Long-term Ambrisentan Therapy Provides Sustained Benefit in Patients with Pulmonary Arterial Hypertension

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Pulmonary Hypertension Association 8th International Conference
June 20, 2008
Houston, TX, USA
Oral Presentation
Long-term Ambrisentan Therapy Provides Sustained Benefit in Patients with Pulmonary Arterial Hypertension

Conflict of Interest Statement:

The following relationships exist for the presenting author:

Grant support (GS), consultant (C), speakers bureau (SB):

American Heart Association: GS
NIH/NCRR: GS
Actelion: GS, SB
Encysive: GS, C
Gilead: GS, C, SB
Lilly-ICOS: GS, C
LungRx: GS, C
Pfizer: GS, C, SB
United Therapeutics: GS, C, SB

Off label use of products will not be discussed in this presentation
Ambrisentan For PAH

- Ambrisentan is approved in the United States and European Union for the treatment of PAH in patients with WHO class II and III symptoms
- Propanoic acid-based ET$_A$-selective antagonist
  - >4000-fold more selective for ET$_A$ compared to ET$_B$
- Highly potent
  - $K_i$ for the ET$_A$ receptor = 0.011 nM
- $T_{1/2}$ of ~15 hours in PAH patients
- Dose-proportional pharmacokinetics
- No clinically relevant drug-drug interactions
  - warfarin
  - sildenafil
ARIES-1 and ARIES-2
Study Design

- Randomized, double-blind, placebo-controlled study
- Age: ≥18 years
- IPAH or APAH secondary to CTD, HIV, anorexigen use
- PAH disease severity
  - 6-minute walk distance criteria of 150-450 meters
  - Right heart catheterization hemodynamics criteria
- ARIES-1: placebo, 5 or 10 mg once daily
  ARIES-2: placebo, 2.5 or 5 mg once daily
- 12-week, double-blinded treatment period
- “Early Escape” option after Week 4

All subjects completing ARIES-1 and -2 and placebo subjects who discontinued due to Early Escape were eligible for a blinded, long-term study (ARIES-E)
ARIES-1 and ARIES-2
12-week Results

• In a combined analysis of the ARIES studies ambrisentan improved:
  – 6-minute walk distance (6MWD)
  – Time to clinical worsening
  – WHO functional class
  – Borg dyspnea index (BDI)
  – SF-36® Health Survey
  – B-type natriuretic peptide (BNP)

• Ambrisentan was well-tolerated, with no serum aminotransferase abnormalities >3xULN observed
ARIES-E
Objective

- To evaluate the long-term safety, durability of improvements in efficacy, and survival of patients with PAH treated with ambrisentan
ARIES-E
Study Design

- Common long-term extension study for patients participating in ARIES-1 or ARIES-2
- Patients who received ambrisentan in previous studies remained on current dose
- Patients who received placebo in previous studies were randomized to ambrisentan
  - ARIES-1: 5 or 10 mg
  - ARIES-2: 2.5 or 5 mg
- First 24 weeks was a blinded, fixed-dose period
- Blinded dose adjustment allowed after Week 24
- Concomitant prostanoid and/or PDE5 inhibitors permitted
ARIES-E
Data Analysis

• Data as of November 2006
• Efficacy and safety assessments were measured from the time of first dose of ambrisentan
• Data is presented for all dose groups combined
• Efficacy data are presented through 48 weeks of treatment
  – observed case (OC) with no imputation
  – last observation carried forward (LOCF)
• Kaplan-Meier analyses for survival and LFTs are presented through 1 year of treatment
• Descriptive statistics are presented without formal hypothesis testing
• All analyses were pre-specified
## Baseline Demographics and Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ambrisentan (N = 383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female (%)</td>
<td>79</td>
</tr>
<tr>
<td>Mean Age (yr)</td>
<td>51 ± 15</td>
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<tr>
<td>Mean Weight (kg)</td>
<td>72 ± 18</td>
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<tr>
<td>Caucasian (%)</td>
<td>77</td>
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<tr>
<td>Mean 6MWD (m)</td>
<td>347 ± 85</td>
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<tr>
<td>Mean BDI</td>
<td>3.9 ± 2.4</td>
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± standard deviation
## Baseline Disease Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ambrisentan (N = 383)</th>
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<tbody>
<tr>
<td>WHO Class I (%)</td>
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<td>WHO Class II (%)</td>
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<td>WHO Class III (%)</td>
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<td>WHO Class IV (%)</td>
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<td>mPAP (mmHg)</td>
<td>$49 \pm 14$</td>
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<tr>
<td>mRAP (mmHg)</td>
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<td>CI (L/min/m²)</td>
<td>$2.5 \pm 0.8$</td>
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<td>PVR (Wood units)</td>
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± standard deviation
Patient Disposition

383 Randomized Patients

65 Discontinued
- 18 Deaths
- 20 Adverse Events\(^a\)
- 27 Other\(^b\)

318 Ongoing
- 298 completed 48 weeks
- 94% (280/298) receiving ambrisentan monotherapy

Disposition through Week 48 with data cut-off of November 2006
a. Includes discontinuation due to Early Escape
b. 3 subjects completed 12 week study and did not enroll into extension
6-Minute Walk Distance Change from Baseline

Change in 6MWD (meters) vs. Weeks

- **Observed Case**
  - Week 0: n=383
  - Week 12: n=360
  - Week 24: n=332
  - Week 36: n=309
  - Week 48: n=290

- **LOCF**
  - Week 0: n=383
  - Week 12: n=375
  - Week 24: n=375
  - Week 36: n=375
  - Week 48: n=375

Mean ± 95% confidence interval
Borg Dyspnea Index
Change from Baseline

Improvement
Change in BDI

Mean ± 95% confidence interval

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<th>Time</th>
<th>OC n=382</th>
<th>LOCF n=382</th>
<th>n=351</th>
<th>n=374</th>
<th>n=328</th>
<th>n=374</th>
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WHO Functional Class Change from Baseline

**Observed Case**

- Week 12: 24%
- Week 24: 31%
- Week 36: 29%
- Week 48: 33%

**LOCF**

- Week 12: 23%
- Week 24: 30%
- Week 36: 26%
- Week 48: 28%
One-year Survival

Kaplan-Meier estimate and 95% confidence intervals

Ambrisentan: 95%
(95% CI: 93%-97%)
Adverse Events

• Long-term safety profile was similar to the 12-week placebo-controlled studies

• Most frequent adverse events
  – Peripheral edema
  – Headache
  – Upper respiratory tract infection
  – Dizziness

• Most AEs of peripheral edema were mild or moderate

• Most AEs were seen in the first 12 weeks of treatment
2.3% of placebo patients had AST/ALT >3xULN in the 12-week placebo-controlled studies
Kaplan-Meier estimate

1-year risk of ALT/AST >3xULN = 2.1%
ARIES-E
Conclusions

- Sustained improvements in:
  - 6MWD
  - Borg dyspnea index
  - WHO functional class

- 1-year survival
  - 95% for all patients

- 94% of the 298 patients with 48 weeks of exposure were still receiving ambrisentan monotherapy

- Long-term incidence of AST/ALT >3xULN was similar to the incidence observed for placebo in 12 weeks