Registry to Evaluate Early and Long-Term PAH Disease Management

Transforming PAH Experience Into Knowledge
Protocol and Goals of the REVEAL Registry

Robyn J. Barst, MD
REVEAL Study Objectives

- To characterize the demographics and clinical course of the patient population diagnosed with WHO Group I PAH
- To evaluate differences in patient outcomes according to WHO Group I classification subgroup
REVEAL Study Objectives

• To compare patient outcomes in patients who do and do not meet prespecified hemodynamic criteria for the diagnosis of PAH
• To identify clinical predictors of short-term and long-term outcomes
REVEAL Study Objectives

• To assess the relationship between PAH medications (individually and in combination) and patient outcomes
• To report temporal trends in treatments and outcomes for newly diagnosed patients
• To collect timely and relevant data that will assist in the evolving research needs of the PAH community
REVEAL Registry™ is a multicenter, observational, U.S.-based study of the clinical course and disease management of pulmonary arterial hypertension (PAH) patients. All consecutive consenting patients diagnosed with WHO Group I PAH according to specific hemodynamic criteria at participating institutions will be enrolled. Participating patients will be followed for a minimum of 5 years from the time of enrollment.
Inclusion Criteria

• Newly diagnosed or previously diagnosed patients with WHO Group I PAH
• >3 months of age at enrollment
Inclusion Criteria

• Documentation of the following hemodynamic parameters by right heart catheterization, performed at any time prior to study enrollment:
  • Mean pulmonary arterial pressure (mPAP) > 25 mm Hg at rest or mPAP > 30 mm Hg with exercise contemporaneous with a pulmonary wedge pressure ≤ 18 mm Hg
  • Pulmonary wedge pressure or LVEDp ≤ 18 mm Hg
  • Pulmonary vascular resistance (PVR) ≥ 240 dynes·sec·cm$^5$ (i.e., ≥ 3.0 Wood units)
Exclusion Criteria

• Patients not eligible for participation in this study are those not meeting the inclusion criteria, including those who:
  • Meet the criteria for inclusion into WHO Groups II, III, IV or V
  • Have not had documentation of hemodynamic criteria for PAH by right heart catheterization at some time preceding study entry and following development of symptoms associated with PAH
  • Do not meet the required hemodynamic criteria for entry into the study
Time Frame and Enrollment Numbers

• First patient-in: March 31, 2006
• Last patient enrolled: December 31, 2007 (with at least 5 years of follow-up through December, 2012)
• Planned Total Sample Size:
  • Approximately 3,500 newly (~500-700) and previously diagnosed (~2,800-3,000) patients enrolled at approximately 50 investigational sites
Outcomes to Be Assessed

• Modified NYHA/WHO functional class
• Six-minute walk distance
• Change in pulmonary function test results
• Change in hemodynamic measurements, when available
• Functional status, including employment, student status, level of independent function
• Occurrence of hospitalizations
• Occurrence of death
• Unexpected hospitalizations and/or deaths deemed to be related to bosentan by the investigator
Data Collection

- Followed until death, withdrawal of consent, loss to follow-up, or end of the study
- Data from the initial screening evaluation and from follow-up visits or telephone discussion coded on eCRFs
- Data from follow-up visits will be recorded on the eCRF on a quarterly basis
- For previously diagnosed patients, a separate eCRF will be completed to collect past medical information
- No additional tests are to be performed as part of Registry participation
Data Input Flow Sheet

1. **Type**
   - Patient Presents

2. **Criteria Met?**
   - Yes
   - No

3. **Exclude Patient**
   - Yes

4. **Retrospective Data**

5. **Entry Data**
   - q 3 mo

6. **Follow-Up Data**
Data Analysis

• To characterize the patient population, quarterly analyses will be provided to participating institutions that display aggregate data (i.e., from all participating institutions) and institution-specific data (from the site of the Investigator). Annual data will also be provided.
Implementation

- First objective can be partially fulfilled with baseline data
  - To characterize the demographics (including zip code) and clinical course of the patient population diagnosed with WHO Group I PAH
  - Baseline data allows evaluation of demographics and past and current medical course
  - Analyses will be descriptive in nature
  - No hypothesis testing
- Most analyses performed on aggregate data and stratified by WHO Group I Classification
  - Patient Characteristics
  - Timing of Symptoms, Presentation, and Diagnosis
  - Medical History, Comorbid Conditions, and Patient Evaluation
  - PAH-Specific Medication Use
What to Consider as Results are Discussed: Registries vs. RCTs

Registries
• Observational
• Broad entry criteria
• Treatment recommendations and decisions by MD and patient
• Hypothesis-generating
• Treatment changes based on MD judgment
• No set visit schedule

Randomized Clinical Trials
• Randomized
• Restrictive entry criteria
• Treatment by protocol
• Hypothesis-testing
• Pre-specified without changes possible outside protocol
• Protocol-mandated visits
Descriptive Nature of Results

• Analyses describe current clinical practice
  • Patient cohort includes survivor bias
  • Analyses show what is happening and not what should be happening
  • Results may raise new questions to evaluate in future analyses
Operational Update

Abby Krichman, RRT
2006 Goals and Accomplishments

• First-Patient-In, March, 2006
  • First patient enrolled at Dr. Elliot’s site on March 30th
• Total of 1,000 patients enrolled by end of 2006 calendar year
  • Exceeded expectations and enrolled 1,427 patients
• Total of 25 sites enrolling patients by end of 2006 calendar year
  • 46 sites were activated with 41 sites enrolling patients
2006 Activities

• First Investigators’ Meeting, February 25, 2006, Boca Raton
• REVEAL Registry Poster at PHA, June, 2006, Minneapolis
• Second Investigators’ Meeting, September 29, 2006, Chicago
  • Unveiled descriptive analyses on 500 patients
• Data on REVEAL Registry presented at CHEST by Dr. McGoon
• Data on REVEAL Registry presented to NIH by Dr. McGoon
• REVEAL Registry Booth
  • ATS
  • PHA
  • CHEST
  • AHA
2007 Goals and Accomplishments

- Complete enrollment of 3,000 patients in the REVEAL Registry by end of 2007 calendar year
  - **August 07: 3,000 patients enrolled**

- Total of at least 50 sites enrolling patients
  - **Total of 56 enrolling sites**
  - **6 Pediatric Sites**

- Minimum of two main publications
  - **2 Manuscripts In-development**
    - Design Manuscript
    - Baseline Demographics Manuscript
2007 Activities

• CHEST: Three abstracts accepted
  • Slide Presentation
    • Baseline Characteristics of the First 1500 Enrolled – Badesch
  • 2 Poster Presentations
    • Medical History and Time to Diagnosis – Elliott
    • Treatment History and Treatment at Baseline – McGoon

• Third Investigator’s Meeting, March 2007, Las Vegas, NV
• Fourth Investigator’s Meeting, November 2007, Half Moon Bay, CA

• REVEAL Registry Booth
  • ATS
  • CHEST
As of Today

• 3,074 patients enrolled at 56 sites*
  • 2,585 enrollment eCRFs completed (84%)

• Monitoring Activities (target 20% of sites annually)
  • 10 Sites received onsite monitoring

*As of October 5, 2007
**Top 15 Enrolling Sites**

<table>
<thead>
<tr>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic, Rochester</td>
</tr>
<tr>
<td>University of Colorado HSC</td>
</tr>
<tr>
<td>University of Pennsylvania Med Center</td>
</tr>
<tr>
<td>Duke University</td>
</tr>
<tr>
<td>Baylor College of Medicine</td>
</tr>
<tr>
<td>UCLA/West Los Angeles VA</td>
</tr>
<tr>
<td>Columbia University Medical Center</td>
</tr>
<tr>
<td>Cleveland Clinic Foundation</td>
</tr>
<tr>
<td>Johns Hopkins Medical Center</td>
</tr>
<tr>
<td>UCSF Medical Center</td>
</tr>
<tr>
<td>University of Alabama</td>
</tr>
<tr>
<td>UCSD Medical Center</td>
</tr>
<tr>
<td>LDS Hospital</td>
</tr>
<tr>
<td>University of Pittsburgh Medical center</td>
</tr>
<tr>
<td>Denver Children’s Hospital</td>
</tr>
</tbody>
</table>
Geographic Representativeness
As of August 2, 2007

[Map of the United States showing the number of cases in each state, with large numbers indicated by red circles.}]
Importance of REVEAL

Supply current information about entire spectrum of PAH
Importance of REVEAL

Largest registry of PAH
(~3500 patients)
Importance of REVEAL

Include “real-world” patients
Importance of REVEAL

Uncover differences among PAH subgroups
Importance of REVEAL

Includes all subgroups of APAH patients
Importance of REVEAL

Includes children