InterMune response to the Appraisal Consultation Document

Idiopathic Pulmonary Fibrosis – Pirfenidone

19th December, 2012
FOREWORD

We thank the Committee for the opportunity to comment on the preliminary Appraisal Consultation Document (ACD) for pirfenidone in the treatment of mild to moderate idiopathic pulmonary fibrosis (IPF). In providing the following response, the manufacturer (InterMune) has sought to address as many of the Committee’s and Evidence Review Group’s (ERG) concerns as possible and has also obtained further guidance and clarification from the IPF expert community.

As a result, InterMune has undertaken a review of the clinical and cost-effectiveness analysis previously presented to NICE. In providing this response, additional information and data analysis has been identified to improve the evidence-base and assist with areas of uncertainty highlighted in the ACD. The proposal within acknowledges the comments received from the Committee and now even more accurately reflects the needs of the IPF experts and patients. In addition the Department of Health has approved a revised discount which may be considered by NICE and this has been presented in a separate PAS submission. We believe that this revised proposal would enable NICE to recommend access to a new treatment option in England and Wales for IPF patients. These patients currently have a high unmet medical need due to a lack of licensed therapies and pirfenidone delivers an innovative and significant step change in the treatment of IPF as an orphan disease.

POSITIONING

After further consultation with clinical experts, InterMune maintains its original position that pirfenidone should be initiated in patients with mild to moderate IPF with a baseline predicted FVC of ≤80%; this is a subgroup of the licensed population (mild to moderate IPF). We believe this represents the population of patients in England and Wales who are most likely to receive treatment with pirfenidone.

This is further supported by new data from a real world experience of pirfenidone in mild to moderate IPF patients in the UK generated within InterMune’s Named Patient Programme (NPP) within the last 12 months. Additional data from the NPP will be presented to support this positioning of pirfenidone as a clinically and cost-effective treatment.

In this response we have focused on best-supportive care as the comparator and have not presented any further analyses for triple therapy as a comparator based on the appraisal committee’s discussion. We acknowledge that with the publication of the PANTHER trial the use of triple therapy will likely decline in England and Wales as discussed by the appraisal committee, but we would highlight that triple therapy is probably still pertinent to the submission as clinicians have indicated that they would still consider maintaining existing patients on triple therapy if there was no decline in lung function. In addition, clinical experts suggest that some use of triple therapy is persisting in new patients where they are treated outside the main tertiary care centres. The British Thoracic Society (BTS) website describes the outcomes from in the interim analysis of PANTHER as unexpected (atypical) and suggests there may be important differences between both the phenotype and management of IPF subjects enrolled in the study and IPF patients seen in clinical practice.
Comments are provided to the Appraisal Committee in relation to the following areas:

**Has all relevant evidence been taken into account?**

To assist the committee in its decision making we have sought to provide further evidence to support the rationale for the positioning of pirfenidone in the submission and provide additional analyses to reduce areas of uncertainty identified in the ACD regarding the clinical and cost-effectiveness of pirfenidone.

**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?**

We believe there are some aspects of the data which require further review by NICE in order to appreciate the evidence base for pirfenidone in this orphan disease and how it relates to the IPF population in England and Wales.

**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?**

InterMune is concerned that the ACD does not fully take account of the evidence base for the technology and how it will benefit IPF patients in England and Wales. Furthermore the evaluation of a readily identifiable sub-population of IPF patients as proposed has not been fully appreciated in the recommendations. Arguments justifying the consideration of this sub-population are provided in this response.

**Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?**

InterMune is concerned that patients with IPF, who are predominantly an elderly population, could be perceived as being discriminated against if pirfenidone is not available as a treatment for IPF. As described on pages 43 and 44 of the original submission very few patients with IPF ever receive a transplant. In addition, patients with pulmonary fibrosis have the highest waiting list mortality of all patients awaiting lung transplantation (Mackay et al, 2007).
EXECUTIVE SUMMARY

- Five factual inaccuracies were identified in the ACD, which have been highlighted to NICE.
- Clinical effectiveness issues have been addressed as follows:
  - Upon consultation with IPF experts it was raised that treatment of patients with a FVC>80% would only occur in rare cases where patients have some form of obstructive disease and a significant decline in FVC during a 6-month period. This was tested in a sensitivity analysis.
  - The actual population selected by clinicians for treatment with pirfenidone is slightly more severe than the whole CAPACITY population and increases the relevance of positioning pirfenidone for patients with a baseline FVC ≤80%.
  - CAPACITY patients with a baseline FVC ≤80% had a mean FVC of [ ] compared to 69.8% in a UK cohort receiving pirfenidone from the Named Patient Programme (NPP). Therefore severity of their disease at initiation of treatment was similar. Other key demographics such as age, sex and the use of concomitant medication such as anti-reflux therapy were very similar in this subgroup of the CAPACITY trials and the NPP population.
  - Patients with a baseline FVC ≤80% are clearly at an increased risk of death as shown in the literature and further analyses presented in this response. Together this increases the relevance and positioning of pirfenidone for patients with a baseline FVC ≤80%.
  - To assist the Committee, further explanation has been provided regarding the reporting of overall survival and the subgroup analyses of the CAPACITY trials.
  - The process of blinded assessment of IPF-related classification of deaths using a standard form in the CAPACITY studies provides a logical, transparent and correct allocation. The uncertainty regarding the classification of death as being related to IPF or not has been addressed as well as identifying a challenge in the Committee's reasoning. In addition, a sensitivity analysis using all cause mortality has been implemented into the cost-effectiveness model whereby incorrect classification of IPF-related vs. non-IPF related death would not impact the cost-effectiveness results.
  - The CAPACITY trials were some of the largest and longest IPF trials ever conducted. The validity of surrogate endpoints such as FVC, 6MWD are reinforced by the opinion of European experts. It is unrealistic to expect IPF trials to be powered for mortality and for a 25% reduction in mortality to be statistically significant would require 2,600 patients and 5 years follow-up in a placebo controlled IPF trial. Indeed medicines such as bosentan for pulmonary arterial hypertension (PAH) were approved based on trial durations of only 12-16 weeks using endpoints such as 6MWD which at the time were questioned as to their validity but have since been demonstrated to translate into long term mortality benefits. Waiting for this data would have meant years of delay before patients could have accessed bosentan.
Cost-effectiveness issues have been addressed as follows:

- We agree with the Committee that the base case modelling approach is acceptable. Selecting survival with the calibrated regression outputs based on GIPF-007, PIPF-004 and PIPF-006 should be considered the most robust result.

- Parametric survival curves (with and without calibration) provide contradicting results in terms of goodness of fit and clinically realistic results. The most clinical plausible parametric curve is one of the worst fitting, and still provides medians that are higher than those currently considered in the cost-effectiveness model (which clinicians currently believe are generally higher than expected).

- Age and gender were included in the regressions. Goodness of fit for IPF-related mortality and hospitalisation were not improved by the inclusion, but SGRQ was significantly improved. Age\(^{3}\) and gender have been included as independent covariates for the SGRQ regression, and has subsequently been used in the amended base case analysis.

- Continued pirfenidone treatment effect in terms of survival is evident based on Kaplan Meier data up to 204 weeks (~4 years) when considering RECAP data. The median survival with pirfenidone is significantly higher than the median survival of 2-5 years reported in the literature.

- Using the RECAP data, there is evidence to suggest that survival benefits will persist for at least 204 weeks (~4 years). Therefore, discontinuation rates were considered from RECAP such that the costs up until this time could be accurately reflected. The ERG acknowledged this assumption was reasonable.

- Uncertainty related to both the prediction of SGRQ and calculation of EQ-5D has been significantly reduced. The prediction of SGRQ has been improved by the additions of age and gender as independent covariates in the regression, which significantly improved goodness of fit. The mapping onto EQ-5D has been improved by considering a cohort of IPF patients as opposed to COPD patients, and calculating an algorithm with less error.

- The probabilistic sensitivity analysis (PSA) has been updated to further explored uncertainty associated with treatment effects by including variation in: Regressions for IPF-related mortality, hospitalisation and SGRQ; Mapping algorithm and IPF-related adjustment factors.

Pirfenidone is considered to be a step change in innovation

- Innovation: transforms patient outcomes; can simultaneously improve quality and productivity; and is good for economic growth. We have a clear body of evidence which supports pirfenidone as an innovative medicine under these definitions.

Details regarding clinical justifications and additional analyses conducted as part of the revised base case model can be found in the ‘Appendix for clinical justifications and additional health economic analyses’ document dated 19.12.12. Details of the implementation of the new PAS and corresponding cost-effectiveness results can be found in the NICE PAS document dated 19.12.12.
CONTENTS OF RESPONSE

Factual inaccuracies in the ACD

Clinical effectiveness issues raised in the ACD
1. Relevance of the IPF population in the CAPACITY studies to IPF patients in England and Wales
2. Reporting of overall survival analyses unclear
3. Subgroup analyses – concerns on power, post-hoc analyses
4. Uncertainty about correct classification of deaths in CAPACITY studies
5. CAPACITY trials were of short duration and uncertainty if benefit persists over time

Cost effectiveness issues raised in the ACD
6. Calibration of parametric survival curves not fully explored
7. Adding age and gender to the regressions
8. Extrapolation of survival benefit past 72-weeks with discontinuation
9. Uncertainty in the estimation of quality of life
10. Concerns that not all model parameters had been included in the probabilistic sensitivity analyses

Pirfenidone not considered to be a step change in innovation

References
### Points of factual accuracy/ error to address

<table>
<thead>
<tr>
<th>Description of problem</th>
<th>Description of proposed amendment</th>
<th>Justification for amendment</th>
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<tbody>
<tr>
<td>Page 8: ‘In another post-hoc analysis, the manufacturer reported that the incidence of idiopathic pulmonary fibrosis-related deaths was lower in the pirfenidone 2403 mg/day group than in the placebo group (12 compared with 25 deaths in the pooled analyses; hazard ratio 0.62 [95% CI, 0.35 to 1.13]). The timeframe for this analysis was not stated by the manufacturer and it is not clear how this differs from the published analysis (Noble et al, 2011), which reported idiopathic pulmonary fibrosis-related mortality rates of 5% in the pirfenidone 2403 mg/day group compared with 8% in the placebo group (18 and 28 deaths respectively; hazard ratio 0.62 [95% CI 0.35 to 1.13], p=0.117) for death at any time within the study duration (mean length of follow-up was not reported).’</td>
<td>This should be reworded to say: “The manufacturer reported that the incidence of idiopathic pulmonary fibrosis-related deaths was lower in the pirfenidone 2403 mg/day group than in the placebo group (12 compared with 25 deaths in the on-treatment pooled analyses; hazard ratio 0.48 [95% CI, 0.24 to 0.95; p=0.030]). (Noble et al, 2011) The timeframe for this analysis is unspecified as this was exploratory (i.e. until patients dropped out). The overall idiopathic pulmonary fibrosis-related mortality rates were 5% in the pirfenidone 2403 mg/day group compared with 8% in the placebo group (18 and 28 deaths respectively; hazard ratio 0.62 [95% CI 0.35 to 1.13], p=0.117). (Noble et al, 2011)’</td>
<td>This analysis was not post-hoc. All HR and CIs are from Noble et al (2011). The confusion arises as the 12 versus 25 deaths is for on-treatment IPF related mortality. As described in the Noble publication (2011) for the CAPACITY studies, on-treatment was defined as the time from randomisation until 28 days after the last dose of study drug. This reporting of on-treatment mortality is in line with WHO safety standards. On-treatment IPF related mortality has a HR of 0.48 (95%CI 0.24-0.95) and not 0.62 (95%CI 0.35-1.13). The timeframe for the analysis is unspecified as was exploratory (i.e. until patients dropped out). The 18 versus 28 deaths is for all-cause IPF related mortality and the corresponding HR and CI are correct. It is important for the Committee to understand these results were not conducted post-hoc but were pre-</td>
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<td>It is often commented in the ACD that ERG were unable to check some things because of lack of access to the patient level data.</td>
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<td>Page 24: The ERG was unable to check statistical heterogeneity in the data presented in the meta-analyses because of the methods chosen by the manufacturer</td>
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<td>Page 28: “It was unable to check the data for this subgroup…….”</td>
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<td>Page 29: “The ERG verified that the results obtained with the manufacturer’s updated model were consistent with the original version but was unable to check data for the discontinuation rates or capsules per day.”</td>
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<td>We note in the ACD that reference is made on several occasions to the inability of the ERG to check the data analysis carried out because they did not have access to the patient level data.</td>
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<td>We would like to make the Committee aware that the InterMune has previously, on several occasions offered NICE/ERG access to the patient level data under confidentiality. For instance, this was done in February this year in email correspondence with the NICE project manager Bijal Joshi dated 27 February 2012 (time 17:19).</td>
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<td>Therefore we would appreciate it if this could be clarified in the ACD. Suggested wording could be:</td>
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<td>“The ERG were not able to check the data, although the manufacturer has offered to make it available for analysis”</td>
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<td>For page 29 we believe we have previously provided an appropriate explanation to this – See the Pro-forma response dated February 2012 – Issue 2. Again in this response it was stated, that if requested by the ERG, the patient level data could also be shared to support the model results.</td>
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<td>It could be misinterpreted that the company have refused access to patient level data to the ERG, rather than an offer was made but to date had not been taken up. We are concerned that it could be perceived that InterMune is “hiding something” rather than being fully transparent.</td>
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<td>Page 36, 59: Statements that the ASCEND study has its first results in 2013</td>
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<tr>
<td>Page 36: Section 4.5 states: ‘and that the first results are due to be reported in 2013’</td>
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<td>Page 59: Section 8.1 states: ‘anticipated date of study completion: December 2013’</td>
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<td>Page 36. This should read: “and the company expects the study to be fully enrolled around the end of 2012, and that results from the study will be available in the first half of 2014” (InterMune, News release 7 Nov, 2012)</td>
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<td>Page 59. This should read “the company expects the study to be fully enrolled around the end of 2012, and that results from the study will be available in the first half of 2014” (InterMune, News release 7 Nov, 2012)</td>
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<tr>
<td>It is important to confirm when the results of the ASCEND trial will be available.</td>
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</table>

| Page 44: “It was also concerned that the manufacturer assumed that this treatment effect then persisted until death, although no evidence for efficacy beyond 72 weeks had been presented in its submission” |
| Delete: |
| “Although no evidence for efficacy beyond 72 weeks had been presented in its submission” |
| Suggest: |
| “Evidence was presented for the open-label extension of the CAPACITY studies called RECAP to support this” |
| It is important for the Appraisal Committee to understand that the phase III CAPACITY studies were 72 weeks in duration and that 96% of these patients went into the open label RECAP study for which data are available for some patients for approximately 4 years. Data were presented in the original STA submission regarding the sustained benefit of pirfenidone – see pages, 13, 14, 18, 158, 193 and 194. It would be incorrect to say there is no evidence beyond 72 weeks. We would like to highlight that patients |
with IPF only live for a median of 2-5 years (104-260 weeks) (Meltzer et al, 2006) from diagnosis and therefore collecting data for over 144 weeks should be viewed in this context. Please see Issues 5 and 8 for further supportive detail.

Page 45: “It had reservations about the manufacturer’s assumption that end-of-life costs for patients with cancer could be applied to deaths that were not related to idiopathic pulmonary fibrosis, because less than half of these deaths in PIPF-004 and PIPF-006 were attributable to cancer.”

Please delete this sentence. This assumption was amended following ERG feedback and the model presented to the Appraisal Committee did not include end of life costs for non IPF related deaths.

‘Costs that are considered to be unrelated to the condition or technology of interest should be excluded’ (ERG Report, February 2011)

It is important that the appraisal Committee fully acknowledges the information provided throughout to the ‘pre AC’ process of dialogue with the ERG rather than selecting earlier concerns that are no longer relevant.
Clinical effectiveness issues raised in the ACD addressed in the InterMune’s response

**Issue 1: Relevance of the IPF population in the CAPACITY studies to IPF patients in England and Wales**

**Relevant quotes from the ACD**

- Page 24, 35: “Concern on relevance of patient population in trials to UK population and that patients with co-morbidities would be excluded”

- Page 29: ‘The ERG noted that the hypothetical mild-to-moderate population simulated in the manufacturer’s economic model was from relevant trials, but that this may not be wholly representative of patients treated in clinical practice in the UK because the trial population may have had milder idiopathic pulmonary fibrosis.’

**InterMune’s response**

- Patients in the CAPACITY trials are relevant to England and Wales, and in particular those for the FVC ≤80% subgroup are representative of IPF patients who will be treated in clinical practice.

- The Committee raised concern that clinicians may consider treatment for patients with a FVC > 80%. However, upon consultation with IPF experts it was raised that this would only occur in some rare cases where patients have some form of obstructive disease and a significant decline in FVC during a 6-month period.

- Therefore, we conducted a sensitivity analysis to include baseline characteristics and 24-week changes for:
  - Patients who had a baseline FVC≤80% (n=244 for pirfenidone, n=233 for placebo), plus
  - Patients who had a baseline FVC>80% and had experienced a relative decline in FVC of 10% of more (n= 23 for pirfenidone, n=25 for placebo)

- Relative declines in FVC were chosen, since this is a more sensitive measure than absolute decline to measure disease progression (Richeldi et al, 2012).

- Results of the sensitivity analysis can be viewed in the NICE PAS document dated 19 December 2012.

- The Committee commented that the patient population simulated in the cost-effectiveness model based on the CAPACITY trials may have had milder IPF than patients who are anticipated to receive treatment in the UK. We agree with this which is why we have positioned pirfenidone for those patients whose baseline predicted FVC is less than 80%.
This positioning is further substantiated by a recent 4 centre, retrospective cohort analysis of the Named Patient Programme that was sponsored by the Royal Brompton Hospital. The NPP has been running since September 2011 and the data collection for this analysis commenced in June 2012. The results of available data were presented at the British Thoracic Society Annual Winter Meeting in December 2012. The investigators are planning to submit a manuscript with the complete dataset in due course.

As shown in Table 1, data were available from four centres in the UK. In the analysis there were 106 patients who had commenced pirfenidone for greater than 3 months prior to 30 Sept 2012. Of these, the number of patients who commenced pirfenidone for greater than 6 months prior to 30 Sept 2012 was 87.

- **Severity of IPF disease:** The mean percent predicted FVC values for patients in the entire CAPACITY trials were 73.1-76.4% compared to 69.8% in the NPP at baseline as shown in the table below. DLco was 46.1-47.8% in the entire CAPACITY trials compared to 38.6% in the NPP. Hence, the values in the CAPACITY trials were slightly higher than the cohort of 106 patients treated with pirfenidone within the NPP programme, which indicates a slightly milder population of patients in the CAPACITY studies compared to the NPP.

- **Age:** On average patients had IPF diagnosed 1.3 years before inclusion into CAPACITY studies (InterMune, DOF). The NPP data shows a delay in treatment initiation after diagnosis of 18 months (the age of patients was 66.6 to 68.0 years between diagnosis and treatment initiation). The mean age of patients across the arms of the PIPF-004 (CAPACITY 2) and PIPF-006 (CAPACITY 1) studies ranged from 65.7-68.0 years which is very similar to that in the NPP. This makes the overall population in the NPP very similar to the CAPACITY studies as reported by Noble et al (2011) and applicable to “real-life” patients in England and Wales.

- **Sex:** Males accounted for 68-75% of the patients in the CAPACITY studies versus 76% of the NPP population.

- This supports the proposed positioning and modelling of pirfenidone in the NICE submission for those patients with a baseline predicted FVC ≤80% as it closely reflects a real life population of patients in England and Wales.
<table>
<thead>
<tr>
<th>Trial/Study</th>
<th>Baseline characteristics</th>
<th>Entire CAPACITY study population</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Pirfenidone (2403 mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>174</td>
</tr>
<tr>
<td></td>
<td>Number</td>
<td>106</td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>81 (76%)</td>
</tr>
<tr>
<td></td>
<td>Mean Age (years)</td>
<td>68.8 (8.5)*</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) FVC % predicted</td>
<td>69.8 (22.6)</td>
</tr>
<tr>
<td></td>
<td>Mean (SD) DLco % predicted</td>
<td>46.4 (9.5)</td>
</tr>
<tr>
<td></td>
<td>Previously smoked</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Never smoked</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Currently smokes</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>Weight (kg)</td>
<td>86.5 (15.9)</td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>70.7 (16.3)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>34/103 (33%)</td>
</tr>
<tr>
<td></td>
<td>IPF diagnosis ≤1 yr</td>
<td>37/103 (36%)</td>
</tr>
</tbody>
</table>

Data are number (%) or mean (SD).

* At diagnosis; ** At start of pirfenidone;
- **Comorbidities:** More than 95% of patients randomised in the CAPACITY studies across treatment groups had at least one comorbidity at baseline. Comorbidities were typical for an elderly population and only severe uncontrolled concomitant disorders which had a clinically relevant probability of death or major disability during the study period were excluded from study participation. In clinical reality in England and Wales those IPF patients with clinically relevant life limiting concomitant disorders or conditions are unlikely to be treated with pirfenidone due to the likelihood of death from non-IPF causes. More than 20% of patients had ischaemic heart disease, more than 50% diabetes and nearly 20% a prior history of neoplasm (Please see Appendix 1 from the ‘Appendix for clinical justifications and additional health economic analyses’ document dated 19.12.12).

- **Concomitant medications:** The most common concomitant medications (i.e. used by ≥50% of patients in any treatment group) are summarised in Table 2 (this table can be found on page 66 of the original STA submission). Most frequently lipid lowering, antithrombotic, antibacterial and acid related medication was taken which would be typical of the types of medicines IPF patients might take. Little data are available from the NPP regarding concomitant medicines although of patients were taking drug for acid-related disorders which is similar to that seen in CAPACITY.

- The IPF population with FVC below 80% best represents the current real world IPF population in England and Wales regarding IPF severity who are likely to receive treatment. Demographics and baseline concomitant disorders, conditions and medication are largely comparable to a typical English and Welsh IPF patient cohort. Patients with life limiting disorders were excluded from CAPACITY studies for methodological and ethical reasons and are unlikely to be treated in daily practice in England as stated in the comorbidities section above.
As presented in the “Updated information and analyses to support the Single Technology Appraisal submission of pirfenidone for the treatment of idiopathic pulmonary fibrosis (IPF)” dated 17 August, 2012, patients with a baseline FVC ≤80% are at risk of increased mortality compared to those with a baseline FVC >80%. The risk increases significantly as the baseline FVC decreases as shown in Table 3.

**Table 3: Predicted FVC% and 1-Year risk of death* (du Bois et al, 2011)**

<table>
<thead>
<tr>
<th>FVC, % predicted</th>
<th>Patient visits (n)</th>
<th>Deaths (n)</th>
<th>HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤50</td>
<td>203</td>
<td>42</td>
<td>7.44 (3.28-16.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>51 to 65</td>
<td>691</td>
<td>65</td>
<td>4.09 (1.87-8.98)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>66 to 79</td>
<td>594</td>
<td>26</td>
<td>1.97 (0.85-4.55)</td>
<td>0.111</td>
</tr>
<tr>
<td>≥80</td>
<td>374</td>
<td>7</td>
<td></td>
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</table>

*Cox proportional Hazards Model

Table 3 indicates that patients with a predicted FVC>80% are not an at risk population from all-cause mortality. On the other hand, once a patient’s predicted FVC reaches 80% or below, the risk of mortality is a significantly increased, which suggests this population is the most at risk and should be prioritised for treatment options that could potentially extend life.

To highlight that the FVC≤80% is significantly more at risk of mortality compared to the FVC>80%, **irrespective of treatment choice**, we conducted an analysis considering the placebo arms of the CAPACITY trials as well as GIPF-007 and GIPF-001 (InterMune funded studies comparing interferon gamma versus placebo). Please see Appendix 2 from the ‘Appendix for clinical justifications and additional health economic analyses’ document dated 19.12.12 for methodological details.
From this it can be concluded:

- The CAPACITY trial populations are relevant to the IPF patient population in the UK, which supports the use of the CAPACITY data in the cost-effectiveness model.
- The actual population selected by clinicians for treatment with pirfenidone is slightly more severe than the whole CAPACITY population and increases the relevance of positioning pirfenidone for the treatment of patients with a baseline FVC ≤ 80%, a population who are at an increased risk of mortality.

**Issue 2: Reporting of overall survival analyses unclear**

**Relevant quotes from the ACD**

- Page 27: The ERG found that the manufacturer’s reporting of the overall survival analyses was unclear. The uncertainties included:
  - how the results were calculated in relation to the different time points studied (that is, whether the data are being presented for up to 72 weeks or beyond 72 weeks)
  - the absence of marked censored data on the graphs
  - the lack of a description of the censoring methods
  - the lack of information on distinguishing a treatment-emergent death that was related to idiopathic pulmonary fibrosis from one that was not
  - knowing the follow-up period for the data
  - some inconsistencies in the hazard ratios (this may be because different time points were used but the ERG noted that this is not discussed in the manufacturer’s submission).

**InterMune’s response**

Each of the above points are addressed below:

- How the results were calculated in relation to the different time points studied (that is, whether the data are being presented for up to 72 weeks or beyond 72 weeks)
As described in the original STA submission on page 105 survival data after the primary point of the analysis (Week 72) should be interpreted with caution because the majority of patients remaining at risk in both studies were lost due to follow up in the survival analysis after Week 72.

Therefore, when interpreting survival and particularly the HR associated with survival, data after 72-weeks were censored as the substantial decrease in follow-up after 72-weeks would lead to underpowered analyses and informative censoring could potentially skew results (Gorouhi, 2009). For these reasons, the HR at 72-weeks was considered to be the most robust result and it is this result which has been used to consider the overall treatment effect of pirfenidone in the cost-effectiveness analysis. This approach was accepted by the ERG in their report.

The hazard ratio for IPF-related mortality differs to that reported by Noble et al (HR 0.62) as it is based on deaths occurring up to week 72, whereas the Noble publication also includes mortality after the 72 week endpoint where all available data up to the treatment completion visit was used, including follow-up after Week 72. The results and rates at 72-weeks were used in the health economic model (please see Section 6 of the original STA submission and the Updated Information and Analysis document dated 17th August, 2012).

- **The absence of marked censored data on the graphs**
  - Kaplan Meier graphs for the following are presented in Appendix 3 from the ‘Appendix for clinical justifications and additional health economic analyses’ document dated 19.12.12. This considers PFS and all-cause mortality for the pooled analysis in the CAPACITY studies and for FVC ≤80% baseline.

- **The lack of a description of the censoring methods**
  - Patients were censored at lung transplant, last followed or for patients that completed the study the visit in the completion of the Treatment Period, meaning the study treatment period which was the same six week interval for all patient who completed the study. Treatment Period was defined as: first dose for a patient through the first visit during the end of study treatment window 20/08/2008 through 30/09/08 for PIPF-004, and treatment window 15/08/2008 through 25/09/08 for PIPF-006.

- **The lack of information on distinguishing a treatment-emergent death that was related to idiopathic pulmonary fibrosis from one that was not**
  - Treatment-emergent death was defined as that occurring after the first dose and within 28 days after the last dose of study treatment. Determination of the cause of death as being IPF-related or not was assessed by the investigator, who remained masked to treatment assignment. (Noble et al, 2011)
- **Knowing the follow-up period for the data**
  - The Study Period consisted of a Treatment Period and a Follow-up Period. The duration of the Treatment Period (duration of intended blinded therapy) for each patient differed depending on when the patient was randomized into the study. Study treatment was to stop during a 6 week window starting on 20 August 2008 and terminating on 30 September 2008 for PIPF-004 (starting on 15 August 2008 and terminating on 25 September 2008 for PIPF-006), which is 72 weeks after the last patient was randomised. All patients still undergoing study assessments at the start of the 6 week window were required to return to the clinic for a "Treatment Completion Visit" or a "Week 72" visit, or both, during the six week window; this visit is the last visit during the Treatment Period. For patients that discontinued regular study assessments prior to the six week window (no visit either within 12 weeks of window or in window) the Treatment Period ended at the start of the 6 week window. Following the completion of the Treatment Period, patients entered the Follow-up Period. (InterMune, DOF SAP)
  - In summary, InterMune attempted to follow all patients through week 72 and the length of follow-up was from randomisation until the last patient completed week 72, this lead to the 6 week interval in which all patients came for the final visit.

- Some inconsistencies in the hazard ratios (this may be because different time points were used but the ERG noted that this is not discussed in the manufacturer’s submission).
  - This is discussed in the original STA submission on page105 and again in this response (see above).

**Issue 3: Subgroup analyses – concerns on, power, post-hoc analyses**

**Relevant quotes from the ACD**

- Page 27/28: “The ERG highlighted uncertainties in the manufacturer’s submission regarding the subgroup analysis of change in FVC according to baseline patient characteristics, and advised caution when interpreting the results:
  - Although the results generally favoured pirfenidone 2403 mg/day, the confidence intervals were wide and often crossed the line of no effect.
  - It was unclear if the analysis was statistically significant and whether it was adequately powered.

- The ERG reviewed the analysis of the subgroup of patients with baseline FVC of 80% predicted or less and noted a number of concerns:
  - The FVC results were presented from the pooled analysis of PIPF-004 and PIPF-006 and results from the individual trials were not provided.
- No methods were presented by the manufacturer describing how the individual patient data were analysed.
- The analyses appeared to be post hoc and it was unclear if they were statistically powered to detect a difference between groups.”

**InterMune’s response**

Each of the above points are addressed below:

- **Although the results generally favoured pirfenidone 2403 mg/day, the confidence intervals were wide and often crossed the line of no effect.**
  - As stated on page 75 (table B5.3.8) of the original STA submission sub-group analyses based on baseline FVC were pre-specified. These categories were FVC <70% predicted, 70% to <80% predicted and ≥80% predicted. As shown on page 97 treatment favoured pirfenidone 2403 mg/d in the FVC <70% and 70 to <80% predicted subgroups but did cross the line of no treatment effect. However, with the increase in understanding of the greater risk of mortality in patients with FVC<80% predicted (du Bois et al, 2011a), we have reinforced that there is a significant greater risk death in patients with a baseline FVC ≤80% (see Issue 1 above), and demonstrated that pirfenidone in the entire FVC ≤80% subgroup has a significant treatment effect. This is supported by meta-analyses presented in the NICE PAS document dated 19.12.12, which shows that FVC, 6MWT, PFS, IPF-related mortality do not cross the line of no effect.

- **It was unclear if the analysis was statistically significant and whether it was adequately powered.**
  - Survival analysis was a pre-specified exploratory endpoint in the CAPACITY studies (InterMune DOF SAP). Kaplan-Meier estimates were used to summarise time from the randomisation date to the event date or the censoring date. The hazard ratio (HR) was determined based on the Cox regression model, with geographic region (USA and ROW) and study as factors, to estimate the magnitude of the effect. All available data up to the treatment completion visit was used, including follow-up after Week 72.
  - The FVC≤80% subgroup from which inferences are drawn represents a large proportion of the entire randomised population in the CAPACITY studies at 69%. As described in Issue 5 below to power a study for survival in IPF is unrealistic. It has been calculated, based on the observed mortality in the recent placebo arms of IPF studies, that for a 25% reduction in mortality to be statistically significant in a placebo-controlled IPF trial, the enrolment of 2,600 patients and 5 years of follow-up would be required (Bradford et al, 2012).
  - Therefore, survival results for the FVC≤80% subgroup should be considered in the same light as results from the entire mild to moderate population.
The ERG reviewed the analysis of the subgroup of patients with baseline FVC of 80% predicted or less and noted a number of concerns:

- The FVC results were presented from the pooled analysis of PIPF-004 and PIPF-006 and results from the individual trials were not provided. The individual results for PIPF-004 and PIPF-006 studies for the FVC ≤80% are shown below. The pooled analyses for the FVC ≤80% is also shown below again (previously presented in the “Updated Information and Analysis” document dated 17th August, 2012.

### Mean Change from Baseline in Percent Predicted FVC (With Imputation) in PIPF-004 and PIPF-006 (Patients with baseline %FVC ≤ 80%) (InterMune, DOF)

<table>
<thead>
<tr>
<th>Week</th>
<th>PIPF-004: Mean Change</th>
<th>PIPF-006: Mean Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pirfenidone 2403 mg/day (N = 126)</td>
<td>Placebo (N = 108)</td>
</tr>
<tr>
<td>12</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>24</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>36</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>48</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>60</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>72</td>
<td>-7.4</td>
<td>-15.6</td>
</tr>
</tbody>
</table>

**Absolute difference** 8.2% 0.7%

**Relative difference** 52.5% 6.7%

### Table 2: Mean Change from Baseline in Percent Predicted FVC (With Imputation) in PIPF-004/PIPF-006 (Pooled analysis): Patients with baseline %FVC ≤80% (InterMune, DOF)

<table>
<thead>
<tr>
<th>Week</th>
<th>Mean Change</th>
<th>Absolute difference</th>
<th>Relative difference</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pirfenidone 2403mg/day</td>
<td>Placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline FVC ≤80%</td>
<td>n=244</td>
<td>n=233</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
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<tr>
<td>24</td>
<td>[ ]</td>
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<td>36</td>
<td>[ ]</td>
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<td>48</td>
<td>[ ]</td>
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<td>[ ]</td>
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<tr>
<td>60</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>72</td>
<td>-8.4</td>
<td>-12.7</td>
<td>4.3</td>
<td>33.7%</td>
</tr>
</tbody>
</table>
A rank ANCOVA, comparing pirfenidone 2403 mg/day versus placebo, with standardized ranked change from Baseline as the outcome variable, treatment and geographic region (USA and ROW) as fixed effects, and standardized ranked Baseline as a covariate. Missing data due to patient death were ranked as worse than any non death and according to time until death. For missing values if the patient was alive on protocol specified visit the imputation was by the smallest sum of differences (SSD) method. If the patient died on or prior to the protocol specified date then was imputed for the assessment. If a patient was not randomized early enough to have had a particular visit by the end of the study no imputation is done

- No methods were presented by the manufacturer describing how the individual patient data were analysed.
  - The methods used were the same for the FVC ≤80% subgroup as for the entire population. This methodology has been previously described in the InterMune response to clarification document in February 2012 following questions from the ERG.
- The analyses appeared to be post hoc and it was unclear if they were statistically powered to detect a difference between groups.
  - The analyses were post-hoc but were based on the evolving knowledge of the increased risk of death for patients who have a baseline FVC ≤80%. This has been described on page 7 of the “Updated information and analyses document” provided on 17th August, 2012 and has been re-iterated in the response to Issue 1 of this document.

**Issue 4: Uncertainty about correct classification of deaths in CAPACITY studies**

**Relevant quotes from the ACD**

- Page 40, 41, 50, 53, 54: The Committee considered the reliability of the data for mortality relating to idiopathic pulmonary fibrosis from PIPF-004 and PIPF-006. It had concerns that this had not been defined in the clinical trials. The Committee heard from the manufacturer that classifying the cause of death as being related to idiopathic pulmonary fibrosis or not was entirely at the investigator’s discretion. The Committee was aware that there was no central adjudication of these decisions, which is usual in trials where investigator opinion or interpretation is exercised, and that this had potentially introduced inconsistency and uncertainty into the classification. The Committee noted that the FDA had specifically questioned whether 4 of the deaths in the pirfenidone arm that had been classified as being unrelated to idiopathic pulmonary fibrosis should actually have been attributed to the disease. The Committee noted these concerns and again observed the small number of deaths in this post-hoc analysis. The Committee observed that reclassifying a small number of deaths as being related to idiopathic pulmonary fibrosis in the pirfenidone arm could make a substantial difference to the hazard ratio for mortality related to idiopathic pulmonary fibrosis that was used in the economic model. The Committee also recognised the concerns in the European public assessment report, which indicated that data showing a reduction in mortality were based on observational data and derived from small
numbers, and that substantiating the claim would require a proper outcome study over several years. The Committee concluded that there was uncertainty about the correct classification of deaths and was therefore cautious in interpreting a possible survival benefit based on these data from small numbers of events and short follow-up.

InterMune’s response

- The relationship of death being IPF-related or not was assessed by the investigator during the blinded phase of the trial and documented in the Case Report Form (CRF) prospectively (see Appendix 4 from the ‘Appendix for clinical justifications and additional health economic analyses’ document dated 19.12.12). The assessment was systematically guided in the CRF by asking sequentially questions about the degree of IPF contributing to death (minor or major), the timing of the event (abrupt, acute, sub-acute), prior IPF disease development (improving, stable, worsening) and other concomitant diseases or conditions which may have contributed to death.

- Such meticulous and diligent prospective documentation allowed the cause of death to be queried before database closure and provides, to our knowledge, the most accurate definition of the cause of death. Additional adjudication is unlikely to provide a more precise categorisation.

- We note the ACD has questioned whether 4 of the deaths in the pirfenidone arm that had been classified as being unrelated to idiopathic pulmonary fibrosis should actually have been attributed to the disease. We would challenge this as if there is concern about the way these deaths were categorised then surely this would cast doubt on all the other deaths; it is not reasonable to selectively choose which deaths to analyse and debate whether they are IPF-related or not.

- However, InterMune recognise that the Committee were most concerned about the classification of deaths in cases where patients died due to pneumonia. Therefore, we have reviewed the CRFs for the four patients who died from pneumonia in the pirfenidone and placebo arms. Two patients dying from pneumonia, whose deaths were categorised as not being related to IPF, were randomised to the pirfenidone arm, whilst two patients dying from pneumonia, whose deaths were categorised as being related to IPF, were randomised to the placebo group. This is shown in the table below.
In summary, the blinded assessment of IPF-related classification conducted in the CAPACITY trials provides a logical, transparent and correct allocation of death.

Furthermore, we have performed a sensitivity analysis, which calibrates the model to all-cause mortality observed in the CAPACITY trials. This should show the impact of an extreme scenario analysis whereby incorrect classification of deaths as IPF-related vs. non IPF-related would not impact the cost-effectiveness results.
• Firstly, the all-cause mortality HR in the CAPACITY trials at 72-weeks was calculated in STATA as [ ] . This was based on data from the CAPACITY trials and used a Cox proportional hazards model on time to death with censoring at 72-weeks (see Appendix 5 from the ‘Appendix for clinical justifications and additional health economic analyses’ document dated 19.12.12). In addition, the all-cause mortality rates in the CAPACITY trials were [ ] and [ ] for pirfenidone and placebo, respectively.

• Secondly, the IPF-related mortality adjustment factors were amended such that all-cause mortality in the model reflected the rates and HR observed in the CAPACITY trials. For best supportive care (BSC) the adjustment factor reduced from [ ] to [ ] whereas for pirfenidone (PFD) the adjustment factor increased from [ ] to [ ] . These factors were extrapolated past the 72-weeks, justification for which is outlined in Issue 8.

• Please see the NICE PAS document dated 19.12.12 for the results of this sensitivity analysis.

**Issue 5: CAPACITY trials were of short duration and uncertainty if benefit persists over time**

*Relevant quotes from the ACD*

• **Page 39, 50, 52:** “The Committee concluded that pirfenidone seemed to have a modest but measurable effect on slowing the decline in lung function, but that there was uncertainty in whether this benefit persisted over time because the trials had a short duration.”

• **Page 44, 55:** “It was also concerned that the manufacturer assumed that this treatment effect then persisted until death, although no evidence for efficacy beyond 72 weeks had been presented in its submission.”

*InterMune’s response*

• The CAPACITY trials (PIPF-004 and PIPF-006) were 72 weeks in duration which makes them some of the longest trials ever conducted in IPF. Current trials that are being conducted for
potential future IPF therapies are only 52 weeks duration (BIBF 1120, 2012). Furthermore, the bosentan studies for pulmonary arterial hypertension (PAH) were only of 12-16 weeks duration had included a total of 579 patients compared to 885 in the CAPACITY trials. If the Japanese SP2 and SP3 studies are included this is a total of 1,259 IPF patients involved in pirfenidone studies.

- Evidence to show that the treatment effects of pirfenidone persist past 72 weeks can be found in the PIPF-012 (RECAP) trial, an open-label extension study for eligible CAPACITY patients who received ≥80% of the scheduled study drug doses in either arm and completed the Week 72 final study visit in PIPF-004 or PIPF-006. In the CAPACITY trials, 779 patients were randomized to treatment with pirfenidone or placebo and 626 patients completed the study. Of these, 603 (96 percent) were enrolled in RECAP.

- Figure 2 below presents the Kaplan Meier plots and extrapolated curves used in the model considering overall survival in pirfenidone and placebo patients from the CAPACITY trials, as well as pirfenidone patients that continued from the CAPACITY trials into RECAP.

  - The extrapolated pirfenidone survival closely emulates the Kaplan Meier plot of pirfenidone up to 204 weeks (~4 years). The median survival for pirfenidone considering this extrapolation in the FVC≤80% population is [X], which is significantly higher than the median survival of 2-5 years reported in the literature (Meltzer et al, 2008).

  - In addition, the extrapolated placebo curve predicts survival well when compared with the Kaplan Meier plot up to week 72 and as shown by the numbers at risk, data post 72-weeks were unreliable as there was significant attrition in the placebo arms. Furthermore, the median survival in the placebo arm is conservative [X] since IPF experts and published literature suggest it is at the higher end of reported median survivals (Meltzer et al, 2008).

  - The evidence of continued pirfenidone treatment effect in terms of survival is therefore evident based on Kaplan Meier data up to 204 weeks (~4 years) when considering RECAP data.
• In September 2012, interim data from RECAP was presented at the European Respiratory Society Annual Congress (Costabel et al, 2012). Analyses were based on patients in RECAP who were newly treated with pirfenidone having switched from placebo in the CAPACITY trials and who had baseline FVC and DLco values that met CAPACITY entry criteria. FVC was measured at baseline, weeks 12, 36 and 60; week 60 was considered the primary time point of analysis.

  o The first analysis examined the proportion of patients at Week 60 with an FVC decline of 10% or greater; as previously discussed, this is highly predictive of mortality. Patients newly treated with pirfenidone in RECAP who experienced a 10% or greater decline in FVC at week 60 was 16.3% compared with 16.8% in the pirfenidone arm of the CAPACITY trials. The proportion of placebo-treated patients meeting this criterion in the CAPACITY trials was significantly greater at 24.8%.

  o The second analysis was based on the mean change from baseline in percent predicted FVC. At week 60 this showed that the mean change in percent predicted FVC in patients newly treated with pirfenidone in RECAP was -5.8%. The mean change over the corresponding
interval during CAPACITY was \(-7.0\%\) in patients treated with pirfenidone and \(-9.4\%\) in patients treated with placebo, which was statistically significant.

- The last analysis examined overall survival from baseline to Week 60. Analyses showed that overall survival at 60 weeks post initiation of therapy was similar in patients newly treated with pirfenidone in RECAP and pirfenidone patients treated in CAPACITY (Figure 3). Placebo patients in CAPACITY showed a much greater rate of mortality in comparison.

**Figure 3: Kaplan Meier estimates with RECAP trial overlaid on pooled CAPACITY studies**

- These results provide further evidence to support the clinical efficacy and safety of pirfenidone in patients with IPF and characterises that the benefits of pirfenidone do persist in the longer term.

- It is important to note that mortality was an exploratory endpoint in the CAPACITY trials.

- A group of European and United States experts has recently argued that it is unrealistic to expect IPF trials to be powered for mortality and that it would hold back development of treatments for IPF (du Bois et al, 2012; Wells et al, 2012).

- Mortality data are not required for drug registration, whether in rare respiratory diseases such as pulmonary hypertension (PAH) and cystic fibrosis (CF) or in common respiratory diseases such as chronic obstructive pulmonary disease (Wells et al, 2012). Had mortality data been required for drug registration, it is highly unlikely that targeted PAH therapies would now be available (Wells et al, 2012). The same is true in CF, where mortality has long been abandoned as a trial end-point (Wells et al, 2012).

- It has been calculated, based on the observed mortality in the recent placebo arms of IPF studies, that for a 25% reduction in mortality to be statistically significant in a placebo-controlled IPF trial,
the enrolment of 2,600 patients and 5 years of follow-up would be required (Bradford et al, 2012); this represents an infeasible commitment for an R&D based pharmaceutical company to make.

- We note the HTA report conducted for the NICE MTA of PAH drugs (before it was terminated) stated the following uncertainties for bosentan:

  
  "Whether the improvement in functional capacity (FC), exercise capacity and haemodynamic measures on treatment shown in the RCTs lasts beyond the duration of these trials, and whether these improvements translate into long-term benefit in survival and quality of life remains uncertain."

- None of the placebo-controlled trials of bosentan in PAH were powered to show a survival benefit. It is now clear that the benefits seen in the surrogate endpoints of haemodynamics, exercise capacity (such as 6MWD), and functional class which were used as endpoints in the pivotal studies do indeed translate into long-term mortality benefits (McLaughlin et al, 2005).

- Similar uncertainties have been expressed for pirfenidone in this ACD

- Scientific literature and expert opinion support and recognise a decrement of 10% in percent predicted FVC as an independent predictor of mortality in patients with IPF (Collard et al, 2003; Latsi et al, 2003; Flaherty et al, 2003; King et al, 2005; Zappala et al, 2010). In addition, emerging studies strongly suggest that even relatively small changes in FVC (e.g. >5% decline) predict a poorer prognosis (du Bois et al, 2011a; du Bois et al, 2011b; Zappala et al, 2010; Taniguchi et al, 2011). The one-year risk of death in patients with IPF is more than 2-fold higher (p<0.001) in patients with a 24-week decline in FVC between 5-10%. The estimated minimal clinically important difference (MCID) in this study was estimated at 2-6% (du Bois et al, 2011a).

- For the surrogate endpoint of 6 minute walk distance (6MWD) a change of 50m is highly predictive of mortality; a 24-week decrement of 50 m was associated with a four-fold increase in the risk of death over the subsequent 12 months (p<0.001) (du Bois et al, 2011c)

- Rapid progress has been made in recent years with changes in FVC and 6MWD both being shown to be independently linked to mortality. The advantages of FVC over the 6MWD and other candidate end-points include excellent measurement characteristics and a consistent linkage between categorical FVC changes and mortality as described above (Richeldi et al, 2012; Latsi et al, 2003; Collard et al, 2003; Flaherty et al, 2003; King et al, 2005; Jegal et al, 2005; du Bois et al, 2011a).

- As a result of the accumulated studies, serial trends in FVC remain the preferred primary endpoint in IPF treatment studies, as recently argued by expert groups (du Bois et al, 2012; Wells et al, 2012).
Cost-effectiveness issues raised in the ACD addressed in the InterMune’s response

**Issue 6: Calibration of parametric survival curves not fully explored**

**Relevant quotes from the ACD**

- Page 43: “The Committee noted that it would have been possible to calibrate parametric survival curves even with the low mortality observed in the trials, and indicated that the manufacturer’s submission did not fully explore this option.”

- Page 44: “The Committee observed that the reduced uncertainty in how FVC and 6-minute walk test distance predict mortality that had been gained by adding data from GIPF-007 was negated by fixing an additional treatment effect using adjustment factors calibrated to mortality data at 72 weeks, and noted that the manufacturer could similarly have adjusted the original parametric equations derived from PIPF-004, PIPF-006 and PIPF-012.”

- Page 43: “However, it accepted that using FVC and 6-minute walk test distance as covariates to predict survival in a microsimulation model was an acceptable approach to modelling the natural history of idiopathic pulmonary fibrosis in these circumstances.”

- Page 43: “The Committee concluded that the outlined structure of the model adhered to the NICE reference case for economic analysis and was acceptable for assessing the cost effectiveness of pirfenidone.”

**InterMune’s response**

- It is important to note that fitting parametric curves to all-cause mortality events from PIPF-004, PIPF-006 and PIPF-012 was our initial approach to modelling survival. However, goodness of fit tests with AIC and BIC contradicted clinical reality with regards to the median survival of IPF patients receiving placebo. Therefore, this approach was abandoned in favour of epidemiological regressions powered by additional data from GIPF-007. Please see Section 6.2.3 of the original STA submission.

- To allay concerns expressed by the Committee, we explored the option of calibrating parametric survival curves to estimate all-cause mortality.

- Analyses were conducted for the FVC≤80% population, as described in Issue 1 this is the most relevant population.

- As previously considered, parametric survival curves (Exponential, Weibull, Gompertz, Log-logistic, and Lognormal) were fit to the Kaplan Meier plots of all-cause mortality recorded in:
  - The placebo and pirfenidone arms of the PIPF-004 and PIPF-006
- PIPF-012 for patients continuing pirfenidone

- The results with RECAP data facilitated more powerful estimations for the survival analyses because there were more events for which the curves could be fitted to (84/692).

- Treatment assignment was considered as an independent variable in the five survival curves since fitting curves by treatment arm had previously gave spurious results with curves crossing over in some cases.

- Adjustment factors multiplied the probability of death in the placebo arm at and after 72-weeks based on the assigned parametric curve, to ensure the all-cause HR observed in the CAPACITY trial was replicated by the extrapolation at 72-weeks (see Appendix 5 from the ‘Appendix for clinical justifications and additional health economic analyses’ document dated 19.12.12).

- All-cause mortality rates were [ ]% and [ ]% in the pirfenidone and placebo arms respectively. The all-cause mortality HR was [ ].

- The following adjustment factors were used in the placebo arm:

  - [ ]

- To determine reliability of the extrapolations, the median for the placebo extrapolation was analysed.

  - [ ]

- Once more, the Lognormal was the best fitting parametric survival curve as measured by AIC and BIC, but produced the most clinically unrealistic median survival estimates for placebo patients with a FVC≤80% [ ]).

- Even with the Gompertz, which was the most clinically plausible parametric curve, the median survival for placebo patients with a FVC≤80% was [ ]. This was markedly higher than that considered in the cost-effectiveness model based on calibrating regressions for placebo patients with a FVC≤80% ( [ ]).
• It is important to note that:

“The Committee also heard that the clinical specialists felt that the life years gained for the different populations were generally higher than would be expected in clinical practice. (page 44)”

• Therefore, we agree with the Committee that the base case modelling approach is acceptable. Selecting survival with the calibrated regression outputs based on GIPF-007, PIPF-004 and PIPF-006 should be considered the most robust result vs. parametric curve fitting, for three reasons:

1. Parametric survival curves (with and without calibration) provide contradicting results in terms of goodness of fit and clinically realistic results.

2. The most clinical plausible parametric curve is one of the worst fitting, and still provides medians that are higher than those currently considered in the cost-effectiveness model (which clinicians currently believe are generally higher than expected).

3. The regressions are more powered for measuring survival due to the inclusion of GIPF-007 data, which consequently results in more clinically plausible results after calibration.

**Issue 7: Omission of age and gender to the regressions**

**Relevant quotes from the ACD**

• Page 43: “The Committee noted that the manufacturer’s approach to mortality predicted risk of death using FVC, 6-minute walk test distance and treatment as independent covariates, but omitted age and gender.”

**InterMune’s response**

• Both age and gender were considered in the calculation of non IPF-related mortality since this was based on general population statistics split by age and gender (Office of National Statistics 2011). Please see Section 6.2.3 of the original STA submission.

• We acknowledge that the regressions could have controlled for age and gender, since these may be important predictors of IPF-related mortality, hospitalisation, and SGRQ.

• Therefore, we conducted an analysis which considered adding age and gender to the regressions to improve goodness of fit and predictive strength. Results are provided in Appendix 6 from the ‘Appendix for clinical justifications and additional health economic analyses’ document dated 19.12.12.

• The goodness of fit for IPF-related mortality and hospitalisation regressions were not improved by the additions of age or gender as independent covariates.

• The goodness of fit for SGRQ was significantly improved with the additions of age and gender as independent covariates, and has subsequently been used in the amended base case analysis.
• Please see the NICE PAS document dated 19.12.12 for the impact of this addition to the base case.

**Issue 8: Extrapolation of survival benefit past 72-weeks**

**Relevant quotes from the ACD**

• **Page 44:** “It was also concerned that the manufacturer assumed that this treatment effect then persisted until death, although no evidence for efficacy beyond 72 weeks had been presented in its submission.”

• **Page 44:** “The Committee was concerned that although the manufacturer had increased the discontinuation rates of pirfenidone from 72 weeks up to 192 weeks in the model based on the PIPF-012 extension study (which only included patients with known high compliance), the hazard ratios for survival based on data up to 72 weeks had been maintained for both the mild-to-moderate population and the subgroup with baseline FVC 80% predicted or less.”

**InterMune’s response**

• As stated in the points of factual inaccuracy, data were presented past 72-weeks considering overall survival of pirfenidone patients continuing into PIPF-012 (RECAP). Please see Figure 5 and Figure 6 of the Updated Analysis and Information document.

• Figures below show the Kaplan Meier plots and extrapolated overall survival curves calculated from the model based on pirfenidone and placebo patients from the CAPACITY trials, as well as pirfenidone patients that continued from the CAPACITY trials into RECAP.

• For the FVC≤80% population:
  
  o The extrapolated pirfenidone survival curve closely emulates the Kaplan Meier plot of pirfenidone up to **204 weeks (≈4 years)**. The median survival for pirfenidone considering this extrapolation is **3** years, which is significantly higher than the median survival of 2-5 years reported in the literature (Meltzer et al, 2008).

  o The extrapolated placebo survival curve predicts survival well when compared with the Kaplan Meier plot up to week 72 and as shown by the numbers at risk, data post 72-weeks were unreliable since there was significant attrition in the placebo arms. Furthermore, the median survival for placebo considering this extrapolation is **conservative at 2** years; the Committee, IPF experts and published literature suggest it is at the higher end of reported median survivals (Meltzer et al, 2008).

• Continued pirfenidone treatment effect in terms of survival is therefore evident based on Kaplan Meier data up to 204 weeks (≈4 years) when considering RECAP data.
• Therefore, assuming the survival benefits with pirfenidone persist over a lifetime appears to be reasonable given that median survival has been estimated as 2-5 years (Meltzer et al, 2008).

• Using the RECAP data, there is evidence to suggest that survival benefits will persist for at least 204 weeks (~4 years). Therefore, discontinuation rates at week 192 were obtained from the RECAP study for patients who were initiated on pirfenidone during the CAPACITY trials, such that the costs up until this time could be accurately reflected.
• A quote from the ERG’s overview of InterMune’s additional analyses and Patient Access Scheme confirms that the approach adopted in balancing survival benefits and observed discontinuations was appropriate:

Page 584 of the Evaluation Report: “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.”

**Issue 9: Uncertainty in the estimation of quality of life**

**Relevant quotes from the ACD**

• Page 45: “The Committee discussed how quality of life had been incorporated into the model. It queried why the clinical trial data had not been directly incorporated but instead the St George’s Respiratory Questionnaire scores had been estimated using FVC and 6-minute walk test distance.”

• Page 45: “The Committee observed that the ERG’s scenario analyses that varied the patients’ quality of life demonstrated this uncertainty, which was reflected in the sensitivity of the ICERs. It was also aware that no decrement to quality of life had been applied in the model to account for adverse effects.”

• Page 46: “Committee concluded that there was considerable uncertainty in the estimation of utilities using the manufacturer’s model.”

**InterMune’s response**

• We acknowledge that the there are two levels of uncertainty in the estimation of quality of life.

• Firstly, regression analysis estimated SGRQ considering FVC and 6MWD as independent covariates. We sought to improve the predictive strength of this regression by considering age and gender as independent covariates (see Issue 7).

  o Goodness of fit and predictive strength was significantly improved with the additions of age⁻¹ and gender as independent covariates, and has subsequently been used in the amended base case analysis.

  o Appendix 6 from the ‘Appendix for clinical justifications and additional health economic analyses’ document dated 19.12.12 shows that FVC, 6MWD, age⁻¹ and gender are all significant predictors of SGRQ (p<0.0001).
Sensitivity analyses considered varying the coefficients of the new regression by upper and lower confidence intervals to explore uncertainty related to quality of life. Please see the NICE PAS document dated 19.12.12 for the impact of these analyses.

Unfortunately, SGRQ clinical trial data could not be used to inform extrapolations of quality of life past 72-weeks with parametric curves or linear declines since quality of life is an unpredictable measure that can fluctuate based on disease severity and symptoms. Therefore, the best prediction of quality of life past 72-weeks was based on independent prognostic factors (FVC, 6MWD, age and gender) which declined over time and therefore were considered biomarkers for disease severity.

Secondly, SGRQ was mapped onto the EQ-5D using a published study in COPD patients (Starkie et al, 2011). Therefore, this new mapping equation has been used in the base case. Please see the NICE PAS document dated 19.12.12 for the impact of this addition.

Sensitivity analyses considered varying the coefficients of the new mapping equation to explore uncertainty related to quality of life. Please see the NICE PAS document dated 19.12.12 for the impact of these sensitivity analyses.

- We note the committee commented that no decrement to quality of life had been applied in the model to account for adverse effects. Recent data presented was by the BTS winter conference in 2012 from single-centre observational study of patients participating in the pirfenidone named patient programme who completed the Self-Report Chronic Respiratory Disease Questionnaire (SR-CRQ). No relationship was found between SR-CRQ scores and adverse effects (Capps et al, 2012) It was concluded that no significant change in quality of life due to adverse effects in those treated with pirfenidone was observed.

- To summarise, uncertainty related to both the prediction of SGRQ and calculation of EQ-5D has been significantly reduced.

- The prediction of SGRQ has been improved by the additions of age and gender as independent covariates in the regression, which significantly improved goodness of fit.
The mapping onto EQ-5D has been improved by considering a cohort of IPF patients as opposed to COPD patients, and calculating an algorithm with less error.

**Issue 10: Concerns that not all model parameters had been included in the probabilistic sensitivity analyses**

*Relevant quotes from the ACD*

- Page 46: “The Committee was particularly concerned that the manufacturer had not used probabilistic sensitivity analyses to explore the uncertainty associated with the estimated treatment effects (survival, hospitalisation and health-related quality of life), or fully explored the uncertainty associated with the hazard ratio for idiopathic pulmonary fibrosis-related mortality, including the adjustment factors for best supportive care and for pirfenidone treatment.”

- Page 46: “The Committee considered that by not exploring these factors, the probabilistic sensitivity analyses did not capture the full range of uncertainty of the ICERs. The Committee concluded that there was a high level of uncertainty associated with the estimates of treatment effect of pirfenidone and mortality related to idiopathic pulmonary fibrosis and thus with the life years gained and QALYs generated using the manufacturer’s model.”

*InterMune’s response*

- We acknowledge that the probabilistic sensitivity analysis (PSA) could have further explored uncertainty associated with treatment effects by including variation in:
  - Regressions for IPF-related mortality, hospitalisation and SGRQ
  - Mapping algorithm from SGRQ to EQ-5D
  - IPF-related adjustment factors

- Therefore, the PSA was updated to include these parameters:
  - Coefficients of the regressions for IPF-related mortality, hospitalisation and SGRQ were varied probabilistically using Normal distributions based on the reported means and standard errors.
  - Coefficients for the mapping algorithm from SGRQ to EQ-5D were varied probabilistically using Normal distributions based on the calculated means. Standard errors were determined based on the upper and lower confidence intervals of the coefficients.
  - IPF-related adjustment factors for pirfenidone and best supportive care were varied probabilistically using Normal distributions based on the base case means. In the absence of reported standard errors or confidence intervals for the calibration factors, standard errors were assumed to be 20% of the mean values.

- Please see the NICE PAS document dated 19.12.12 for the impact of these additions to the PSA.
Pirfenidone not considered to be a step change in innovation

Relevant quotes from the ACD

- Page 48: “The Committee discussed whether pirfenidone was an innovative treatment. It considered that pirfenidone had an innovative mechanism of action but that it could not be considered a step change in the management of idiopathic pulmonary fibrosis, given its modest effect observed over a short duration and the lack of evidence relating this to outcomes that are important to patients.”

InterMune’s response

A step-change can be considered as a “sudden, discontinuous change”. Pirfenidone is a step change in IPF as there have been no licensed therapies that have been rigorously tested and approved. Since PANTHER, no options are available for patients (barring transplant) and pirfenidone represents a brand new paradigm in IPF management.

Innovation, Health and Wealth is the NHS Chief Executive’s report on the identification, adoption and spread of innovation in the NHS. Innovation, Health and Wealth defines innovation as “an idea, service or product, new to the NHS or applied in a way that is new to the NHS, which significantly improves the quality of health and care wherever it is applied” (DH, 2011)

Innovation, Health and Wealth describes three reasons why innovation and adoption at pace are important not just to the NHS but to society and the economy as well (DH, 2011):

- Innovation transforms patient outcomes;
  - Pirfenidone has demonstrated a significant delay of progression free survival and significant slowing of decline in 6MWD which has been associated with an improved quality of life

- Innovation can simultaneously improve quality and productivity;
  - Pirfenidone has shown cost effectiveness and has been associated with reduced hospitalisation costs

- Innovation is good for economic growth.
  - Pirfenidone is the first medicine that directionally changes management of IPF from a purely supportive, palliative care resource investment towards a disease specific, course modifying treatment

We feel pirfenidone meets the above criteria for IPF patients and the NHS.
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