STARTS-1 and -2

A randomized, double-blind, placebo controlled, dose ranging, parallel group study of oral sildenafil in the treatment of children, aged 1-17 years, with pulmonary arterial hypertension (PAH)

Dunbar Ivy, MD

Disclosure

- The University of Colorado School of Medicine received fees for Dr Ivy to be a consultant to Pfizer
- Dr Ivy received travel and meals to attend STARTS review meetings

Natural History of IPAH: NIH Registry\textsuperscript{1,2}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{natural_history_ipah.png}
\caption{Median survival: 2.8 years (n=194)\newline Pediatric median survival: 0.8 years (n=16)}
\end{figure}

NIH = National Institutes of Health. Predicted survival according to the NIH equation. Predicted survival rates were 69%, 56%, 46%, and 38% at 1, 2, 3, and 4 years, respectively. The numbers of patients at risk were 231, 149, 82, and 10 at 1, 2, 3, and 4 years, respectively. Patients with primary pulmonary hypertension, now referred to as idiopathic pulmonary hypertension.


Survival of Pediatric PAH In Combined Netherlands Cohorts: 1991 - 2005

\begin{figure}
\centering
\includegraphics[width=\textwidth]{survival_netherlands.png}
\caption{Survival of Pediatric PAH In Combined Netherlands Cohorts: 1991 - 2005}
\end{figure}

PAH Subgroups

- Number of patients at 0, 1, 3, 5, and 10 years from diagnosis:
  - with shunt
  - without shunt

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|}
\hline
Years from Diagnosis & PAH Subgroups & Years from Diagnosis & PAH Subgroups \\
\hline
0 & 16 & 16 & 16 & 16 \\
2 & 8 & 8 & 8 & 8 \\
4 & 4 & 4 & 4 & 4 \\
6 & 2 & 2 & 2 & 2 \\
8 & 2 & 2 & 2 & 2 \\
10 & 2 & 2 & 2 & 2 \\
12 & 2 & 2 & 2 & 2 \\
14 & 2 & 2 & 2 & 2 \\
16 & 2 & 2 & 2 & 2 \\
\hline
\end{tabular}
\end{table}

Objectives & Endpoints

- **Primary efficacy endpoint**
  - Percentage change from baseline in peak VO$_2$ at Week 16
- **Secondary efficacy endpoints**
  - Change from baseline in mean pulmonary artery pressure (mPAP)
  - Change from baseline in pulmonary vascular resistance index (PVRI)

Study Criteria

- **Inclusion**
  - Aged 1-17 years with PAH (WHO Group 1)
  - IPAH, HPAH, APAH-CHD, PAH-CTD
  - > 8 kg
  - VO$_2$ Peak $\geq$10 mL/kg/min and $\leq$28 mL/kg/min
- **Exclusion**
  - Unrepaired CHD with saturation <88%
  - ERA / Prostanoid / Nitrate / PDE-5 / L-arginine

Study Design – Treatment Allocation

<table>
<thead>
<tr>
<th>Body Weight(kg)</th>
<th>Placebo Allocation Ratio</th>
<th>Low Dose (Dose) Allocation Ratio</th>
<th>Medium Dose (Dose) Allocation Ratio</th>
<th>High Dose (Dose) Allocation Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥8 - 20</td>
<td>1</td>
<td>10 mg 1</td>
<td>20 mg 2</td>
<td>40 mg 1</td>
</tr>
<tr>
<td>&gt;20 - 45</td>
<td>1</td>
<td>10 mg 1</td>
<td>20 mg 1</td>
<td>40 mg 1</td>
</tr>
<tr>
<td>&gt;45</td>
<td>1</td>
<td>10 mg 1</td>
<td>40 mg 1</td>
<td>80 mg 1</td>
</tr>
</tbody>
</table>

Patients NOT randomized by disease etiology or severity

Sildenafil Study Design

- **Screening**
  - (Can occur up to 3 weeks before randomization (-21 to -1 days)
- **Randomization Day 1**
- **Double-blind Treatment phase**
  - (16 weeks; day 1 thru day 112)
- **Forced Titration**
  - (1 week; day 1 thru day 7)
- **Weeks 2-16**
- **Follow-up**
  - (30-40 days)
Subject Accountability

324 Screened
235 Randomised
234 Treated

60 Randomised
60 Treated
30 (50%) Dev Ab
29 Analysed

42 Randomised
42 Treated
28 (67%) Dev Ab
24 Analysed

56 Randomised
55 Treated
28 (50%) Dev Ab
26 Analysed

77 Randomised
77 Treated
29 (38%) Dev Ab
27 Analysed


Five Year Duration to Recruit 115 Subjects Capable of Exercise Capacity Testing

Disease Etiology

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>Placebo</th>
<th>Sildenafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects (N=234)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPAH</td>
<td>35%</td>
<td>33%</td>
</tr>
<tr>
<td>APAH-CHD</td>
<td>65%</td>
<td>67%</td>
</tr>
<tr>
<td>Developmentally able subjects (N=115)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IPAH</td>
<td>33%</td>
<td>36%</td>
</tr>
<tr>
<td>APAH-CHD</td>
<td>67%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Baseline VO\textsubscript{2} Peak Hemodynamics

<table>
<thead>
<tr>
<th>Mean (SD)</th>
<th>Normal Values</th>
<th>Placebo</th>
<th>Sildenafil Low/Medium/High (Combined)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VO\textsubscript{2} Peak, ml/kg/min</td>
<td>30 – 35</td>
<td>20 (4) n=30</td>
<td>18 (4) n=85</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>12 – 15</td>
<td>59 (22) n=59</td>
<td>63 (22) n=172</td>
</tr>
<tr>
<td>CI, L/min/m\textsuperscript{2}</td>
<td>2.5 – 4</td>
<td>4 (2) n=59</td>
<td>3 (2) n=167</td>
</tr>
<tr>
<td>PVRI, dyne.sec.cm\textsuperscript{-5}.m\textsuperscript{2}</td>
<td>&lt;160</td>
<td>1167 (759) n=57</td>
<td>1590 (1175) n=165</td>
</tr>
</tbody>
</table>
Placebo-adjusted Percent Change
\( VO_2 \) Peak

Low (n=24)
Medium (n=26)
High (n=27)
Low/Med/High (n=77)

\( VO_2 \) peak (% change from baseline to Week 16) Comparison to Placebo (n=29) with 95% CIs


Estimated treatment effects
(±95% confidence interval) in STARTS-1

High Dose
N=77

Medium Dose
N=55

Low Dose
N=42

Placebo
N=60

Placebo/Non Random N=5

STARTS-1

STARTS-2

Patient Disposition in STARTS-1 and -2

Sildenafil Dose Changes

Table 1. Summary of Dose Changes

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low (n=55)</td>
</tr>
<tr>
<td>TubeFeeding (%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>At least 1 weight gain, n (%)</td>
<td>26 (51)</td>
</tr>
<tr>
<td>1 up titration</td>
<td>20 (37)</td>
</tr>
<tr>
<td>2 up titrations</td>
<td>6 (11)</td>
</tr>
<tr>
<td>Dose increase due to weight increase*</td>
<td>19 (35)</td>
</tr>
</tbody>
</table>

A maximum of 2 up titrations and 1 dose increase were allowed during the study.
Kaplan-Meier Estimated Survival From Start of Sildenafil Treatment in STARTS-1 and -2

As of August 2011 37 deaths
Hazard ratios for mortality were 3.38 (95% CI, 1.23–9.27) H vs L

Baseline Characteristics and Mortality

- 76% (28/37) of deaths were IPAH (vs 9/37 for APAH-CHD)
- 76% (28/37) of the subjects who died had baseline PVRI above or equal to the median (15.1 Wood units m²)
- 68% (25/37) had mPAP greater than or equal to the median (62 mmHg)
- 73% (27/37) had RAP greater than or equal to the median (7.0 mmHg)
Peak VO\textsubscript{2} 1 Year

**Study End**

- Dec 2012
- Total of 42 deaths (18%)
  - Low: 5/55 (9.1%)
  - Medium: 13/74 (17.6%)
  - High: 24/100 (24%)
- 5 additional deaths after August 2011
  - 3 medium
  - 2 placebo / high
  - 4/5 down titrated after August 2011

**Study Problems**

- Open-label; no control group in LT extension
- Patients not censored at study withdrawal but followed until death
- 30% (11/37) of patients who died withdrew from study and f/u treatment unknown
  - No treatment protocol after withdrawal
  - Death median of 287 days (9-1202 days)
Why was high dose sildenafil associated with increased mortality?

- High output syndrome?
- Pro-arrhythmia?
- Exposure?
- Withdrawal effect?
- Disease related?
- Co-morbidity?
- Unknown

Conclusions

- Primary endpoint of STARTS-1 did not meet predefined statistical p value
- Dose-related increase in mortality
  - True for randomized dose, last dose on treatment, last dose, modal dose
- Survival in treatment naïve children 76-91% on H/M/L dose sildenafil monotherapy
- Problems in extension phase lead to difficulty in interpretation of long term results

My Practice

- Inform all families of FDA warning
- Continue to use generic sildenafil
- No abrupt discontinuations
- Down titrate patients from high dose if possible
- Consider alternate therapy (PDE-5 / ERA)
- Informed consent
- Continue to use in PICU / NICU / CICU and < 1 year old