | Total costs (£) | Total QALYs | ICER vs. BSC (£/QALY) | ICER vs. next best option (£/QALY) |
|---|---|---|---|---|
| BSC | 3084 | 2.98 | – | – |
| Azathioprine and prednisolone | 4313 | 2.66 | Dominated | Dominated |
| NAC triple therapy | 5021 | 3.03 | 41,811 | Extended dominance |
| Inhaled NAC | 5029 | 3.37 | 5037 | 5037 |
| Sildenafil | 12,008 | 3.11 | 68,116 | Dominated |
| Pirfenidone | 70,118 | 3.34 | 190,146 | Dominated |
| BIBF | 139,613 | 4.01 | 132,658 | 209,246 |

In North America, the annual per capita cost of patients with IPF was estimated around US$ 20,000, 2.5 to 3.5 higher than the national healthcare expenditure.[9]

In Singapore, cost-effectiveness analysis conducted by Agency for Care Effectiveness, Ministry of Health Singapore showed the base-case incremental cost-effectiveness ratios (ICERs) for nintedanib and pirfenidone compared with best supportive care were above SG 105,000 per QALY gained, and was not a cost-effective use of healthcare resources at the price proposed by the manufacturer. If nintedanib or pirfenidone were listed in the Medication Assistance Fund (MAF), it was estimated 59 people with IPF in Singapore will benefit from the assistance. The annual cost impact was estimated to be between SG 500,000 to <SG 1million in the first year of listing either agent on the MAF. [40]

In Malaysia, both pirfenidone and nintedanib were registered with National Pharmaceutical Regulatory Agency (NPRA). Only Nintedanib 100 mg and nintedanib 150 mg capsule were listed in the Ministry of Health (MOH) drug formulary, indicated for the treatment of IPF in adults, with recommended dose of 150 mg twice daily, to be administered approximately 12 hours apart. The 100 mg twice daily dose is only recommended to be used in patients who do not tolerate the 150 mg twice daily dose. However, pirfenidone is not available in the MOH formulary.

It was reported that the treatment cost of pirfenidone could reach up to RM9,300 per month while nintedanib costs could reach to RM10,000 per month per patient. Currently, it was reported that in MOH, nintedanib costs approximately RM 3,500 per month. While pirfenidone costs were RM 4,240 per month (pirfenidone still not listed in the MOH formulary yet). Therefore, estimated annual treatment cost of patients with IPF using pirfenidone is RM 50,880, and using nintedanib is RM42,000.

In Malaysia, a total of 124 patients with IPF were reported since 2017 to September 2020 from three centers (National Respiratory Institute, Hospital Serdang and Hospital Taiping). Out of this, 80 patients were classified as having mild or moderate IPR (64.5%) with the remaining were having severe IPF. The number of mild or moderate IPR cases by year reported from these centers were 18(2017), 22(2018), 24(2019) and 16(2020), respectively with average of 20 cases reported per year. Hence,

considering this figures, estimated annual treatment cost of using nintedanib or pirfenidone is between RM840,000 to RM1,017,600 for mild or moderate IPF patients in Malaysia. However this estimation is limited by the unavailability of data on number of patients requiring pirfenidone such as those contraindicated to nintedanib.

However, there is scarcity of local data with regard to utility of the interventions (drugs), as well as cost and utility of the comparator namely best supportive care in Malaysia.

## 5.5 ORGANISATIONAL

Education is required for patients and healthcare providers regarding all adverse events which may occur in patients beginning pirfenidone administration. When considering pirfenidone administration, adequate informed consent must be obtained regarding efficacy and safety, and administration must proceed on the basis of sufficient patient understanding. [41]

The Japan guidelines stated that it should be recommended to individual patients based on informed consent taking full account of the points that nintedanib administration is frequently accompanied with adverse events, including diarrheoa, liver damage, nausea and cases of platelet decrease. [41]

Patients with IPF in the chronic phase should be treated with pirfenidone or nintedanib. In this guideline, therapy using NAC monotheraphy was not recommended in majority of patients with IPF in the chronic phase. For combination of pirfenidone and nintedanib, judgement on hold or recommendation regarding co-administration of pirfenidone and nintedanib to patients with IPF in the chronic phase was still on hold. [41]

The American Thoracic Society in their guidelines stated recommendation against the use of the following agents for the treatment of IPF is strong: [14]

- Corticosteroid monotherapy
- Colchicine
- Cyclosporine A
- Combined corticosteroid and immune-modulator therapy
- Interferon g 1b
- Bosentan
- Etanercept

Meanwhile, the recommendation against the use of the following agents for the treatment of IPF is weak; that is, these therapies should not be used in the majority of patients with IPF, but may be a reasonable choice in a minority: [14]

- Combined acetylcysteine and azathioprine and prednisone (against use)
- Acetylcysteine monotherapy (against use)
- Anticoagulation (against use)
- Pirfenidone

Pirfenidone has UK marketing authorisation for the treatment of mild-to-moderate IPF in adults. The National Institute of Clinical Care and Excellence (NICE) recommended pirfenidone as an option for treating IPF only if the patient has a FVC between 50% and 80% predicted and the manufacturer provides pirfenidone with a discount agreed in the Patient Access Scheme. Treatment with pirfenidone should be discontinued if there is evidence of disease progression (a decline in percent predicted FVC of 10% or more within any 12 month period).[41] Similarly, nintedanib is recommended as an option for treating idiopathic pulmonary fibrosis, only if the person has a forced vital capacity (FVC) between 50% and 80% of predicted and the company provides nintedanib with the discount agreed in the Patient Access Scheme and treatment is stopped if disease progresses (a confirmed decline in percent predicted FVC of 10% or more) in any 12-month period. The recommended dosage of nintedanib is 150 mg twice daily.[38]

The National Institute for Health and Clinical Excellence (NICE) stated there was no evidence to support the use of any disease-modifying pharmacological intervention drugs to increase the survival of patients with IPF. They do not recommend use of any of these drugs either alone or in combination, to modify disease progression in IPF: ambrisentan, bosentan, azathoprine, co-trimoxazole, mycophenolate mofetil, prednisolone, sildenafil, warfarin. [11]

In contrast, the Singapore Ministry of Health's Drug Advisory Committee has not recommended listing nintedanib or pirfenidone in their Medication Assistance Fund (MAF) for treating IPF, due to limited clinical benefits and unacceptable cost-effectiveness compared with best supportive care, at the price proposed by the manufacturer.[40]

### 5.6 LIMITATION

Our review has several limitations. The selection of the studies and appraisal was done by one reviewer. Although there was no restriction in language during the search, only English full text articles were included in the report. Few head-to-head comparisons or trials of antifibrotic specifically pirfenidone and nintedanib against current practice were made in the included studies. However, there is lack of longer term data on the measure of effectiveness. Some of the studies did indirect comparison through network meta-analysis, however the results should be interpreted with caution. Included studies which had a high risk of bias in the systematic review or network meta-analysis may affect the methodological quality. Lack of local data on cost and utility of the interventions and comparator namely best supportive care prohibit the generation of local cost-utility analysis.

## 6.0 CONCLUSION

Based on the above review, there was sufficient good level of evidences on pirfenidone and nintedanib to be used in the treatment of patients with IPF. Evidence demonstrated that pirfenidone and nintedanib were effective in improving FVC from baseline and slowing rate of FVC decline, compared to placebo in adult patients with

IPF. Pirfenidone was effective in lowering risk of decline in percent predicted FVC of ≥10% over one year, compared to placebo in these patients.

Pirfenidone demonstrated treatment benefit for mortality outcomes (all-cause and other mortality outcomes; IPF-related mortality, treatment-emergent all-cause mortality, and treatment-emergent IPF-related mortality), progression free survival (reduce risk of disease progression at one year), six-minute walk distance (reducing proportion of patients with a ≥50m decline in 6MWD), dyspnoea (fewer patients in the pirfenidone group experienced a ≥20-point increase in the UCSD SOBQ score or death at one year), compared with placebo.

Nintedanib demonstrated benefit in reducing rate of acute exacerbation compared to placebo.

Pirfenidone was approved by the European Medicines Agency for the treatment of mild-to-moderate idiopathic pulmonary fibrosis, approved in several countries (Japan,India ,China,United States). Nintedanib was approved by the United States Food and Drug Administration for use in IPF, and approved in the EU, Canada, Japan, Switzerland, and few other countries.

Long term treatment with pirfenidone or nintedanib was reported as safe and generally well tolerated with gastrointestinal and skin related events were commonly reported adverse events following pirfenidone, and these were mostly mild to moderate. While following nintedanib use, diarrhoea is the most common adverse event.

In a cost-effectiveness analysis conducted in UK, the ICER ranged from £132,658 to £145,310 per QALY gained for nintedanib and £172,198 to £190,146 per QALY gained for pirfenidone, compared with BSC.In the base case deterministic pairwise comparison with pirfenidone, nintedanib was found to have fewer acute exacerbations and resulted in less cost and more QALY gained. The cost effectiveness acceptability curve showed nintedanib dominates pirfenidone at any threshold level.

In Malaysia, a total of 124 patients with IPF were reported since 2017 to September 2020 from three centers (National Respiratory Institute, Hospital Serdang and Hospital Taiping). Out of this, 80 patients were classified as having mild or moderate IPR (64.5%) with the remaining were having severe IPF. The number of mild or moderate IPR cases by year reported from these centers were 18(2017), 22(2018), 24(2019) and 16(2020), respectively with average of 20 cases reported per year. Estimated annual treatment cost of patients with IPF using pirfenidone is RM 50,880, and using nintedanib is RM42,000. Hence, considering this figures, estimated annual treatment cost of using nintedanib or pirfenidone is between RM840,000 to RM1,017,600 for mild or moderate IPF patients in Malaysia. However this estimation is limited by the unavailability of data on number of patients requiring pirfenidone such as those contraindicated to nintedanib.

Adequate informed consent should be obtained prior pirfenidone or nintedanib administration, and sufficient education to patients is required.

## 7.0 REFERENCE


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## APPENDIX 1: HIERARCHY OF EVIDENCE FOR EFFECTIVENESS

### DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

*SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001)*

## APPENDIX 2: SEARCH STRATEGY

| **Ovid MEDLINE® In-Process & Other Non-indexed Citations and Ovid MEDLINE® 1946 to present** |
|---|

| | |
|---|---|
| 1 | (Idiopathic adj1 pulmonary fibros?s).tw. |
| 2 | IPF.tw. |
| 3 | Idiopathic adj1lung fibros?s.tw. |
| 4 | (Idiopathic adj1 lung fibrosis).tw. |
| 5 | (Famil$ adj1 idiopathic pulmonary fibros?s).tw. |
| 6 | 1 or 2 or 4 or 5 |
| 7 | Anti-fibro$.tw. |
| 8 | Antifibro$.tw. |
| 9 | Pyridone*.tw. |
| 10 | Pyridinone*.tw. |
| 11 | Pirfenidone.tw. |
| 12 | Nintedanib.tw. |
| 13 | Ofev.tw. |
| 14 | Tyrosine kinase inhibitor*.tw. |
| 15 | 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 |
| 16 | 6 and 15 |
| 17 | limit 16 to (english language and humans and english)(775) |
| 18 | limit 17 to (systematic review and meta analysis and randomized controlled trial)188 |

| **OTHER DATABASES** | |
|---|---|
| EBM Reviews – Cochrane Central Registered of Controlled Trials | Similar MeSH, keywords, limits used as per MEDLINE search |
| EBM Reviews – Database of Abstracts of Review of Effects | |
| EBM Reviews – Cochrane database of systematic reviews | |
| EBM Reviews – Health Technology Assessment | |
| NHS economic evaluation database | |
| PubMed | Similar MeSH, keywords, limits used as per MEDLINE search |
| INAHTA | |
| US FDA | |

## APPENDIX 3: EVIDENCE TABLE

Only available upon request.