Controversies in Clinical Trials

Pirfenidone for Idiopathic Pulmonary Fibrosis (IPF)
Controversies to be highlighted by IPF Story

- Post-hoc analyses
- Primary end point selection
  - Changing prespecified endpoints
  - Surrogate endpoints
- Missing Data
- FDA approval/regulation
What is IPF

- Idiopathic pulmonary fibrosis (IPF) is a progressive and fatal disease characterized by scarring of the lungs that thickens the lining of the lungs, causing an irreversible loss of the ability to transport oxygen.
- IPF ultimately robs a patient of the ability to breathe.
- There is no known cause, no FDA approved treatments and no cure for IPF.
IPF Facts

- median age at time of diagnosis is 63
- IPF affects about 128,000 people in the United States, with about 48,000 new cases diagnosed annually.
- 40,000 people die each year to IPF, the same as to breast cancer.
  - 2/3 of IPF patients die within 5 years of diagnosis
- IPF is five times more common than cystic fibrosis and Lou Gehrig’s Disease (or ALS), yet the disease remains virtually unknown to general public and IPF receives a fraction of the research funding.
  - IPF: approx. $18 million per year
  - Cystic Fibrosis: $85 million per year
  - ALS: $48 million per year
IPF Symptoms/signs

- Dry cough
- Chronic dyspnea
- Inspiratory crackles on exam
- Restriction and diffusion impairment on PFT
- Hypoxemia
**IPF Diagnosis**

- In the absence of alternative causes, “classic” HRCT findings are sufficient for diagnosis.
  - Subpleural predominant reticulation favoring the lower lung fields,
  - Paucity of ground glass, and
  - Honeycombing
- If the HRCT is consistent, but not classic, then surgical biopsy showing usual interstitial pneumonia (UIP) is required.
  - Temporally heterogeneous pattern
  - honeycombing
  - Fibroblastic foci
Treatment of IPF

- No FDA approved treatment
- Until recently, published guidelines suggest treatment with corticosteroids and cytotoxic agents.
  - Based upon opinion only – No supportive data
  - The majority of patients do not respond.
  - We do not recommend therapy unless patient is progressing rapidly.
- Lung transplantation
Clinical Trials

- **A Placebo-Controlled Trial of Interferon Gamma-1b in Patients with Idiopathic Pulmonary Fibrosis**
  - 330 IPF patients randomly assigned in a 1:1 ratio to receive interferon gamma-1b or placebo subcutaneously three times weekly
  - No difference in primary endpoint (progression free survival):
    - 10% decline in FVC, or
    - 5 mmHg increase in A-a gradient, or
    - Death
  - No difference in measures of lung function, gas exchange, or quality of life.
  - Trend towards benefit in survival (10% vs. 17%, p=0.08)
  - Post-hoc analysis suggested *survival* benefit in those with mild-moderate disease (4% vs. 12%, p=0.04)
Kaplan–Meier Estimates of Progression Free Survival among Patients with Idiopathic Pulmonary Fibrosis.

Figure 1. Kaplan–Meier Estimates of Progression-free Survival among Patients with Idiopathic Pulmonary Fibrosis.

InterMune Press Release

InterMune Announces Phase III Data Demonstrating Survival Benefit of Actimmune in IPF
Reduces Mortality by 70% in Patients with Mild to Moderate Disease
Former InterMune CEO
Convicted of Wire Fraud

—Company Found to Have Disseminated
Misleading Information About Results
of Clinical Trial of Its Interferon Product

SAN FRANCISCO, CAL. 9/29/09—After 3 days
of deliberations, a jury has convicted W. Scott
Harkonen, M.D., the former CEO of InterMune,
Inc., of wire fraud under 18 USC §1343 for the
creation and dissemination of “false and misleading
information” about the efficacy of drug Actimmune
(interferon gamma-1b) as a treatment for idiopathic
pulmonary fibrosis. The conviction arose from a
press release issued by Harkonen on August 28,
2002, announcing the results of a clinical trial sup-
pessedly demonstrating that the biologic product
enabled patients with IPF to live longer. (The headline
read “InterMune Announces Phase III Data Demon-
strating Survival Benefit of Actimmune in IPF: Reduces
Mortality by 70% in Patients with Mild to
Moderate Disease.”)

In fact, the trial did not demonstrate a benefit.
Actimmune was not approved for the treatment of
IPF, but that indication accounted for most of Inter-
Mune’s sales of the product, which can cost approxi-
mately $50,000 per year.

Further Troubles for Sequenom

—Investigations, Shareholder Lawsuit Follow
Alleged Mishandling of Data on Fetal Test

SAN DIEGO, CAL. 10/6/09—The U.S. Attorney
for the Southern District of California and the Nasdaq
stock exchange have opened investigations into
Sequenom over its mishandling of test data and results
of its test for Down’s syndrome and other conditions
in fetuses, called SEQureDx. The estimated annual
sales of a successful test would be about $2 billion.

The company announced last week that it was fir-
ing five employees, including its President and CEO
Harry Stylli and its Senior VP of Research Elizabeth
Dragon. Two other employees, CFO Paul Hawran
and VP for Commercial Development of Prenatal Di-
gnostics Steve Owings, resigned.

The company said it is cooperating with the probe
and has met with the U.S. Attorney and the Federal
Bureau of Investigation. It also has held discussions
with the Securities and Exchange Commission.

UPDATE: On November 13, some Sequenom
shareholders filed suit in U.S. District Court for the
Southern District of California over the mishandling
of data from SEQureDx. The complaint alleges breach
of fiduciary duties by several people and insider trad-
ing by Owings. Other defendants are Stylli, Dragon,
Hawran, the former VP of Regulatory Affairs, Qual-
Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial

- 826 patients with mild to moderate IPF.
  - FVC 55-90%, DLCo 35-90%.
- Randomized 2:1
- Primary endpoint was survival
- Study stopped after 2nd interim analysis failed to show minimum benefit.
- No difference in measures of lung function, gas exchange, or quality of life.
Clinical Trials

- Other IPF trials:
  - Bosentan
    - Build-1: negative study, but post-hoc analysis showed benefit in progression free survival among patients with surgical lung biopsy.
    - Build-3: negative study.
  - Ambrisentan
    - stopped due to lack of efficacy at interim analysis
  - Sildenafil
    - negative study
  - NAC
    - Slowed progression of IPF when added to prednisone plus azathioprine
    - PANTHER –
      - multi-armed study including NAC alone and combined with other therapy ongoing.
      - Imuran + Prednisone arm stopped early due to increased mortality in treatment arm.
  - Warfarin
    - ACE – stopped early – lack of efficacy and increased adverse events.
Pirfenidone

- Experimental animal models of pulmonary fibrosis suggest anti-inflammatory, antioxidant, and antifibrotic effects
- A Japanese phase 2 study suggested benefit
  - Primary outcome was lowest O2 sat during 6MET
  - The study was stopped early given greater risk of IPF exacerbations in the placebo group.
Taniguchi Phase 3 study

- 275 patients randomized
- Primary endpoint: Change in FVC
  - Primary endpoint changed midway through trial
  - Initial primary endpoint was lowest O2 saturation during 6 min walk.
- Missing data imputed by LOCF
- Secondary endpoints:
  - Progression free survival
  - Progression = 10% decline in FVC
  - Change in lowest SpO2 during 6MET

Taniguchi et al, Eur Respir J. 2010 Apr;35(4):821-9
Change in FVC (Primary end-point)
Change in FVC (Primary end-point)
Secondary and tertiary endpoints

- PFS better in the high dose pirfenidone compared with placebo
  - 11 patients died, 3 high dose, 4 low dose, and 4 placebo
- No difference in lowest SpO2
- No difference in acute exacerbations
Taniguchi study

- If you were to assigned to peer-review this study, what would you say?
- What are the problems with this study?
Change in Primary Endpoint

- Original primary end-point was change in lowest oxygen saturation during 6-min steady-state exercise test.
- During the course of this trial, views on appropriate primary end-points in IPF evolved.
- The decision to change end-points involved members of the DSMB who recommended change after a discussion of blinded interim comparative data (i.e. they had knowledge of whether there were significant differences between study groups with respect to the primary and secondary end-points).
- “the credibility and integrity of the trial is compromised. It is simply impossible for readers to assess the impact of this knowledge on the decision.”
Problems with LOCF

- LOCF may be appropriate, but it may not.
- What biases might LOCF introduce for the hypothetical subjects below?

Swigris and Fairclough et al., ERJ 10/2010
Mixed model results

**Table 3** Mixed model analysis of changes in vital capacity from baseline: adjusted means of vital capacity changes at the last visit in treatment groups and comparisons of the means

<table>
<thead>
<tr>
<th>Group</th>
<th>Estimate</th>
<th>SE</th>
<th>p-value#</th>
</tr>
</thead>
<tbody>
<tr>
<td>High dose</td>
<td>-0.09289</td>
<td>0.02248</td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>-0.06855</td>
<td>0.03003</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>-0.14349</td>
<td>0.02179</td>
<td></td>
</tr>
<tr>
<td>Difference High versus low dose</td>
<td>-0.02434</td>
<td>0.03752</td>
<td>0.5166</td>
</tr>
<tr>
<td>Difference High dose versus placebo</td>
<td>0.05060</td>
<td>0.03131</td>
<td>0.1062</td>
</tr>
<tr>
<td>Difference Low dose versus placebo</td>
<td>0.07494</td>
<td>0.03710</td>
<td>0.0435</td>
</tr>
</tbody>
</table>

#: both-sided p-values.
Capacity studies

- PIPF 004: 435 pts
  - Patients randomized 2:2:1 to receive pirfenidone 2403 mg/d (174 patients), placebo (174 patients), or pirfenidone 1197 mg/d (87 patients)

- PIPF 006: 344 pts
  - Patients randomized 1:1 to receive pirfenidone 2403 mg/d (171 patients) or placebo (173 patients)

- Primary endpoint for each study was change in FVC at week 72 (compared with ranked ANCOVA)

Noble et al, Lancet. 2011 May 21;377(9779):1760-9
Statistical Analyses

- Primary Endpoint: Change in FVC at 72 weeks
- Primary efficacy analysis: Ranked ANCOVA
- Missing data: Missing values as a result of death were assigned the worst rank in ANCOVA analyses, and worst possible outcome in mean change analyses (eg, FVC=0) and categorical analyses. Other missing data were imputed with the average value from three patients with the smallest sum of squared differences at each visit with data that were not missing.
Change in FVC

**Absolute difference**
- Pirfenidone 2403 mg/day (n=174):
  - Weeks: 0-12: -1.4% 2.5% 4.6% 4.8% 4.1% 4.4%
  - Weeks: 12-24: -4.4%
- Pirfenidone 1197 mg/day (n=87):
  - Weeks: 0-12: 5.2% 6.3% 8.2% 8.4% 8.1% 8.3%
  - Weeks: 12-24: -1.5%
- Placebo (n=174):
  - Weeks: 0-12: -0.4% 2.8% 2.4% 1.9% 0.6% 0.6%
  - Weeks: 12-24: -3.1%

**Relative difference**
- Pirfenidone 2403 mg/day (n=171):
  - Weeks: 0-12: 53.5% 65.2% 63.7% 52.3% 38.3% 35.3%
  - Weeks: 12-24: 31.9%
- Placebo (n=173):
  - Weeks: 0-12: -31.5% 62.1% 48.2% 27.3% 7.6% 6.5%
  - Weeks: 12-24: 28.9%

**p value**
- Pirfenidone 2403 mg/day (n=345):
  - Weeks: 0-12: 0.031 0.001 0.005 0.172 0.501
- Placebo (n=347):
  - Weeks: 0-12: 0.003 <0.0001 <0.0001 <0.0001 0.0003 0.005
<table>
<thead>
<tr>
<th></th>
<th>Study 004</th>
<th>Study 006</th>
<th>Pooled data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pirfenidone 2403 mg/day (n=174)</td>
<td>Placebo (n=174)</td>
<td>Absolutely difference (95% CI)</td>
</tr>
<tr>
<td>Categorical change in FVC ≥ 10%</td>
<td>35 (20%)</td>
<td>60 (35%)</td>
<td>14-4 (7-4 to 21.3)</td>
</tr>
<tr>
<td>Progression-free survival time†</td>
<td>--</td>
<td>--</td>
<td>0.64 (0.44 to 0.95)</td>
</tr>
<tr>
<td>Mean change in 6MWT distance (m)</td>
<td>-6.04</td>
<td>-7.68</td>
<td>16.4 (-10.9 to 43.7)</td>
</tr>
<tr>
<td>Mean change in DLco (% predicted)</td>
<td>-7.9</td>
<td>-9.9</td>
<td>2.0 (-0.4 to 4.4)</td>
</tr>
<tr>
<td>Mean change in dyspnoea score∥</td>
<td>12.1</td>
<td>15.2</td>
<td>-3.1 (-8.5 to 2.3)</td>
</tr>
<tr>
<td>Mean change in worst SpO2 during 6MWT (%)</td>
<td>-1.5</td>
<td>-2.3</td>
<td>0.8 (-0.2 to 1.8)</td>
</tr>
<tr>
<td>Time to worsening in idiopathic pulmonary fibrosis</td>
<td>--</td>
<td>--</td>
<td>0.84 (0.50 to 1.42)†</td>
</tr>
<tr>
<td>Categorical change in HRCT-diagnosed fibrosis</td>
<td></td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

FVC= forced vital capacity. 6MWT=6-minute walk test. DLco=haemoglobin-corrected carbon monoxide diffusing capacity. SpO2= peripheral oxygen saturation. HRCT=high-resolution CT. NA=not applicable.

*Rank ANCOVA (pirfenidone 2403 mg/day vs placebo), unless otherwise indicated. †Cochran-Mantel-Haenszel row mean score test (pirfenidone 2403 mg/day vs placebo) based on five categories (severe decline, ±20%; moderate decline, <20% but ±10%; mild decline, <10% but ±0; mild improvement, >0 but <10%; and moderate improvement, ±10%). §Hazard ratio (95% CI) based on the Cox proportional hazard model with geographic region (USA vs non-USA) as a stratum. ¶Log-rank test (pirfenidone 2403 mg/day vs placebo). ||Based on the University of California San Diego Shortness of Breath Questionnaire: total score ranges from 0 to 120, with larger scores indicating greater shortness of breath. ||Cochran-Mantel-Haenszel row mean score test (pirfenidone 2403 mg/day vs placebo) based on five categories (much better, better, same, worse, or much worse); assessed in study 006 only.

Table 2: Secondary efficacy endpoints at week 72.
Progression Free Survival Capacity 004

Hazard ratio 0.64 (95% CI 0.44–0.95; \( p=0.023 \))

<table>
<thead>
<tr>
<th>Number at risk</th>
<th>Week 0</th>
<th>Week 12</th>
<th>Week 24</th>
<th>Week 36</th>
<th>Week 48</th>
<th>Week 60</th>
<th>Week 72</th>
<th>Week 84</th>
<th>Week 96</th>
<th>Week 108</th>
<th>Week 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone 2403 mg/day</td>
<td>171</td>
<td>167</td>
<td>160</td>
<td>157</td>
<td>148</td>
<td>138</td>
<td>55</td>
<td>23</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pirfenidone 1197 mg/day</td>
<td>87</td>
<td>86</td>
<td>79</td>
<td>74</td>
<td>68</td>
<td>64</td>
<td>27</td>
<td>11</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>173</td>
<td>162</td>
<td>150</td>
<td>136</td>
<td>126</td>
<td>116</td>
<td>44</td>
<td>21</td>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Progression Free Survival
Capacity 006

Hazard ratio 0.84 (95% CI 0.58–1.22; p=0.355)*
Progression Free Survival
Pooled studies

Hazard ratio 0.74 (95% CI 0.57–0.96; p=0.025)*
### Mortality – Exploratory endpoint

<table>
<thead>
<tr>
<th></th>
<th>Pirfenidone 2403 mg/day (n=345)</th>
<th>Placebo (n=347)</th>
<th>Hazard ratio* (95% CI)</th>
<th>p value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>27 (8%)</td>
<td>34 (10%)</td>
<td>0.77 (0.47-1.28)</td>
<td>0.315</td>
</tr>
<tr>
<td>Idiopathic-pulmonary-fibrosis-related mortality‡</td>
<td>18 (5%)</td>
<td>28 (8%)</td>
<td>0.62 (0.35-1.13)</td>
<td>0.117</td>
</tr>
<tr>
<td><strong>On-treatment§</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>19 (6%)</td>
<td>29 (8%)</td>
<td>0.65 (0.36-1.16)</td>
<td>0.141</td>
</tr>
<tr>
<td>Idiopathic-pulmonary-fibrosis-related mortality‡</td>
<td>12 (3%)</td>
<td>25 (7%)</td>
<td>0.48 (0.24-0.95)</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Data are number (%). *Based on the Cox-proportional hazard model. †Log-rank test (pirfenidone 2403 mg/day vs placebo). ‡Assessed by the investigator, who remained masked to treatment assignment. §Defined as the time from randomisation until 28 days after the last dose of study drug.

**Table 3:** All-cause and idiopathic-pulmonary-fibrosis-related mortality in the pooled population.
What would you do?

- Moc FDA Vote
What has happened

- FDA advisory panel recommended approval
- FDA decision was to not approve Pirfenidone as of now
- ASCEND Trial
ASCEND Study Design: Overview

- Randomized, double-blind, placebo-controlled trial
- Eligible patients randomized (1:1) to treatment with pirfenidone 2403 mg/d or matched placebo for 52 weeks
- Centralized review of HRCT, SLB, spirometry and deaths instituted to confirm eligibility and ensure high-quality efficacy assessments
- 127 sites in 9 countries (U.S., Australia, Brazil, Croatia, Israel, Mexico, New Zealand, Peru, and Singapore)
ASCEND Study Design: Pre-Specified Efficacy Endpoints

- Primary Endpoint: %FVC Change from Baseline to Week 52
  - Primary analysis: Rank ANCOVA model
  - Magnitude of effect: categorical analysis of 2 clinically important thresholds of change (≥10% decline or death, no decline)

- Key Secondary Endpoints*
  - 6MWT distance (6MWD) change in meters from Baseline to Week 52
  - Progression-free survival (PFS)†

- Additional Secondary Endpoints
  - All-cause mortality (ASCEND alone and pooled with CAPACITY)
  - Treatment-emergent IPF-related mortality (ASCEND alone and pooled with CAPACITY)
  - Dyspnea change from Baseline to Week 52 (UCSD SOBQ score)

* Tested for multiple comparisons using the Hochberg procedure
† Defined as time to first occurrence of death, confirmed ≥10% absolute decline in FVC, or confirmed ≥50 m decline in 6MWD
Primary Efficacy Analysis: %FVC Change at Week 52

Proportion of Patients with %FVC Decline ≥10% or Death

<table>
<thead>
<tr>
<th>Week</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td></td>
</tr>
<tr>
<td>39</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td></td>
</tr>
</tbody>
</table>

Pirfenidone (N=278)

Placebo (N=277)

Relative Difference

|                    | 54.0%** | 58.0%** | 57.8%** | 47.9%* |

*p<0.000001*

*Rank ANCOVA (pirfenidone vs. placebo)*

**Rank ANCOVA p<0.0001**
Primary Efficacy Analysis: %FVC Change at Week 52

Proportion of Patients with Clinically Important Thresholds of %FVC Change

- **47.9% Reduction**
- **132.5% Increase**

<table>
<thead>
<tr>
<th>Patients (%)</th>
<th>≥10% Decline or Death</th>
<th>No Decline (Change &gt;0%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pirfenidone (N=278)</td>
<td>[Bar Graph]</td>
<td>[Bar Graph]</td>
</tr>
<tr>
<td>Placebo (N=277)</td>
<td>[Bar Graph]</td>
<td>[Bar Graph]</td>
</tr>
</tbody>
</table>

\[ p<0.000001^\ast \]

\*Rank ANCOVA (pirfenidone vs. placebo at week 52)
## Pre-Specified Mortality Analyses: ASCEND and CAPACITY (52-week data) Pooled

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>HR (95% CI)</th>
<th>P-value†</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.52 (0.31–0.87)</td>
<td>0.0107</td>
</tr>
<tr>
<td>Treatment emergent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPF-related mortality*††</td>
<td>0.32 (0.14–0.76)</td>
<td>0.0061</td>
</tr>
</tbody>
</table>

* Deaths adjudicated by mortality assessment committee (ASCEND) or investigator (CAPACITY) as directly related to IPF and does not include deaths in CAPACITY beyond one year
†† Occurring during treatment period (from first dose up to 28 days after last dose of study drug)
‡ Log-rank test