STARTS-1 and -2

A randomized, double-blind, 16 week placebo controlled, dose ranging, parallel group study of oral monotherapy sildenafil in treatment naive children, aged 1-17 years, with pulmonary arterial hypertension (PAH). STARTS-1 was followed by sildenafil dose extension study STARTS-2

Disclosures

• The University of Colorado contracts with Actelion, Gilead, Pfizer, United Therapeutics for Dr Ivy to be a consultant
• Investigator Initiated grants: Gilead
• Steering Committee: GSK / Actelion
STARTS-1 Study Criteria

- **Inclusion**
  - Aged 1-17 years with PAH (WHO Group 1)
  - IPAH, HPAH, APAH-CHD, PAH-CTD
  - ≥ 8 kg
  - $\text{VO}_2\text{Peak} \geq 10 \text{ mL/kg/min and } \leq 28 \text{ mL/kg/min}$

- **Exclusion**
  - Unrepaired CHD with systemic arterial oxygen saturation <88%
  - ERA / Prostanoid / Nitrate / PDE-5 / L-arginine

STARTS-1 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)

## STARTS-1 Study Design – Treatment Allocation

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

STARS-1 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**
- Weeks 2-16

**Follow-up**
- (30–40 days)
STARTS-1 Subject Accountability

- 324 Screened
- 235 Randomised
  - 234 Treated

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

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

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

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

Time to Recruit 115 Subjects Capable of Reliable 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 VO₂ 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>V₀₂ 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/m²</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⁻⁵.m²</td>
<td>&lt;160</td>
<td>1167 (759) n=57</td>
<td>1590 (1175) n=165</td>
</tr>
</tbody>
</table>
Placebo-adjusted Percent Change

$\text{VO}_2$ Peak

Low (n=24)
- Placebo (n=29)

Medium (n=26)

High (n=27)

Low/Med/High (n=77)

$\text{VO}_2$ Peak (% change from baseline to Week 16) Comparison to Placebo (n=29) with 95% CIs

$\text{VO}_2$ Peak = 3.81

Medium = 11.33

High = 7.98

Low/Med/High = 7.71

$p = 0.056$

Effects of Sildenafil on PVRI and mPAP in Children

**PVRI**
- Low (n=37)
- Medium (n=51)
- High (n=68)
- L/M/H (n=156)

(Change from baseline to week 16) comparison to placebo (n=52) with 95% CIs (dyne·s·cm⁻⁵·m²)

**mPAP**
- Low (n=39)
- Medium (n=55)
- High (n=71)
- L/M/H (n=165)

(Change from baseline to week 16) comparison to placebo (n=56) with 95% CIs (mmHg)
% Change in VO$_2$ Peak by Etiology

VO$_2$ Peak %Change from Baseline to Week 16 Comparison to Placebo with 95%CI
PVRI: Analysis by Etiology

IPAH

CHD unrepaired

CHD repaired

Ratio Comparison (Active/Placebo) with 95% CIs

- Low dose
- Medium dose
- High dose
- High/Med/Low

0.2 0.4 0.6 0.8 1.0 1.2 1.4 1.6 1.8

Low dose
Medium dose
High dose
Combined dose
Patient Disposition in STARTS-1 and -2

- **Placebo**: N=60
- **Low Dose**: N=42
- **Medium Dose**: N=55
- **High Dose**: N=77
- **Placebo/Non Random**: N=5

**STARTS-1**
- **Low Dose**: n=13
- **Medium Dose**: n=19
- **High Dose**: n=23

**STARTS-2**
- **Low Dose**: N=55
- **Medium Dose**: N=74
- **High Dose**: N=100
# 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>Down titrations, n (%) †</td>
<td>0</td>
</tr>
<tr>
<td>At least 1 up titration, n (%)</td>
<td>28 (51)</td>
</tr>
<tr>
<td>1 up titration</td>
<td>20 (36)</td>
</tr>
<tr>
<td>2 up titrations</td>
<td>8 (15)</td>
</tr>
<tr>
<td>Dose increases due to weight increases §</td>
<td>18 (33)</td>
</tr>
</tbody>
</table>

A maximum of 2 up titrations and 1 down titration were allowed during the study. Doses received after dose titrations were equivalent to those in other dose groups (see Methods). *An additional 2 down titrations occurred in patients who were treated with placebo in STARTS-1 but not randomized in STARTS-2.
STARTS-2: 1 Year VO$_2$ Peak

![Bar chart showing VO$_2$ peak for different groups over 1 year compared to baseline.]

- **Low / Low**
- **Medium / Medium**
- **High / High**
- **Placebo / Low**
- **Placebo / Medium**
- **Placebo / High**

**Y-axis:** PEAK VO$_2$ ML/KG/MIN

**X-axis:** Groups:
- Low / Low
- Medium / Medium
- High / High
- Placebo / Low
- Placebo / Medium
- Placebo / High

**Legend:**
- Blue (Baseline)
- Red (Year 1)
Kaplan-Meier Estimated Survival From Start of Sildenafil Treatment in STARTS-1 and -2

Hazard ratios for mortality were 3.50 (95% CI, 1.29–9.51) H vs L
Kaplan-Meier Estimated Survival From Start of Sildenafil Treatment in STARTS-1 and -2

Kaplan-Meier Estimated Survival From Start of Sildenafil Treatment in STARTS-1 and -2

Baseline Characteristics and Mortality

- 74% (26/35) of deaths were in IPAH children
- 74% (26/35) of the subjects who died had baseline PVRI ≥ to the median (15 Wood units/m\(^2\))
- 69% (24/35) had mPAP ≥ to the median (62 mmHg)
- 71% (25/35) had RAP to the median (7.0 mmHg)
Baseline Characteristics and Mortality

- 40% (14/35) were FC III/IV at baseline
- All deaths judged by investigator as disease related
Regulatory / DMC Actions

• May 2011: EMA approves sildenafil for pediatric use in children with PAH
• August 2011: STARTS DMC mandates decrease in sildenafil dose
• October 2011: EMA warns against use of high dose
• August 2012: FDA warns against use of sildenafil 1-17 y.o.
  – high dose of Revatio had a higher risk of death than children taking a lower dose
  – low doses of Revatio are not effective in improving exercise ability in the 16 week randomized placebo controlled trial
Study Limitations

- No control group in LT extension
- 26% (9/35) of patients who died withdrew from STARTS-1/-2 study and f/u treatment unknown
  - No treatment protocol after withdrawal
  - Death median of 147 days (9-406 days) after off study treatment
Conclusions

• Primary endpoint of STARTS-1 did not meet predefined statistical p value – peak VO2 for all sildenafil treated patients vs PBO
• Dose-related increase in mortality observed at 3 years
• Survival in treatment naïve children 88-94% at 3 years on L/M/H dose sildenafil monotherapy
• Survival in STARTS similar to 3 year survival in 3 recent registries (UK, Netherlands, US)