# Pirfenidone for the treatment of idiopathic pulmonary fibrosis

# ERG overview of manufacturer's additional analyses and Patient Access Scheme (PAS).


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## Introduction

SHTAC were requested to provide an overview of additional analyses undertaken by InterMune UK and Ireland for the STA of pirfenidone for the treatment of idiopathic pulmonary fibrosis. In addition SHTAC were also requested to provide an overview of a Patient Access Scheme (PAS) for the use of pirfenidone which had been submitted for approval to the Department of Health.

This addendum to the original ERG report is set out in two parts. Part one provides the ERG's critique and comment on the additional analyses presented on the clinical and cost effectiveness of pirfenidone for IPF, the interpretation of these data by the manufacturer, and notes key issues for the committee's consideration. Part two provides the ERG's critique and comment on the proposed PAS.

## Part I: Additional analyses.

The manufacturer provided a document containing:

- A completed Section 4 on the innovative nature of pirfenidone
- Subgroup analysis of patients in the CAPACITY Phase III studies (PIPF-004 and PIPF-006) with a baseline forced vital capacity (FVC) ≤ 80% predicted
- Subgroup analysis of patients in the CAPACITY Phase III studies (PIPF-004 and PIPF-006) with a baseline FVC ≤ 80% predicted, excluding those with borderline obstructive disease
- The methods and results of updated cost-effectiveness model including:
    1. Amended pills per day: to correct an error in the original submission
    2. Amended discontinuation rates: to account for long term data available from the open label continuation of the CAPACITY trials
    3. New modelling of FVC ≤ 80% predicted, excluding those with borderline obstructive disease: to account for an imbalance observed in the CAPACITY trials
    4. New modelling of triple therapy incorporating data from a recent RCT publication
    5. New pooled comparator analysis: in an attempt to address likely comparator mix based on expert clinical advice.

The manufacturer also provided data in a number of appendices, including a clarification of systemic steroid use in the CAPACITY trials and a discussion of the case for pirfenidone to be considered under the NICE End of Life Criteria.

The extent of these new analyses have meant that the ERG has been unable to undertake a full and complete assessment of some of these aspects in the time available. Where this is the case this has been made clear in this report. In keeping with the original ERG report, we refer to the PIPF-006 study as CAPACITY-1 and PIPF-004 study as CAPACITY-2 when the two trials are discussed separately, or CAPACITY trials when discussed together.

The innovative nature of pirfenidone

Since the original manufacturer's submission for pirfenidone the NICE manufacturer submission (MS) template document has been updated to include a section on innovation. In this additional analysis document the manufacturer has provided details of their view of the innovative nature of pirfenidone, responding to the questions set out in the updated MS template document. Clinical advice to the ERG is that pirfenidone is part of a new wave of therapies in which new pathways are targeted. This represents a step-wise change from previous models of drug development and can be seen as being innovative. However, this is also true of other putative agents. Palliative care for people with IPF is lacking so the suggestions made would broadly improve the care of patients.

Subgroup analysis of CAPACITY trial data in those with a baseline forced vital capacity (FVC) ≤ 80% predicted

The manufacturer provides additional analyses of outcomes for a subgroup of participants from the two CAPACITY trials who had a FVC at baseline ⩽80% predicted (excludes those with 'milder' disease). In the original MS, subgroup analyses for this participant group were presented, and in this additional analyses submission document the manufacturer provides data from analyses of a greater range of outcomes than previously presented. The manufacturer states on page 7 of the additional analysis document that the original subgroup analysis indicated that pirfenidone was more effective in those with a baseline FVC ⩽80% predicted compared to baseline FVC ≥80% predicted. The ERG reiterate comments made in the original ERG report (see ERG report page 39) that data were not presented specifically using this cut-off of FVC in the original MS; that the confidence intervals for the analyses from which the manufacturer concluded that this group was more effective crossed the line of

no effect; that it is unclear whether this subgroup analysis was planned a priori and/or whether it was powered to detect a difference. In the additional analysis document the manufacturer states that these subgroups were analysed from individual patient data, this was not made clear in the original MS. In addition the manufacturer, in their discussion of this subgroup in the present analyses, does not refer to comments reported in the original MS that this cut-off is arbitrary and that clinicians would also expect to use outcomes from HRCT and $DL_{co}$ to be more precise (page 246 MS). The manufacturer does describe the lack of formal definitions for determining severity of IPF, and evidence showing relationships between baseline FVC % predicted and mortality, which the ERG note is an appropriate reflection of the situation.

Additional analyses for this subgroup are presented for FVC, PFS, Mortality and the 6MWT distance based on analysis of the individual patient data from the two CAPACITY trials. Analysis does not include this subgroup from the SP2 and SP3 trials (included in the original MS) as the manufacturer does not have the individual patient data from these RCTs. The manufacturer does not discuss the limitation of these analyses however the ERG suggest that these additional analyses should be interpreted cautiously as they appear to be post hoc analyses.

*FVC % predicted.*

The manufacturer provides details of an analysis of this subgroup on the change in FVC % predicted between pirfenidone and placebo from a pooled analysis of the CAPACITY trials. On page 7 of the additional analysis document the manufacturer states that the decrease in % predicted FVC in the subgroup with a baseline FVC $\leqslant$80% was clinically significant. The ERG are unable to check the data presented in Table 1 (page 8 of the addendum), however, note that at 72 weeks a statistically significant effect for pirfenidone in this subgroup was demonstrated (absolute difference 4.3, relative difference 33.7% p=0.0052). Details of the statistical analyses are not presented.

Clinical advice to the ERG suggests that FVC $\leqslant$80% is clinically plausible as a subgroup and would therefore be acceptable to clinicians and patients. This may mean that some patients with co-existing emphysema would be excluded from being prescribed pirfenidone as their FVC may be preserved initially. However, it would also mean that the small subset of

patients who remain stable, with little change in lung function for prolonged periods of time, are not treated with pirfenidone.

The ERG note that although the categories for subgroups based on baseline FVC % predicted were slightly different in the original MS, the data from the individual trials that were presented on the basis of a similar subgroup in the original MS did not show a consistent effect on FVC % predicted. The manufacturer does not present data from the individual CAPACITY trials in their additional submission document for this to be assessed for this subgroup.

The ERG note a likely error in the reporting of the numbers of participants in Table 1 in the additional analyses addendum, which suggests the total number for pirfenidone was 244 and for placebo was 233. As the numbers of participants in these groups were 345 and 347 respectively, the ERG have assumed the numbers presented are for the subgroups with a baseline FVC ≤80% rather than the total groups.

*Progression free survival (PFS)*

The manufacturer present results from a subgroup analysis for those with baseline FVC ≤80% predicted on progression free survival, using pooled individual patient data from the two CAPACITY trials. This shows that the hazard ratio for the subgroup (0.68, 95% CI 0.49, 0.94, p=0.0196) demonstrated a significant reduction in the risk of death or disease progression (by 32%) in the pirfenidone treated participants. The ERG are unable to check these data and reiterate again that this was not an a priori planned subgroup analysis. In the original MS the PFS for the overall population in the pooled group showed a 26% reduction in risk of death or disease progression (MS page 104), however, this was not a consistent finding between the individual CAPACITY trials (where one showed a significant reduction and one did not).

*Mortality*

An analysis of all-cause mortality for the subgroup with baseline FVC ≤80% is also presented in the additional analysis addendum. Similarly to above, the ERG are unable to check these data, and note that this was not a planned analysis at the outset of the trials. The analysis presented shows a 44% relative reduction in the risk of all-cause mortality in the pirfenidone treated group compared to the placebo treated group (IPF-related mortality showed a 61%

relative reduction in risk). The manufacturer note the limitations in interpreting these data owing to the reduced numbers of participants followed up after 72 weeks, and therefore state that the hazard ratio for IPF-related mortality used in the cost effectiveness analysis was that based on 72-weeks. The hazard ratio used (0.35) indicates a more favourable risk reduction (65%) with pirfenidone than the ratio estimated from the extended analysis. The manufacturer stated that they were unable to analyse mortality rates for the subgroup with baseline FVC ≥80% due to the low mortality rate in these participants. Clinical advice to the ERG concurs with this and suggests that mortality as an outcome in these populations is always unreliable due to small sample sizes and lack of power to detect a true difference. Overall the most reliable conclusion to make is that there is no apparent harmful effect from pirfenidone.

*6MWT distance*

Data presented for the subgroup analyses for the distance walked on the 6MWT can not be checked by the ERG. These show that there was a statistically significant difference in the distance walked between those treated with pirfenidone and those treated with placebo in the pooled CAPACITY trials in the subgroup with baseline FVC ≤80%. There was no statistically significant effect in the baseline FVC >80% subgroup.

*Meta-analysis of the FVC ≤80% subgroup of participants*

The manufacturer presents a series of meta-analysis of outcomes for the subgroup FVC ≤80% from the two CAPACITY trials. Data were not available from the SP2 and SP3 studies for this subgroup for the manufacturer to include in the meta-analysis.

Meta-analyses for change in FVC, 6MWT distance, PFS and risk of IPF-related mortality favoured pirfenidone. The meta-analysis for all-cause mortality showed a trend favouring treatment with pirfenidone. The manufacturer notes statistical heterogeneity was observed in the meta-analysis for FVC, as was also seen in the meta-analyses of the total group presented in the original MS. The ERG note that with the exception of the 6MWT heterogeneity was present in all meta-analyses presented. The extent of heterogeneity, as estimated by the $I^2$ test, ranged from 61% to 80%. The meta-analyses show that in the CAPACITY 1 study subgroup results on these outcomes were not statistically significantly improved with pirfenidone. For the CAPACITY 2 study results favoured pirfenidone. The ERG are unable to check the data used from the two CAPACITY trials for this subgroup of participants with that presented earlier on pages 7-10 of the additional analysis submission

because data for the individual trials were not summarised in the earlier section. In addition, the ERG have assumed that, as per the original MS, the mean values used were generated from the least squares mean from a rank ANCOVA which the ERG are unable to check (see discussion of this in ERG report, pages 23-4). The manufacturer does not stipulate the approach taken.

*Summary of ERG comments on the subgroup analyses*

- The ERG were unable to check the data presented for this subgroup in most cases
- Individual patient data were analysed, however, no methods of the analyses used are presented by the manufacturer.
- Caution is required in the interpretation of these data as they appear to be based on post hoc hypotheses, and it is unclear if these analyses are statistically powered to detect a difference.
- The manufacturer only presents data from the pooled CAPACITY trials, no data from individual CAPACITY trials are shown except in the meta-analyses. However the meta-analyses use mean scores rather than mean change scores for these outcomes and the ERG are unable to check these.
- The manufacturer provides no overall interpretation of the results seen. No discussion is made of the plausibility that those starting treatment with pirfenidone, who are slightly less 'mild' based on FVC % predicted, should do better.

<u>Subgroup analysis of CAPACITY trial data in those with a baseline FVC ≤ 80% predicted, excluding those with borderline obstructive disease</u>

The manufacturer provides additional analyses of outcomes for another subgroup of participants from the two CAPACITY trials. Having observed the mean change from baseline in % predicted FVC over 72 weeks in the two CAPACITY trials, the manufacturer noted the placebo group in CAPACITY 1 showed a different pattern of decline than that observed in the pirfenidone treated participants in both CAPACITY trials and the placebo treated participants in the CAPACITY 2 trial. The manufacturer hypothesise that this lessening in the rate of decline may be related to a higher proportion of participants with more obstructive physiology in the placebo group in the CAPACITY 1 trial. The manufacturer refers to evidence which suggests that obstructive lung disease has been shown to be associated with less decline in lung volume despite similar progression to fibrosis in the lungs (see page 13 of the additional analysis submission) to support their supposition.

Data is presented in Table 5 of the additional submission which shows that [redacted] of participants randomised to placebo treatment in the CAPACITY 1 trial had a baseline $FEV_1$/FVC ratio <0.8. In the pirfenidone arm at baseline the rate of participants with $FEV_1$/FVC ratio <0.8 was [redacted]. The proportion of participants with $FEV_1$/FVC ratio <0.8 in the CAPACITY 2 trial were [redacted] and [redacted] in the pirfenidone and placebo groups respectively. The ERG are unable to check these data. No differences between groups were observed on any other baseline measures in the two CAPACITY trials, participants were well matched, and it is therefore unclear whether the difference is purely a factor of chance or because of the threshold chosen.

The threshold used to establish obstructive disease ($FEV_1$/FVC ratio <0.8) was chosen by the manufacturer to be conservative to ensure that participants with borderline obstructive physiology were excluded. The manufacturer notes that the threshold of the ratio of $FEV_1$/FVC that establishes obstructive disease is uncertain, and discusses thresholds used in a number of different publications. In the NICE clinical guideline 101 for Chronic Obstructive Pulmonary Disease, the recommendation for diagnosis is $FEV_1$/FVC ratio <0.7. The manufacturer does not discuss this in their submission.

The ERG clinical advisors note that the threshold chosen by the manufacturer's is an arbitrary one. Whilst some clinicians may not have difficulty with this, for some it may be that this would be difficult to use in practice and it may be difficult to justify to patients.

The manufacturer proposes that the imbalance in obstructive disease may help explain the different FVC outcomes seen across the two CAPACITY trials. The ERG note that the manufacturer has previously attempted to identify the reasons for the differences seen on outcomes between the two CAPACITY studies, but that at that time nothing of note was identified.

Limited data analyses are presented for this subgroup. A meta-analysis is presented which shows the pattern of effect on % predicted FVC when those with borderline obstructive disease were excluded (FVC1/FVC ≥ 0.8), however, minimal statistical analysis of this data is presented, and very limited interpretation is offered. The manufacturer also present a meta-analysis which shows the pattern of effect on % predicted FVC in the population with obstructive disease but provide no commentary on this analysis. The manufacturer does not provide details of the effect of this subgroup on any of the other relevant outcomes.

*Summary of ERG comments on the subgroup analyses*

- The ERG were unable to check the data presented for this subgroup
- The manufacturer presents a reasoned case for the possibility that this subgroup may have contributed to the difference in results seen.
- The threshold used may not be wholly appropriate, and the data is largely based on observation rather than statistical testing.
- Caution is required in the interpretation of these data as they appear to be based on post hoc hypotheses, and it is unclear if these analyses are statistically powered to detect a difference

Methods of the updated cost-effectiveness model

*Amended pills per day*

The manufacturer used a different estimate for the average number of pirfenidone pills per day per patient. In the original submission, cycle-specific average number of pills had been estimated (7.84 for cycle 1, 7.86 for cycle 2, 7.87 for cycle 3, and 7.89 for the following cycles), whereas the addendum reports an amendment using the age-weighted average number of pills (7.65) which is applied to all cycles of the model.

The manufacturer comments that this change is due to a slight miscalculation due to an incorrect csv file in the original submission. The ERG does not have access to the original trial data, or the csv file mentioned, and so is unable to check these analyses. The ERG have tested the effect of this change to the results of the cost effectiveness analyses, see Table 2.

*Amended discontinuation rates*

The manufacturer updated the discontinuation rates for the pirfenidone arm with data from the RECAP trial (an on-going open label extension study from CAPACITY). The same discontinuation rates as the original submission up to week 72 (cycle 3) were used (derived from the CAPACITY trials). The rates for the following cycles were assumed to vary linearly up to week 192 (cycle 8) for which the cumulative rate was derived from the RECAP trial and assumed constant thereafter for patients' lifetime. A similar approach was taken to estimate discontinuation rates specific to the FVC ≤80% patients' subgroup. The ERG considers this approach to be reasonable, although it does not have access to the RECAP trial individual patient data and so is unable to check the discontinuation rates used.

The manufacturer states that despite the higher discontinuation rate, the IPF-related mortality hazard ratio of 0.53 is still adequate to reflect survival of mild to moderate patients in the pirfenidone arm, and suggests that this may be a consequence of patients on treatment receiving significantly more benefit as treatment persists. Limited detail is reported on the results of the survival analyses conducted, and the ERG suggests that while there may be some uncertainty around the long term IPF-related mortality due to the higher discontinuation rates, the assumptions adopted seem reasonable. The impact of this change to the results of the cost effectiveness analyses is reported by the ERG in Table 2.

*Exclusion of patients with baseline predicted FVC >80*

As described above, the manufacturer conducted an additional subgroup analysis for patients with FVC ≤80%. The addendum describes briefly the estimation of the IPF-related mortality and of the discontinuation rates for this subgroup. Discontinuation rates for this subgroup were assumed to differ slightly from the whole population. Despite the limited detail provided, the approach taken to estimate IPF-related mortality seems sound; however the ERG restates that this is a post-hoc analysis and its results should be considered cautiously. The ERG has tested the effect of this change to the results of the cost effectiveness analyses, see Table 2.

*Exclusion of patients with borderline obstructive disease*

As described above, the manufacturer conducted an additional subgroup analysis for patients with FVC ≤80% without borderline obstructive disease (FEV1/FVC ≥0.8). The addendum describes briefly the estimation of the IPF-related mortality and of the discontinuation rates for this subgroup. Discontinuation rates for this subgroup were assumed the same as those for the FVC ≤80% subgroup of patients. Despite the limited detail provided, the approach taken to estimate IPF-related mortality seems sound; however the ERG restates that this is a post-hoc analysis and its results should be considered cautiously. The ERG have tested the effect of this change to the results of the cost effectiveness analyses, see Table 2.

*Triple therapy comparison*

In the original submission the manufacturer did not consider ‘triple therapy’ (N-acetylcysteine, azathioprine, prednisone) owing to limited evidence available at that time. Since the original submission interim results from an RCT comparing triple therapy with placebo have been published (the PANTHER trial), and the manufacturer has therefore used data from this trial, through an indirect comparison, to model pirfenidone compared to triple therapy. The

manufacturer uses the hazard ratio (HR) for all-cause mortality for placebo versus triple therapy from the PANTHER trial and compares this with the HR for IPF-related mortality for placebo versus pirfenidone (from the CAPACITY trials). Changes in FVC and 6MWT distance were taken from the placebo arms of the CAPACITY trials, and hospitalisations were assumed to be equivalent to best supportive care. The manufacturer notes that this more than likely over-estimated the ICER since placebo had significantly more hospitalisations in the PANTHER study.

The HR for all-cause mortality presented in the additional submission document is in line with that presented in the PANTHER trial publication. The IPF-related mortality HR of pirfenidone versus triple therapy is derived by multiplying the HR for all-cause mortality in the PANTHER trial (for triple therapy vs. placebo) with the HR for IPF-related mortality from the CAPACITY trials (for pirfenidone vs. placebo). This leads to an indirect HR of pirfenidone versus triple therapy of 0.06.

In addition, the manufacturer also models outcomes for triple therapy for the subgroup with baseline FVC ≤80% predicted. In this they indirectly compare the triple therapy HR of all-cause mortality from the PANTHER trial (the whole group HR) with the HR for IPF-related mortality from the subgroup data from the CAPACITY trials. This led to an indirect HR of pirfenidone versus triple therapy of 0.04.

The ERG note a number of limitations with the approach to indirect comparison undertaken:

- The manufacturer does not provide summary details of the PANTHER trial in their additional analysis submission and do not discuss the suitability of these data for an indirect comparison.
- The ERG note that the participants in the PANTHER trial appear to have some minor differences at baseline compared to those in the CAPACITY trials. The baseline FVC % predicted and $DL_{CO}$ appear to suggest participants may have had more severe IPF than those in the PANTHER trial. This is based on observation of the data only and differences may not be of clinical significance, however, may affect the suitability of comparing these populations indirectly.
- The indirect comparison is based on data of all-cause mortality from the PANTHER trial versus data on IPF-related mortality from the CAPACITY trials.
- The HR for the subgroup was based on the comparison of whole group data from the PANTHER trial versus the subgroup data from the CAPACITY trials.

In addition to the limitations with the approach to the indirect comparison the ERG also note some issues regarding the data from the PANTHER study. The ERG notes the low numbers of deaths in the PANTHER study (1 in the placebo arm and 8 in the triple therapy arm), and also notes that there is a low mortality rate in the placebo arm of the PANTHER study. Clinical advice to the ERG notes that the mortality rate in the placebo arm of the PANTER trial was lower than might be expected in this population.

The prednisone doses used in the PANTHER trial were higher than would be used in current practice in the UK and this is an important factor which may be contributing to the outcomes seen in the PANTHER trial.

Cumulative discontinuation rates for triple therapy were extracted by the manufacturer from the data presented in the PANTHER trial using study adherence rates published in a supplementary appendix of the study. In the supplementary appendix of the study the proportions who had stopped taking all three drugs appear to be calculated on those who completed assessments. This suggested that the proportion who had discontinued at week 60 in the pirfenidone arm was 40%. However, in the text of the main PANTHER publication it is stated that 20/77 participants in the triple therapy arm discontinued all three treatments. This would suggest 26% of participants discontinued by the end of the study. It is uncertain why this difference exists. The manufacturer uses cumulative discontinuation rates per cycle from the higher estimate given in the PANTHER study.

The ERG note that the total model costs for triple therapy are less than for best supportive care. Whilst this may appear counter-intuitive, predicted overall survival for triple therapy is much shorter than for best supportive care. The hospitalisation costs are related to overall survival, and therefore the total costs for triple therapy are lower than for best supportive care. The ERG have not extensively checked the model since the additional analyses have been completed, however based on our previous analyses of the original model we consider that the results presented for total costs of triple therapy reasonably reflect the model assumptions adopted.

The ERG also note that in the additional analyses document (p.21-22) the manufacturer discussed having undertaken a sensitivity analysis assuming a relative effectiveness of triple therapy equivalent to BSC; however, these cost-effectiveness results were not reported. Within the model, there is an option to run the analyses with the same effectiveness for triple therapy as placebo. The ERG notes that the results from this analysis for pirfenidone versus triple therapy are similar to those for pirfenidone versus BSC.

The ERG has checked the results from the analyses for triple therapy. The model results predict that about [redacted] of mild to moderate patients with triple therapy will die within 6 months and this is clearly inconsistent with the Panther trial. The Panther trial had about 11% dying in this period in the triple therapy arm. Furthermore the analyses for the subgroups FVC $\leqslant$ 80% assume an even higher mortality rate for the triple therapy group ([redacted] die within 6 months). This inconsistency leads the ERG to conclude that the analyses presented by the manufacturer for triple therapy are flawed.

The ERG therefore have a number of concerns over the methods used by the manufacturer to estimate the relative effectiveness of triple therapy versus pirfenidone, and recommends cautious interpretation of the results reported for this comparison. Results can be seen in Table 1 below.

*Pooled comparator analysis*

The manufacturer has presented some of the results as a pooled comparator with a proportion of patients taking BSC or triple therapy. The cost-effectiveness results for the comparison of pirfenidone with the "pooled comparator" strategy presented by the manufacturers is expected to be an ICER ranging between those obtained for each of the scoped comparisons, see Table 1. The ERG notes that this comparison is not specified in the NICE scope and is therefore not relevant to the current appraisal.

The scoped interventions are possible treatment options for patients with mild to moderate IPF. In a fully incremental analysis, interventions are considered to be mutually exclusive such that the adoption of one intervention excludes the others and all patients receive the same treatment. Hence, a fully incremental analysis enables the identification of the most cost-effective intervention, providing useful information to be considered in the process of decision-making on health technology adoption. The ERG recommends consideration of the results from the fully incremental analyses for the scoped comparisons, rather than for those of the pooled comparator.

For the pooled comparator strategy the manufacturer assumes that there was an uptake 70%, 30% between BSC and triple therapy in cycle 1, linearly decreasing to 100%, 0% in cycle 10. Clinical advice to the ERG suggests that the use of triple therapy in current practice varies widely, however the assumptions used for the current usage and the decline in use appear reasonable.

Results

Results for the changes to the results in the original submission are presented in the new submission (and the PAS document, see below for more details). For these analyses, the manufacturer uses a larger number of patients in their sampled population and a larger number of analyses, based upon the ERG suggestions in the ERG report. The ERG considers the number of patients used in the analyses to be reasonable. The base case analysis presented by the manufacturer has been reproduced here in Table 1.

Table 1: Updated base case ICERs presented in the additional submission document

| Technologies | Total costs (£) | Total LYG | Total QALYs | Inc costs (£) vs. pirfenidone | Inc LYG vs. pirfenidone | Inc QALYs vs. pirfenidone | ICER: pirfenidone vs. comparator |
|---|---|---|---|---|---|---|---|
| Pirfenidone | [redacted] | [redacted] | [redacted] | - | - | - | - |
| Best Supportive care | 36,370 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Triple therapy | 24,711 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Pooled comparator | 34,673 | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

The ERG has checked the model results for the new analyses and consider them to be consistent with those produced from the previous model submitted. The ERG has analysed the individual impact of each change on the model results (Table 2). The Table shows that changes to the number of pills and the discontinuation rate have a small impact on the ICER. The subgroups chosen both have a significant effect on the ICER. The probability of pirfenidone being cost-effective compared to BSC at a willingness-to-pay threshold of £30,000 per QALY gained is [redacted] for mild to moderate IPF patients and for the FVC ≤ 80% including and excluding obstructive disease subgroups.

The manufacturer reports the results of deterministic sensitivity analyses (DSA) for the FVC≤80% subgroup conducted on the same parameters as in the original submission for all mild and moderate IPF patients. Similarly, only a few parameters were subject to DSA. A probabilistic sensitivity analysis (PSA) was presented although no details on how the PSA was conducted are provided. The lowest ICER reported for the comparison of pirfenidone and BSC is approximately [redacted] per QALY gained for the subgroup of patients with FVC⩽ 80% without borderline obstructive disease (FEV1/FVC ⩾0.8).

Table 2: Impact of manufacturer new amendments to the original submission on model results

| Scenario | Treatment | Cost (£) | QALY | ICER (£/QALY) | ICER, % change from original base case |
|---|---|---|---|---|---|
| Base case results | Pirfenidone | [redacted] | [redacted] | | |
| | BSC | 36,378 | [redacted] | | |
| | Incremental | [redacted] | [redacted] | [redacted] | - |
| Reduction in number of pills of pirfenidone per day | Pirfenidone | [redacted] | [redacted] | | |
| | BSC | 36,379 | [redacted] | | |
| | Incremental | [redacted] | [redacted] | [redacted] | [redacted] |
| Amended discontinuation rate for pirfenidone | Pirfenidone | [redacted] | [redacted] | | |
| | BSC | 36,398 | [redacted] | | |
| | Incremental | [redacted] | [redacted] | [redacted] | [redacted] |
| Patient subgroup for FVC ≤ 80% only | Pirfenidone | [redacted] | [redacted] | | |
| | BSC | 34,274 | [redacted] | | |
| | Incremental | [redacted] | [redacted] | [redacted] | [redacted] |
| Patient subgroup for no obstructive disease | Pirfenidone | [redacted] | [redacted] | | |
| | BSC | 35,187 | [redacted] | | |
| | Incremental | [redacted] | [redacted] | [redacted] | [redacted] |
| Patient subgroup for FVC ≤ 80% only and no obstructive disease | Pirfenidone | [redacted] | [redacted] | | |
| | BSC | 33,741 | [redacted] | | |
| | Incremental | [redacted] | [redacted] | [redacted] | [redacted] |

*Summary of ERG comments on the methods and results of the updated cost-effectiveness model*

- The ERG were unable to check the estimation of the average number of pills per day and discontinuation rates for pirfenidone; however, the approaches presented by the manufacturer seem reasonable and to have been appropriately incorporated in the model. These amendments had a small impact on the ICER.
- Subgroup analyses for patient populations reduced the ICER significantly; however, the probability of pirfenidone being cost-effective compared to BSC at a willingness-to-pay threshold of £30,000 per QALY gained is [redacted] for these subgroups. The ERG

recommends caution in the interpretation of the results presented for these post-hoc analyses.

- A cautious interpretation of the results reported for the analyses related to triple therapy is also recommended, given the lack of a robust evidence base for the relative effectiveness of triple therapy versus pirfenidone.
- The pooled comparator analysis is not specified in the NICE scope for this appraisal.

Application of the NICE end of life criteria

In Appendix 2 of the additional analysis document the manufacturer provides details of a case for IPF to be considered under the NICE end of life criteria.

The manufacturer considers pirfenidone to be indicated for patients with a short life expectancy (normally less than 24 months per NICE end-of-life criteria), as some IPF patients will die within a year (Ley, 2011). However, the initial MS refers to a median life expectancy of three years for patients with mild to moderate IPF (Navaratnam et al, 2011) as well as IPF being expected to lead to death within 2-5 years (Meltzer et al, 2008).

Additionally, the estimated life expectancy in the manufacturer's model is approximately [redacted] for patients receiving BSC. Clinical advice to the ERG confirmed that the median life expectancy for IPF patients is expected to be more than two years.

**Part II: Patient Access Scheme.**

The manufacturer provided a document containing details of a proposed Patient Access Scheme (PAS) and the effect the proposed PAS has on the cost effectiveness of pirfenidone.

The PAS applies a discount [redacted] to the list price of pirfenidone and states this will be available for all licensed indications (i.e. the mild to moderate population with IPF). The proposed PAS will be available until NICE guidance is revised.

Although the discount is available to all with mild to moderate IPF the manufacturer do not provide analyses showing the effect of the discount to the whole population. The analysis is shown for the two subgroups FVC ≤80% and FVC ≤80% $FEV_1$/FVC ratio ≥0.8 (excluding borderline obstructive disease). The manufacturer states this was because they observed more benefit in these subgroups.

Pages 12 to 20 of the PAS document outline the results of the two subgroup analyses on outcomes of FVC, PFS, mortality, 6MWT. These results were discussed in the additional analysis document and the ERG comment on these can be seen in Part I of the present document.

In section 4.3 of the PAS document, the manufacturer describes the application of the discount to the 28 day therapy pack in the model. The ERG confirmed that the discount was applied exclusively to this pack from which pirfenidone cost is estimated for day 15 onwards.

The manufacturer presents the clinical effectiveness data for the subgroups used in the economic model in pages 22 to 27. These data were discussed in the additional analysis document (and as such are not repeated here) with the exception of a few minor differences. These are unlikely to affect the final analyses and are not detailed here.

The manufacturer provides cost effectiveness results for pirfenidone compared to BSC, triple therapy and their pooled comparator (BSC and triple therapy) for the chosen subgroups. Results are presented without the PAS and with the PAS as per NICE guidance. However, the manufacturer has not reported results with the PAS for mild and moderate IPF patients.

Results reported by the manufacturer for the PAS show that the probability of pirfenidone being cost-effective compared to BSC at a willingness-to-pay threshold of £30,000 per QALY gained is [redacted] for the FVC ≤ 80% including and excluding obstructive disease subgroups (and would also be for mild to moderate IPF patients). However, compared to triple therapy, the probability of pirfenidone being cost-effective at a willingness-to-pay threshold of £30,000 per QALY gained becomes [redacted]. The ERG recommends caution in the interpretation of these results given the limitations noted above concerning this comparison.

The ERG has checked the results with the PAS discount and consider that the results shown are consistent with results presented for the subgroup analyses without the discount (FVC ≤ 80%, FVC ≤ 80% excluding borderline obstructive disease), notwithstanding the caveats about the subgroups discussed in Part 1 of this document.

The impact of the PAS on the model results is shown below in Table 3 for all patients with mild to moderate IPF. The [redacted] discount in the 28 day therapy pack cost reduces the ICER proportionally to [redacted] per QALY gained. Cumulatively, the new amendments (i.e. reduced drug cost and reduction in number of pills of pirfenidone per day and amended discontinuation rate for pirfenidone) reduce the ICER further by [redacted] of the baseline ICER.

Table 3: Impact of manufacturer PAS and new amendments to the original submission on model results

| Scenario | Treatment | Cost (£) | QALY | ICER (£/QALY) | ICER, % change from original base case |
|---|---|---|---|---|---|
| Base case results | Pirfenidone | [redacted] | [redacted] | | |
| | BSC | 36,378 | [redacted] | | |
| | Incremental | [redacted] | [redacted] | [redacted] | - |
| Reduced drug cost for pirfenidone (PAS) | Pirfenidone | [redacted] | [redacted] | | |
| | BSC | 36,375 | [redacted] | | |
| | Incremental | [redacted] | [redacted] | [redacted] | [redacted] |
| Reduced drug cost for pirfenidone (PAS) with new amendments* | Pirfenidone | [redacted] | [redacted] | | |
| | BSC | 36,367 | [redacted] | | |
| | Incremental | [redacted] | [redacted] | [redacted] | [redacted] |

*reduction in number of pills of pirfenidone per day and amended discontinuation rate for pirfenidone

*Summary of ERG comments on the methods and results of the updated cost-effectiveness model*

- The discount presented in the PAS reduces the ICER proportionally; however, pirfenidone is [redacted] for patients with mild to moderate IPF at a willingness to pay threshold range of £20,000 to £30,000 per QALY gained.

ERG overall summary of additional analysis and PAS

The ERG considers the manufacturer's approach to the amendments to the number of pills per day and discontinuation rates for pirfenidone reasonable. Subgroup analyses and triple therapy comparisons reduced the ICER significantly; however cautious interpretation of the results reported for these analyses is recommended given the lack of a robust evidence base.

The discount presented in the PAS reduces the ICER proportionally, but [redacted] the willingness to pay threshold range of £20,000 to £30,000 per QALY gained for patients with mild to moderate IPF.