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Title: Pirfenidone For Treating Idiopathic Pulmonary Fibrosis: An Evidence Review Group Perspective of A NICE Single Technology Appraisal

Short running header: Pirfenidone for treating idiopathic pulmonary fibrosis: an ERG perspective

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Abstract (249 words)

The National Institute for Health and Care Excellence (NICE) published guidance on the use of pirfenidone (Esbriet®, Roche) for the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF) in 2013. NICE decided to review existing guidance following publication of an additional clinical trial, and invited the company for pirfenidone to submit evidence of its clinical and cost-effectiveness for the treatment of mild to moderate IPF when compared with best supportive care or nintedanib; nintedanib was a comparator only for moderate IPF. An independent Evidence Review Group (ERG) critiqued the company submission and this paper summarises their report and subsequent NICE guidance. The key clinical effectiveness evidence was based on three randomised controlled trials (RCTs) and an open-label extension study. Supportive data were provided from two additional RCTs conducted in Japan, while one additional open-label study was included for safety outcomes. Meta-analysis of the three key RCTs found pirfenidone to be effective at reducing disease progression compared with placebo, but statistically significant differences were not identified in all of the RCTs. A statistically significant reduction in all-cause mortality was only demonstrated when pooling data across studies. The treatment effects of pirfenidone and nintedanib were broadly similar, based on an indirect comparison using network meta-analysis, although they have slightly different adverse event profiles. There remains considerable uncertainty in the cost-effectiveness estimates for pirfenidone versus best supportive care particularly due to uncertainty regarding the duration of treatment effect and the method used to implement the stopping rule within the economic model.

Key points for decision makers

- Pirfenidone is effective at reducing disease progression compared with placebo in patients with mild to moderate idiopathic pulmonary fibrosis (IPF).
- There is a lack of head-to-head data comparing pirfenidone to nintedanib, but based on an indirect comparison, the treatment effects of pirfenidone and nintedanib appear to be broadly similar although they have slightly different adverse event profiles.
- The estimates of cost-effectiveness for pirfenidone versus best supportive care were all above £20,000 per quality-adjusted life year (QALY) gained and were associated with uncertainty in both the population with mild to moderate IPF and the subgroup with moderate IPF.
- The committee did not want to withdraw an existing treatment option for moderate disease, and decided not to make any changes to the existing NICE guidance as pirfenidone had been considered a reasonably innovative treatment at the time of the previous appraisal and it had not seen any clinical evidence contradictory to that considered previously.

Main text

1. Introduction

The National Institute for Health and Care Excellence (NICE) is an independent organisation whose responsibilities include providing national guidance to the NHS in England on health technologies. The NICE Single Technology Appraisal (STA) process usually covers new single health technologies within a single indication, soon after the UK market authorisation [1]. The manufacturer submits evidence on the clinical and cost-effectiveness of the technology, including a de novo economic model, and an independent Evidence Review Group (ERG) review this submission. The NICE Appraisal committee (AC) consider the evidence submitted by the company and the ERG, alongside testimony from experts and other stakeholders in order to develop national recommendations for England reported within a Final Appraisal Determination (FAD). An Appraisal Consultation Document (ACD) is initially produced if the recommendations from the AC are restrictive or additional clarification is required from the manufacturer about their submission. All stakeholders have an opportunity to comment on the ACD before the AC meets again to produce the FAD.

NICE published Technology Appraisal (TA) 282 which provided guidance on pirfenidone (Esbriet ®, Roche) for treating idiopathic pulmonary fibrosis (IPF) in 2013 [2]. Following publication of the Assessment of Pirfenidone to Confirm Efficacy and Safety in Idiopathic Pulmonary Fibrosis (ASCEND) study, NICE reviewed TA282 under its STA process. This paper is a summary of the ERG report for the review of TA282 and a summary of the subsequent NICE guidance for pirfenidone for treating idiopathic pulmonary fibrosis (TA504) [3]. Full details of all relevant appraisal documents can be found on the NICE website [4].

2. The Decision Problem

Pirfenidone is licensed in the EU for the treatment of mild to moderate IPF in adults [5]. Current guidelines do not propose a formal staging system for the classification of disease severity but there is a general acceptance that a percent predicted forced vital capacity (FVC) of <50% and a diffusing capacity for carbon monoxide (DLco) <35% defines severe disease. In TA282 pirfenidone was recommended as an option for treating idiopathic pulmonary fibrosis only if the person has an FVC between 50% and 80% predicted [2]. Nintedanib is licensed in the EU for the treatment of IPF in adults,[6] and was recommended by NICE in January 2016 (TA379) as an option for treating IPF in the same population eligible for treatment with pirfenidone [7]. The recommendations in TA282 and TA379 were dependent on pirfenidone and nintedanib being provided with the discounts agreed in their respective Patient Access Schemes (PASs).

In both TA282 and TA379 it is recommended that treatment should be discontinued if there is any evidence of disease progression (an absolute decline of 10% or more in predicted FVC within any 12-month period) [2, 7]. Clinical advisors to the ERG for TA504 reported that, to their knowledge, the stopping rule is being rigorously applied in clinical practice, but they agreed that the stopping rule is clinically problematic as a prior decline in lung function does not predict a future decline, and periods of stability can sometimes only be identified retrospectively. They noted that in clinical practice the stopping rule is only applied when the lung function decline (>10% FVC or >15% DLco decline over any 12-month period) has been confirmed as not being due to a temporary

and reversible infection. They also noted that in clinical practice treatment may continue if FVC falls below 50% or DLco falls below 35% provided the decline in FVC is less than 10% per year.

NICE issued a final scope in November 2015 to appraise the clinical and cost-effectiveness of pirfenidone within its licensed indication for the treatment of mild to moderate IPF in adults [8]. The review considered the whole of pirfenidone's marketing authorisation and the review objectives included a consideration of whether to change the guidance for patients with an FVC above 80% predicted and whether to remove the stopping rule [3]. Nintedanib and best supportive care (BSC) were listed as relevant comparators but, based on the recommendations in TA379, nintedanib was listed as a comparator only for the subgroup of patients with a percent predicted FVC of between 50% and 80%. The final scope specified that if evidence allowed, subgroup analysis by disease severity, defined by FVC (such as above and below 80% FVC) and/or diffusing capacity for carbon monoxide (DLco), should be considered.

3. The Independent ERG Review

3.1 Clinical-effectiveness evidence provided by the company

The company submitted a systematic review of randomised controlled trial (RCT) evidence comparing pirfenidone with placebo in adults with mild or moderate IPF [9]. The review identified three multi-centre international RCTs: ASCEND [10] and the two CAPACITY (Clinical Studies Assessing Pirfenidone in idiopathic pulmonary fibrosis: Research of Efficacy and Safety Outcomes, 1 and 2) [11] studies. ASCEND and CAPACITY 1 compared pirfenidone at the UK licensed dose of 2,403mg per day with placebo, whilst CAPACITY 2 compared pirfenidone at doses of 2,403mg per day and 1,197mg per day with placebo. It also identified two multi-centre Japanese RCTs (SP2 and SP3), which compared lower doses of pirfenidone which were licensed in Japan but not in the UK [12, 13]. The five trials included more than 1,700 patients with IPF. To be included in the key trials, patients had to have a predicted FVC of >50% and <90% (ASCEND) or simply >50% (CAPACITY 1 and 2); approximately 25% of these patients were considered to have mild disease, i.e. predicted FVC of >80%. The ASCEND and SP3 trials had 52 weeks follow-up, the CAPACITY trials had 72 weeks follow-up, and the SP2 trial was terminated early at 36 weeks. All but the ASCEND study had been part of the evidence considered in TA282.

The company reported random effects meta-analyses that indicated that, when trial data were pooled, there was a beneficial treatment effect for pirfenidone compared with placebo for FVC, mortality and PFS (see Table 1).

Insert Table 1 h*ere: Findings from company's random effects meta*-analyses

However, a statistically significant difference ($p<0.05$) in favour of pirfenidone was not observed in each individual trial. This was the case for the CAPACITY 1 trial for the binary outcome of a ≥10% decline in percent predicted FVC or death ($p=0.440$) (see Table 2) and for change from baseline in FVC/VC (ml) ($p=0.508$) (see

Table 3); and for the ASCEND trial (p=0.105) and the pooled CAPACITY trials at 72 weeks (p=0.315) for all-cause mortality (Table 4). Similar treatment effects were found for in the company's meta-analysis of PFS at 52 weeks (see Table 1), but again it should be noted that a statistically significant difference in favour of pirfenidone was not demonstrated in the CAPACITY 1 trial at 72 weeks: HR: 0.84; 95% CI, 0.58 to 1.22, p=0.355).

Insert Table 2 here: Categorical analysis of change from baseline in percent predicted FVC or death

Insert Table 3 here: Mean change from baseline in FVC/VC (ml)

Insert Table 4 here: All-cause mortality rates in the CAPACITY 1 & 2 studies

The company provided subgroup analyses, according to disease severity (mild versus moderate, with mild being FVC >80% of predicted), for both PFS and OS when pooling data across ASCEND, and CAPACITY 1 and 2. Whilst the treatment-by-subgroup interaction test was not statistically significant for either outcome, the reduction in OS was not statistically significant in the mild subgroup (HR at 72 weeks of 0.90, 95% CI 0.27 to 2.99, p=0.8610) but remained statistically significant in the moderate subgroup (HR at 72 weeks of 0.58, 95% CI 0.36 to 0.94, p=0.0240). For PFS, the treatment effect was statistically significant for both the mild (HR=0.64 at 72 weeks, 95% CI 0.52 to 0.79, p<0.0001) and moderate (HR=0.53 at 72 weeks, 95% CI 0.35 to 0.79, p<0.0017) subgroups.

A random effects meta-analysis of CAPACITY 1 & 2 (data from week 48) and ASCEND (data from week 52) suggested that pirfenidone reduces the decline in 6-Minute Walking Distance (6MWD) (Mean difference [MD]: 22.9m, 95% CI (10.58 to 35.23, p-value not reported), but in terms of individual trials the difference was only statistically significant in ASCEND and CAPACITY 1 (see supplementary material). A random effects meta-analysis did suggest that pirfenidone is associated with a reduction in the University of San Diego Shortness of Breath Questionnaire (UCSD SOBQ) compared with placebo (MD -3.19, 95% CI: -5.74, to -0.63), although the difference did not meet the threshold for clinical importance. None of the individual trials found a statistically significant treatment effect for UCSD SOBQ (see supplementary material). Only the two CAPACITY trials reported outcomes for the St George's Respiratory Questionnaire (SGRQ) and there was no evidence of a statistically significant treatment effect in either trial (see supplementary material). Four trials (CAPACITY 1 & 2, SP3, SP2) reported data on the change from baseline in DLco, but none found a statistically significant treatment effect compared with placebo for this outcome measure and meta-analysis was not conducted.

For the outcome of acute exacerbation, the definitions used varied across the trials. The ASCEND study reported much higher rates in the control arm (14% in ASCEND versus 0% and 2% in CAPACITY trials 1 and 2 respectively). A random effects meta-analysis of the ASCEND, CAPACITY trials and SP3 found a treatment effect in favour of pirfenidone (OR 0.64, 95% CI: 0.38 to 1.06, p-value not reported).

The company submitted evidence from one ongoing, non-controlled, open-label extension of the ASCEND and CAPACITY trials (RECAP). The company stated that results were similar to the comparisons reported for the trials. The company also provided non-randomised comparisons of patients who received pirfenidone in the

ASCEND and CAPACITY trials against patients who received best supportive care who were enrolled in registry studies for overall survival (the HRs are confidential and cannot be reported here).

The company presented safety evidence from ASCEND, CAPACITY 1 & 2, SP3, SP2, RECAP [14] and PIPF-002, [15] an ongoing open-label, compassionate-use, safety study in US patients with either IPF or secondary pulmonary fibrosis. Adverse events of any intensity with the highest frequency across all trials were nausea, rash, dizziness, dyspepsia and anorexia, and these were all relatively frequent compared with placebo (no statistically significant p-values for between-group differences were reported, except for IPF). SP3 and SP2 also reported a very high frequency of photo-sensitivity (much higher than the CAPACITY trials). Similar, albeit slightly higher, frequencies of these and other adverse events were found in an integrated population from the RECAP extension study. Meta-analyses of treatment-emergent serious adverse events using data from ASCEND, CAPACITY 1 & 2 and SP3 at week 52 showed no difference between the pirfenidone and placebo groups (OR: 0.90, 95% CI: 0.70 to 1.15, p-value not reported).

In the absence of head-to-head RCTs evaluating nintedanib against pirfenidone the company performed an indirect treatment comparison using Bayesian random effects network meta-analysis (NMA). NMAs were conducted separately for 11 outcomes relevant to the decision problem and key adverse event outcomes. A total of eight studies (ASCEND, CAPACITY 1 and 2, SP3, INPULSIS 1 and 2, TOMORROW and PANTHER) were included but the number of studies contributing to each NMA differed by outcome. [10, 11, 13, 16-19] Results of the NMA are summarised in Table 5, and the results of four of these outcomes (overall survival [OS], PFS, time to treatment discontinuation and acute exacerbations) were used to inform the economic model. Based on the NMA, the treatment effects for pirfenidone were broadly similar to those for nintedanib for all outcomes, with the pairwise treatment effects indicating that neither treatment is statistically significantly more effective. NMA of safety data indicated that pirfenidone is associated with reduced odds of diarrhoea compared to nintedanib, and increased odds of rash as compared to nintedanib. For discontinuation due to adverse events and serious cardiac adverse events, the treatment effects for pirfenidone were broadly similar to those for nintedanib, with the pairwise treatment effects indicating that neither treatment is associated with more adverse events.

Insert Table 5 near here: Treatment effects from company's base-case random effects meta-analysis

3.1.1 Critique and interpretation of the clinical evidence

The company submission (CS) addressed the population specified in the scope and subgroup analyses were provided for patients with an FVC above 80% predicted (described as mild IPF in the CS) and between 50% and 80% predicted (described as moderate IPF in the CS), but no subgroups results were presented by DLco status.

The final selection of three trials (ASCEND, CAPACITY 1 and CAPACITY 2) for the main clinical efficacy review was considered appropriate by the ERG, as was the inclusion of the trials from Japan, SP3 and SP2, as supporting evidence. An additional relevant trial was also identified by the ERG and included as supporting

evidence: this was a multicenter Chinese trial, which compared pirfenidone plus N-acetylcysteine (NAC) with placebo plus NAC in adult patients with mild or moderate IPF (Huang 2015) [20].

The ERG noted that there were between-trial differences across some baseline characteristics in the three key trials (ASCEND, CAPACITY 1 & 2), such as mean FVC or 6MWD at baseline, although subgroup analyses suggested that these and other variables did not influence treatment effect. However, the ERG had some concerns regarding the generalisability of the trial populations. The patients included in the main clinical trials for pirfenidone may not be wholly representative of the population likely to receive pirfenidone in clinical practice as real-life patients often have comorbidities, more severe disease, take concomitant medications and have a higher mortality risk compared with those patients enrolled within the clinical trials [21]. Patients with IPF and comorbid obstructive airway disease were excluded from the three main RCTs, but would be considered for treatment in current practice in the UK provided they have a percent predicted FVC of between 50% and 80%.

Overall, the ERG assessed the potential risk of bias in ASCEND and CAPACITY 1 & 2 to be low across most domains, with the exception of reporting bias and "other bias", which were judged to be "moderate" because of inconsistencies between some of the outcome measures and analyses specified in the trial protocols and those presented in the CS, and because of the possible influence of uncontrolled variables such as rate of disease progression. The supporting trials, SP3, SP2 and Huang et al. (2015), were at a higher or more unclear risk of bias across many domains than the ASCEND and CAPACITY trials.

The ERG also noted that, for FVC outcomes, statistically significant differences were observed in ASCEND and CAPACITY 2 but not in CAPACITY 1. In response to an ERG request to explain the differences between the trials on this outcome, the company stated that "the natural variability in rates of FVC percent predicted decline of this heterogeneous disease" might explain differences in outcomes both within and across trials [22]. This pattern of non-significant differences for CAPACITY 1 was also observed for PFS and one of the functional measures used to define progression (a 50m decline or more in 6MWD or death).

The ERG accepted that there were fewer overall deaths in the pirfenidone arms than in the placebo arms of the ASCEND and CAPACITY trials and that, in some pooled analyses, these differences were statistically significant at the 5% level. However, in the meta-analysis of overall survival from ASCEND, CAPACITY 1 and CAPACITY 2, the ERG noted that the reduction in mortality was lower when including 72 week data from the CAPACITY trials instead of 52 week data. The ERG noted that there appeared to be a markedly increased rate of mortality in the CAPACITY trials between the data reported for 52 weeks and for 72 weeks (see Table 4), and the reasons for this were unclear.

The ERG noted how the effect of the, "intrinsic variability in rates of FVC decline" [11] might explain differences in some outcomes across trials. Participants in the trials included in the CS were not stratified by rate of progression, so it is possible, for example, that the placebo arm might have had more participants with more rapidly progressing disease than the intervention arm. As a result, the true treatment effect of the intervention relative to placebo is uncertain. This could work either for or against the intervention.

The ERG noted that whilst there is a lack of statistical evidence to support a difference in clinical effectiveness for OS by disease severity, the effect of treatment on OS is more uncertain in the mild subgroup.

The ERG noted that, overall, some adverse events (AEs) were frequent, but that these were generally mild or moderate in severity, and the majority of safety data were from trials with a follow-up of no more than 72 weeks. However, two ongoing studies would address some outstanding issues: RECAP and PIPF-002.

The ERG considered the NMA to be of good methodological quality, and the choice of random effects model was appropriate given the stated concerns in terms of heterogeneity between the studies. The ERG's key concerns were in the use of the earlier 52 week follow-up data for key time-to-event outcomes (all-cause mortality and PFS), rather than the full 72 week data available, and the difference in the treatment effects observed at these two time points despite the claim of proportional hazards (PH) over both the observed and unobserved time period.

The definition of PFS used across the pirfenidone trials was not consistent although where possible, individual patient data (IPD) were re-analysed to provide results based on a consistent definition. However, this could not be done for all of the trials which contributed to the NMA. The ERG considered that the NMAs which combined data from studies using different PFS definitions should be interpreted with caution. The ERG also noted that the treatment effect for a number of clinically important and patient-reported outcomes was either not statistically significant (DLco and SGRQ) or did not meet the threshold for a clinically important difference (UCD SOBQ).

3.2 Cost-effectiveness evidence provided by the company

The company submitted a fully executable economic model as part of their submission to NICE [9]. The analysis was undertaken from the perspective of the UK National Health Service (NHS) and Personal Social Services (PSS) over a lifetime horizon. The CS presented analyses for three populations: mild to moderate IPF (the ITT-trial population); mild IPF (percent predicted FVC >80%); and moderate IPF (percent predicted FVC between 50% and 80%). BSC was included as a comparator for all three populations but nintedanib was only included as a comparator for the moderate population.

In the company's base-case, patients initiating pirfenidone are assumed to discontinue treatment at the rate observed in the trials; and therefore no stopping rule is applied in the base-case. The stopping rule defined by NICE which formed the basis for the positive recommendation for pirfenidone and nintedanib is however applied to nintedanib in the company's base-case. A scenario analysis is also presented where the stopping rule is applied to both nintedanib and pirfenidone. The company's original analysis presented results for a revised PAS that resulted in a reduced discount for pirfenidone relative to the PAS accepted in TA282.

The company's base-case model used three main health states: progression-free; progressed and dead. The progression-free and progressed states were further divided into on and off treatment sub-states. The company's model adopted a cohort-based partitioned survival approach whereby the OS, PFS and discontinuation curves for pirfenidone were extrapolated from the Phase III trial data over a lifetime horizon using parametric functions and these curves were used to determine the proportion of patients residing in each state over time. Treatment effects

for PFS and OS were incorporated by applying HRs (BSC versus pirfenidone and nintedanib versus pirfenidone) from the NMA, which were based on outcomes at 48 or 52 weeks in the company's base-case analysis. In the company's original base-case analysis these were applied over the whole life-time irrespective of time on treatment but sensitivity analyses explored shorter durations of treatment effect.

The company's model used a price year of 2014-15 and included costs for drugs treatments, patient monitoring, adverse events, acute exacerbations, lung transplants and end of life care. The utility values attached to the health states were estimated by mapping from the SGRQ outcomes collected in the CAPACITY trials to the EQ-5D using a published algorithm.

Based on the company model when incorporating the revised PAS for pirfenidone, the ICER for pirfenidone versus BSC was £21,387 per QALY gained in the ITT population, £24,187 per QALY gained in the mild subgroup and £21,318 per QALY gained in the moderate subgroup. The results for pirfenidone versus nintedanib when incorporating both the nintedanib PAS and the revised pirfenidone PAS (moderate subgroup) are confidential.

The company presented a series of scenario analyses. The ICERs were mostly sensitive to the assumption regarding the time horizon, the duration over which the treatment effect is assumed to remain constant, the parametric distributions for OS in patients initiating pirfenidone, the treatment effects taken from the NMAs for OS, and the inclusion of stopping rules for pirfenidone and nintedanib.

3.2.1 Critique of the cost-effectiveness evidence and interpretation

The company's model which was based on a single point of disease progression failed to capture the ongoing progressive nature of IPF as patients in the progressed state were assumed not to experience any further quality of life decrement from subsequent declines in lung function. The ERG considered that this may have resulted in lifetime QALY gains being overestimated. Furthermore, the company's model assumed that all disease progression is equally detrimental regardless of the starting level of FVC, which was not deemed appropriate following clinical advice.

In the company's model acute exacerbations are disconnected from the outcomes of progression and survival and are instead included as a simple cost and utility decrement during each model cycle. Clinical advisors to the ERG suggested that patients who have experienced an exacerbation would usually be considered to have progressed. The ERG therefore considered that the company's model failed to accurately reflect the relationship between acute exacerbations and progression.

When the stopping rule was implemented in the company model, patients were assumed to stop treatment when disease progression occured. However, because the OS, PFS and discontinuation curves from the trials were modelled independently of each other, treatment discontinuations had no impact on OS. Therefore, the ICERs presented by the company using the stopping rule could represent a lower bound of the true ICER when the stopping rule is implemented in clinical practice, as the life-time costs of treatment were reduced when the

stopping rule was applied in the model, but the incremental QALYs were not reduced by the shorter duration of treatment.

In the company's base-case, the treatment effects are estimated from a random effects model including all Phase II and III trials using data up to 52 weeks. The ERG considered that: (i) the treatment effects estimated using data up to 72 weeks are more appropriate and consistent with the company's assumption of proportional hazards; (ii) SP3 should be excluded from the base-case as this is a different (Japanese) population with a different dose and statistical adjustments were required as HRs were not reported. The ERG further considered that the CODA sample estimated from the NMA should be used in the economic model instead of the median HR.

The ERG considered that it was overly optimistic to assume that the treatment effects estimated during the trials using the proportional hazards (PH) assumption would be expected to hold over the patient's entire lifetime irrespective of the duration of treatment.

The ERG noted that the Weibull and Gompertz distributions provided a similar fit to the observed OS but different long-term extrapolations. The ERG considered the Gompertz distribution provided a more realistic long-term extrapolation for OS than the Weibull distribution which was used in the company base-case.

The ERG further observed that there was a discrepancy between the model's prediction of OS for patients initiating BSC and the observed trial data for OS in patients who were randomised to placebo. The CS did not comment on this discrepancy and instead focused on a comparison of the model prediction with registry data for patients receiving BSC, even though the registry data did not match the trial data for patients randomised to placebo.

3.3 Additional Work Undertaken by the ERG

A number of analyses were undertaken by the ERG which informed the ERG's preferred base-case. The main changes within the ERG's preferred base-case were:

- use of treatment effects estimated from the NMA from the CODA samples of the predictive distributions, using data up to 72 weeks, excluding SP3
- exploration of different durations for the extrapolation of the treatment effect (2 years and entire model duration)
- presentation of results both with and without the stopping rule (see concerns described above regarding company's implementation of the stopping rule)
- use of the Gompertz distribution for OS (rather than the Weibull)
- capping utility estimates for individuals at a maximum of 1.0
- adjustment of utility by age
- inclusion of the costs associated with end of life care for all patients irrespective of the cause of death
- amendments to dose reductions/interruptions assumed in the company's model for pirfenidone and nintedanib
- amendment of minor programming errors in the economic model

The ERG's preferred base-case was presented as a range to reflect the uncertainty regarding the duration of treatment effect and the impact of the stopping rule. In each population, the lower range of the ICER incorporated a life-time treatment effect and included the stopping rule and the upper range of the ICER incorporated a 2-year treatment effect but excluded the stopping rule. For the ITT population the ICERs incorporating the PAS ranged from £27,124 to £115,751 per QALY gained. For the mild population (percent predicted FVC >80%) the ICERs incorporating the PAS ranged from £31,722 to £186,260 per QALY gained. For the moderate population (percent predicted FVC 50 to 80%), the ICERs for pirfenidone versus BSC ranged from £27,432 to £104,915 per QALY gained when incorporating the PAS.

In response to a request from the committee, the ERG also provided ICERs for two additional exploratory analyses. The first updated the efficacy estimates in the model to incorporate the results of the NMA when including SP3 and the second included the stopping rule for nintedanib but not for pirfenidone. Both analyses implemented these changes within the model previously used to generate the ERG-preferred base-case ICERs.

3.4 Conclusions of the ERG Report

The trials have some issues with generalisability. There is some evidence to support a statistically significant reduction in the decline in percent predicted FVC compared with placebo, but a statistically significant treatment effect was not demonstrated in one of the trials (CAPACITY 1), which weakens the strength of the evidence for this outcome. The available evidence suggests that there is a statistically significant reduction in all-cause mortality for pirfenidone compared with placebo, but there remains uncertainty regarding whether the size of the treatment benefit for overall survival is constant over time due to variation in the treatment effect estimated using data from 52 weeks and 72 weeks. The safety evidence was generally at low risk of bias but was limited, and questions remain over AE rates in the long-term.

The subgroup analyses by disease severity (percent predicted FVC 50 to 80% versus >80%) presented by the company for the outcomes of PFS and OS were not sufficient to support the use of subgroup-specific treatment effects according to disease severity.

Based on the NMA, the treatment effects for pirfenidone were broadly similar to those for nintedanib for all outcomes, with the pairwise treatment effects indicating that neither treatment is statistically significantly more effective. The NMA incorporating data up to 72 weeks was preferred by the ERG as it includes all of the relevant evidence and is consistent with the company's assumption regarding PHs during the observed period.

The company's model did not incorporate the stopping rule in an appropriate manner and the analyses incorporating the stopping rule are likely to overestimate the benefits of pirfenidone compared with BSC. There remains considerable uncertainty in the cost-effectiveness estimates for pirfenidone versus BSC due to uncertainty regarding the duration of treatment effectiveness beyond the trial period. The company's model fails to capture the progressive nature of the disease, because it only allowed a single progression and assumed a constant utility in the progressed state but it is unclear what effect this has had on the ICER.

3.5 Draft guidance in the ACD

The committee concluded that, when using the reduced discount in the revised PAS, the most plausible ICERs for pirfenidone versus best supportive care were above the range that could be considered cost effective. However, in NICE's previous guidance on pirfenidone, the drug was regarded as cost effective for patients with an FVC between 50% and 80% predicted when applying the original PAS. The committee recommended that no changes be made to the original guidance in TA282 in the ACD.

3.6 Additional evidence submitted by the company in response to the ACD

In response to the ACD, the company provided revised cost-effectiveness analyses [23]. These were based on the ERG's adaptation of the company's model with the following changes:

- no comparison against nintedanib was presented
- the discount from the original PAS from TA282 was applied
- treatment effect was varied from 8 years to lifetime (graphical results were provided from 2 years to lifetime)
- an additional subgroup analysis was presented for patients with percent predicted FVC ≥50% and <90%
- in addition to the ERG's preferred parametric curve (the Gompertz) the company presented results for two alternative methods for extrapolating OS; the Weibull, and a weighted parametric model.
- the model was populated with CODA samples for the HR for OS at 72 weeks generated by the company using the posterior distribution from the company's original NMA instead of the predictive distribution

3.7 ERG's critique of the additional evidence submitted

The company had not provided any analysis of clinical effectiveness for the population with percent predicted FVC ≥50% and <90% and therefore, it was not possible for the ERG to assess the validity of the company's claim that *"there is no evidence of a tre*atment-interaction when the FVC < 90% subgroup is explored". The ERG did not agree with the company's argument that a subgroup analysis for patients with FVC <90% predicted was justified on the basis that the majority of evidence from the ASCEND and CAPACITY trials was from patients with predicted FVC below 90%.

The ERG did not agree with the methods used to generate the weighted parametric curve and considered that the weighted survival curve estimated by the company had limited credibility. The ERG was not convinced that the Weibull curve provided a more plausible extrapolation of OS than the Gompertz curve based on the company's comparison of survival estimates from the INOVA registry data with survival estimates projected by the different parametric curves. The ERG was not convinced that the data from the INOVA registry could be used to justify a constant treatment effect over 8 years and concluded that there was considerable uncertainty regarding whether the treatment effect observed in the trials persists up to 8 years or beyond. The ERG re-ran the company's analyses using the ERG's original NMA methods (i.e. using the predictive distribution) but having excluded the nintedanib trials and included SP3 (based on the committee's conclusions in the ACD) and found that this had minimal impact on the cost-effectiveness estimates.

The company's response to the ACD had argued that there was no difference in the efficacy of pirfenidone by baseline percent predicted FVC and the data from the trial populations should be assessed in their entirety. The ERG considered it reasonable to consider separately the cost-effectiveness of pirfenidone in patients with percent predicted FVC ≥80% versus those with percent predicted FVC <80% as there was some evidence from Albera et al. that prognosis differed in these groups, and this difference justified considering whether the cost-effectiveness was consistent across the subgroups [24].

4. Key Methodological Issues

The partitioned survival approach adopted in the company's model meant that the outcomes of OS, PFS and discontinuation were modelled independently of each other; this effectively assumes that treatment discontinuations, either following disease progression or for other reasons, do not to affect OS. Such an approach can be appropriate in situations where treatment discontinuation in clinical practice is likely to follow that observed in the trials and the aim of the model is simply to extrapolate QALY gains beyond the trial period. However, in this case the company needed to incorporate a stopping rule which was not applied in the trials. This required some assumptions to be made regarding the impact on clinical outcomes of patients discontinuing treatment according to the stopping rule. Whilst clinical advisors to the ERG commented that it is hard in this case to understand the relationship between treatment discontinuation and clinical outcomes, the ERG does not believe the company's assumption that there is no relationship between treatment duration and treatment outcomes to be plausible. The ERG considered that the use of a partitioned survival modelling approach was therefore not appropriate in this case.

The company's base-case model appeared to be based on two contradictory positions regarding the PH assumption for PFS and OS. On the one hand, the CS argued that the PH assumption was supported by the trial evidence, and this was used to support the use of a constant HR which was applied over the whole model timeframe. On the other hand, the company argued that the NMA should use only data up to 52 weeks, because there are no data to support an assumption of PH for nintedanib versus placebo beyond 52 weeks. The ERG considered that including data up to 72 weeks was consistent with the company's assumption that PHs hold during and beyond the trial period. However, the ERG also noted that the observed reduction in treatment effect between 52 weeks and 72 weeks would not be expected under the PH assumption. The ERG's exploratory analyses demonstrated the importance of exploring alternative assumptions regarding the extrapolation of the treatment effect beyond the trial period. This is particularly important in disease areas where the prognosis is heterogeneous and the mechanism of treatment is not fully understood, making it hard to judge whether a PH assumption beyond the treatment period is reasonable.

5. NICE Guidance

The committee recommended no change to the existing NICE guidance that recommended pirfenidone as an option for treating idiopathic pulmonary fibrosis in adults only if:

- the person has a forced vital capacity (FVC) between 50% and 80% predicted
- the company provides pirfenidone with the discount agreed in the PAS and

- treatment is stopped if there is evidence of disease progression (an absolute decline of 10% or more in predicted FVC within any 12-month period).

It should be noted that the PAS referred to in the recommendations was the original PAS from TA282 and not the revised PAS proposed in the company submission.

The company submitted an appeal against the first FAD (released in September 2016) in which it was claimed that the committee had failed to take into account the totality of the data with respect to 'adults with mild to moderate idiopathic fibrosis' (i.e. the population covered by the licensed and specified in the scope) and the Committee should not have considered the subgroup with FVC between 80% and 90% of predicted as a relevant population for decision making. This appeal point was upheld because the Appeal Panel considered that the Committee had acted unfairly because they had not demonstrated in the September 2016 FAD that they had considered the whole population as defined in the scope as one population before considering any subgroups, and their use of subgroups, based on the reasoning presented in the September 2016 FAD, was unreasonable. The Appeal Panel also upheld a separate appeal point that the Committee's assessment of clinical effectiveness was perverse because the FAD had stated both that "it was not clear whether pirfenidone was more, less or equally effective in the group with FVC above 80% predicted" and that it was "more likely to be less effective" in this group. The Appeal Panel concluded that the Appraisal Committee's assessment of the clinical effectiveness of pirfenidone in any subgroups should be clearly documented, including any uncertainty in the available evidence. The Committee met following the appeal decision and addressed the points upheld by the Appeal Panel. The FAD was revised to reflect the committee's discussion, but the recommendations for pirfenidone were unchanged. Although this second FAD was subject to an appeal, the appeal was dismissed on all grounds and the Committees' recommendations remained unchanged in the final guidance. Here we summarise some of the Committee's key considerations which supported the recommendations in the final guidance.

The committee recognised that the recommendation for nintedanib in TA379 was based on the comparison of nintedanib with pirfenidone, rather than nintedanib with best supportive care. The committee concluded that it was therefore more appropriate for decision making to compare pirfenidone only with best supportive care.

The committee concluded that patients with an FVC above 80% predicted were under-represented in the clinical trials and that the trial evidence was most generalisable to patients with an FVC of up to 90% predicted. However, the committee agreed to accept that pirfenidone has the same relative effectiveness in patients with an FVC above 80% predicted and in patients with an FVC of 80% predicted or less.

The committee concluded that the company's evidence did not conclusively show that patients continue to benefit from pirfenidone after disease progression. However, the committee recognised the comments from clinical experts that some patients may benefit after disease progression. It concluded it was appropriate to consider cost-effectiveness analyses with and without the stopping rule. However, the committee concluded that the analyses that included a stopping rule were associated with uncertainty as the ERG and company expressed differing views in the meeting on whether the implementation of the stopping rule would under or over-estimate the ICERs.

The committee agreed to take both the Weibull and Gompertz curves into account in its decision-making because they considered that the true risk of death might lie between the two distributions, but closer to the Gompertz distribution. The committee concluded that the evidence did not justify assuming a constant mortality benefit for 8 years, but it was reasonable to assume a constant benefit up to 5 years.

The committee concluded that the ICERs for pirfenidone versus best supportive care that matched their preferred assumptions for the population specified in the marketing authorisation (i.e. FVC above 50% predicted), when including the stopping rule and assuming a 5-year treatment effect, were between £25,706 and £28,870 per QALY gained depending on whether the Gompertz or Weibull survival curves were used. They further concluded that these ICERs were uncertain for the following reasons;

- the modelled population did not include as many patients with an FVC above 80% predicted as expected in NHS practice and this may increase the ICER
- the impact of the stopping rule on the ICER was uncertain
- there was still uncertainty about how long the survival benefit of pirfenidone would last (it could be less than 5 years).

The committee concluded that pirfenidone could not be considered a cost-effective use of NHS resources for adults with mild to moderate idiopathic fibrosis because the ICERs were above £20,000 per QALY gained and were associated with some uncertainties that had the potential to substantially increase the ICER.

The committee concluded that the most plausible ICERs for the subgroup with a starting FVC of between 50% and 80% predicted were between £24,933 and £27,780 per QALY gained (for Weibull and Gompertz survival curves respectively) and were also subject to uncertainties that may substantially increase the ICER. However, the Committee understood that pirfenidone had been considered reasonably innovative at the time of the previous appraisal, and it had not seen any clinical evidence contradictory to that considered previously. It was therefore not minded to change this recommendation and withdraw an existing treatment option for patients with moderate disease, despite the relatively high ICERs.

The committee were aware that removing the stopping rule increased the ICERs and therefore concluded that pirfenidone could not be considered cost-effective without the stopping rule given that the ICERs with the stopping rule were already in the £20,000 to £30,000 per QALY gained range and associated with uncertainty.

6. Conclusions

Whilst the ASCEND study has provided additional evidence supporting the clinical effectiveness of pirfenidone in patients with mild to moderate IPF, there remains considerable uncertainty as to whether the benefits observed in the trial will persist in the long-term and the estimates of cost-effectiveness were particularly sensitive to this uncertainty. The implementation of the stopping rule based on disease progression within an economic model based on partitioned-survival was problematic and resulted in additional uncertainty in the ICERs for these analyses but the committee concluded that pirfenidone was not cost-effective without the stopping rule.

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SD, CC, JH [formerly named Jean Sanderson], ME and RR drafted the manuscript and take responsibility as guarantors of the content. All authors have given their approval for the final version to be published. This summary has not been externally reviewed by PharmacoEconomics

Compliance with ethical standards

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Conflicts of interest

SD, RR, CC, JH and ME have no potential conflicts of interest.

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Table 1: Findings from company's random effects meta-analyses for pirfenidone versus placebo

Outcome	Trials	Time-point (weeks)	Measure (95% CI)	Difference, p-value
Decline ≥10% FVC or death	ASCEND, [10] CAPACITY 1 & 2 [11]	52	OR 0.50 (0.31–0.82)	NR
Change from baseline in FVC/VC (ml)	ASCEND [10], CAPACITY 1 & 2 [11] and SP3 [13]	52	MD 3.4, (1.87 to 4.94)	NR
Mortality	ASCEND, [10] CAPACITY 1 & 2 [11]	52	HR 0.52 (0.31 to 0.88)	0.011
		72	HR 0.64, (0.41 to 0.99)	NR
PFS[a]	ASCEND [10], CAPACITY 1 & 2 [11] and SP3 [13]	52	HR 0.63 (0.53 to 0.74)	NR

[a] *The definitions of PFS varied across trials, albeit with a common element of a confirmed ≥10%* decline from baseline in percent predicted FVC or VC

Abbreviations: FVC: Forced Vital Capacity ; VC: Vital Capacity; PFS: Progression Free Survival; OR: Odds ratio; HR: Hazard ratio; MD: Mean difference; NR: Not reported

Table 2: Categorical analysis of change from baseline in percent predicted FVC or death (adapted from Table 18 of the company submission [9])

Study	Time point (weeks)	Treatment group	Decline ≥10% FVC or death, n (%)	p-value [a]
ASCEND[10]	52	PFN 2,403mg/day (n=278)	46 (16.5)	p<0.001
		PBO (n=277)	88 (31.8)	
CAPACITY 1[11] [b]	72	PFN 2,403mg/day (n=171)	39 (22.8)	p=0.440
		PBO (n=173)	46 (26.6)	
CAPACITY 2[11] [b]	72	PFN 2,403mg/day (n=174)	35 (20.1)	p=0.001
		PBO (n=174)	60 (34.5)	

[a] Rank ANCOVA (pirfenidone 2,403mg/day vs placebo).

[b] Note: For the CAPACITY trials the data presented are from the original publication (Noble 2011[11]), which only reports decline of > 10% FVC and not decline of > 10% or death

Abbreviations: FVC, Forced vital capacity; PFN, pirfenidone; PBO, placebo

Table 3: Mean change from baseline in FVC/VC (ml) (adapted from Table 21 of the company submission [9])

Study	Time point	Treatment group	Mean decline in FVC/VC	Difference, p-value [a]
ASCEND[10]	52 weeks	PFN 2,403mg/day (N=278)	FVC: 235 ml	Absolute difference: 193ml Relative difference: 45.1% p<0.001
		PBO (N=277)	FVC: 428 ml	
CAPACITY 1[11]	72 weeks	PFN 2,403mg/day (N=171)	FVC: 379 ml	Absolute difference: -5ml Relative difference: -1.4% p =0.508
		PBO (N=173)	FVC: 373 ml	
CAPACITY 2[11]	72 weeks	PFN 2,403mg/day (N=174)	FVC: 318 ml	Absolute difference:157ml Relative difference: 33% p =0.004
		PBO (N=174)	FVC: 475 ml	
SP3[13]	52 weeks	PFN 1,800mg/day (N=108)	VC: 90 ml	PFN 1,800 mg/day vs. PBO: Absolute difference: 70ml Relative difference: NR p=0.042
		PFN 1,200mg/day (N=55)	VC: 80 ml	
		PBO (N=104)	VC: 160 ml	
SP2[12]	9 months	PFN 1,800mg/day (N=72)	VC: 30 ml	Absolute difference: 100ml Relative difference: NR p=0.037
		PBO (N=35)	VC: 130 ml	

[a] Rank ANCOVA: ASCEND, CAPACITY 1 & 2 (pirfenidone 2,403mg/day vs placebo); SP2 and SP3 (pirfenidone 1,800mg/day vs. placebo)

Abbreviations: FVC, Forced vital capacity; VC, Vital capacity; PFN, pirfenidone; PBO, placebo; NR, not reported

Table 4: All-cause mortality rates in the CAPACITY 1 & 2 and ASCEND studies (adapted from Table 33 of the company submission [9])

Patients	Time-point (weeks)	PFN n (%)	PBO n (%)	HR (95% CI) [a]	p-value [b]
ASCEND[25, 10]		n=278	n=277		
	52	11 (4.0)	20 (7.2)	0.55 (0.26, 1.15)	0.105
CAPACITY 1[c]		n = 171	n = 173		
	52	6 (3.5)	9 (5.2)	0.66 (0.24 – 1.84)	0.435
	72	13 (7.6)	15 (8.7)	0.87 (0.41 – 1.82)	0.704
CAPACITY 2[c]		n = 174	n = 174		
	52	5 (2.9)	13 (7.5)	0.37 (0.13 – 1.05)	0.049
	72	8 (4.6)	15 (8.6)	0.51 (0.22 – 1.20)	0.116
CAPACITY 1 & 2[11] [c]		n=345	n=347		
	52	11 (3.2)	22 (6.3)	0.49 (0.24-1.01)	0.047
	72	27 (8)	34 (10)	0.77 (0.47-1.28)	0.315

[a] Cox proportional hazards model

[b] Log-rank test (pirfenidone 2,403mg per day vs placebo)

[c] Data taken from Appendix 11 of the company submission

[d] Data from the CAPACITY 1 & 2 studies were censored at one year for the 52 week analysis presented in the company submission; the 72-week data were taken from those published in Noble 2011[11]

Abbreviations: HR, hazard ratio; PFN: pirfendione; PBO: placebo

Table 5: Treatment effects from company's base-case random effects meta-analysis

Outcome	Number of trials*		Treatment effect, median (95% credible interval)		
	PFN	NTB	PFN vs placebo	NTB vs placebo	PFN vs NTB
Lung Capacity					
Change from baseline in Percent Predicted FVC/VC (%)	4	3	3.39 (1.94,4.84)	3.33(2.34,4.5)	0.05 (-0.81,1.80)
Change from baseline in FVC/VC (L)	4	3	0.12 (0.04,0.20)	0.12 (0.04,0.21)	0.00 (-0.11,0.12)
FVC decline ≥10% Percent Predicted (OR)	3	2	0.58 (0.40,0.88)	0.65(0.42,1.02)	1.12(0.60,2.01)
Physical Functioning and HRQoL					
Change in 6MWD	3	1	22.70 (8.82,36.31)	6.00 (-28.25,40.66)	16.63 (-20.83,53.81)
SGRQ	2	3	-1.24 (-4.94,2.39)	-2.11 (-5.48,0.37)	0.88 (-3.45,5.94)
Time to event outcomes					
All-Cause Mortality up to 52 wks (HR)	4	3	0.52 (0.30, 0.88)	0.71 (0.43,1.16)	0.73 (0.35,1.50)
All-Cause Mortality up to 72 wks (HR)			0.62 (0.38, 0.99)	0.71 (0.43, 1.16)	0.87 (0.44, 1.72)
PFS HR up to 52 wks (HR)	4	2**	0.63 (0.50, 0.80)	0.74(0.51,1.08)	0.85 (0.55,1.34)
PFS HR up to 72 wks (HR)			0.63 (0.50, 0.78)	0.74 (0.51,1.07)	0.85(0.55,1.31)
Other					
Acute Exacerbations (OR)	4	3	0.62 (0.29,1.39)	0.55 (0.26,1.09)	1.14 (0.41,3.44)
All-cause Discontinuation of Treatment (OR)	4	3	1.28 (0.91,1.78)	1.42 (1.01,2.01)	0.90 (0.55,1.44)
Adverse events					
Diarrhoea (OR)	3	3	1.39 (0.94, 2.11)	7.32 (4.82, 11.13)	0.19 (0.11, 0.35)
Rash (OR)	3	2	3.85 (2.38, 6.29)	1.29 (0.49, 3.35)	2.99 (1.03, 8.88)
Discontinuation due to adverse event (OR)	4**	3	1.58 (1.04, 2.39)	1.52 (1.01, 2.29)	1.04 (0.58, 1.85)
Serious cardiac events (OR)	3**	3**	1.36 (0.54, 3.46)	0.64 (0.17, 1.49)	2.11 (0.65, 11.34)

Abbreviations: 6MWD, 6-Minute Walking Distance; FVC, forced vital capacity; HR, hazard ratio; NTB, nintedanib; OR, odds ratio; PFN, pirfenidone; PFS, progression free survival; SGRQ, *St George's Respiratory Questionnaire*; VC, vital capacity

* number of trials are summarised for interventions relevant to the decision problem only. Full network also includes N-acetylcysteine (NAC) and triple therapy trials (PANTHER)

** uses pooled HR for INPULSIS studies