Ambrisentan Therapy in Patients with Pulmonary Arterial Hypertension: 3-Year Outcome
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RJ Oudiz, M Allard, C Blair, and H Gillies on Behalf of the ARIES Study Group
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Rj Oudiz¹, M Allard², C Blair², and H Gillies² on Behalf of the ARIES Study Group

BACKGROUND

Ambrisentan for Pulmonary Arterial Hypertension (PAH)

Ambrisentan is a once-daily, oral, propanoic-acid based ETA-selective endothelin receptor antagonist approved at doses of 5 mg and 10 mg for the treatment of PAH.

ARIES-1 and ARIES-2 were the pivotal 12-week placebo-controlled trials that led to the approval of ambrisentan for PAH.¹

– In these studies, ambrisentan improved exercise capacity and delayed clinical worsening in patients with PAH.

Following the 12-week trials, patients continued treatment with ambrisentan in a long-term extension study (ARIES-E).²

– In ARIES-E, 2-year ambrisentan treatment was associated with sustained improvements in exercise capacity and a low risk of clinical worsening and death.

– Ambrisentan was generally well-tolerated, with a low risk of aminotransferase abnormalities over the 2-year study period.

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² Gilead Sciences Inc., Foster City, CA, USA.

METHODS

ARIES-E Study Design

Common long-term extension study for patients participating in ARIES-1 or ARIES-2.

Patients who received placebo in previous studies were randomized to ambrisentan.

– ARIES-1: 5 or 10 mg once daily.
– ARIES-2: 2.5 or 5 mg once daily.

Patients who received ambrisentan in previous studies remained on their current dose for the first 24 weeks.

First 24 weeks was a blinded, fixed-dose period.

After the blinded fixed-dose period, investigators were allowed to adjust the dose as clinically needed.

– Available doses: 2.5mg, 5mg, 10mg.

Concomitant prostanoid and/or PDE5 inhibitors were permitted.

OBJECTIVE

This analysis was designed to evaluate the longer-term (3-years) safety and efficacy of ambrisentan in patients with PAH treated in the ARIES studies.

The poster was presented Wednesday, October 26, 2011 in the Pulmonary Vascular Disease session during CHEST 2011 in Honolulu.
ARIES-E Data Analysis

Efficacy and safety assessments were measured from the time of the first dose of ambrisentan.

– Data is presented by randomized dose through 3 years of treatment from ARIES-1, ARIES-2 and ARIES-E.

6MWD, WHO functional class, and Borg Dyspnea Index (BDI) data are presented for 1 year (48 weeks), 2 years (96 to 108 weeks), and 3 years (144 to 156 weeks).

– Placebo patients were randomized to ambrisentan 12 weeks later.

Missing data were imputed using last observation carried forward (LOCF).

Kaplan-Meier analyses for survival, clinical worsening, safety, and LFTs are presented through 3 years (156 weeks) of treatment for all patients who received ambrisentan.

– Survival status was collected retrospectively after study closure for subjects with an unknown outcome at the end of the study.

Descriptive statistics are presented without formal hypothesis testing.

RESULTS

Table 1—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>Age, yr</td>
<td>51 ± 15</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>72 ± 18</td>
</tr>
<tr>
<td>Caucasian, %</td>
<td>77</td>
</tr>
<tr>
<td>WHO Class I, %</td>
<td>3</td>
</tr>
<tr>
<td>WHO Class II, %</td>
<td>43</td>
</tr>
<tr>
<td>WHO Class III, %</td>
<td>46</td>
</tr>
<tr>
<td>WHO Class IV, %</td>
<td>8</td>
</tr>
<tr>
<td>6MWD, meters</td>
<td>347 ± 85</td>
</tr>
<tr>
<td>Borg Dyspnea Index, Score</td>
<td>3.9 ± 2.4</td>
</tr>
<tr>
<td>mPAP, mmHg</td>
<td>49 ± 14</td>
</tr>
<tr>
<td>mRAP, mmHg</td>
<td>8 ± 5</td>
</tr>
<tr>
<td>Cardiac Index, L/min/m²</td>
<td>2.5 ± 0.8</td>
</tr>
<tr>
<td>PVR, wood units</td>
<td>11 ± 7</td>
</tr>
</tbody>
</table>

Mean ± standard deviation; Baseline assessed prior to first dose of ambrisentan except historical hemodynamic measurements; Data presented by randomized dose; ARIES-1 and ARIES-2 placebo subjects RHC measurements were performed at least 12 weeks before ambrisentan initiation.
Ambrisentan Dose Adjustments

At 3 years, for those patients still on ambrisentan in the study:

- Almost half of the patients randomized to 2.5 mg were titrated to 5 mg and 10 mg
- A third of the patients randomized to 5 mg were titrated to 10 mg

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Table 2—Number of Patients on Ambrisentan by Dose Group Through 3 Years

<table>
<thead>
<tr>
<th>Dose</th>
<th>Patient Number at Randomization</th>
<th>Patient Same Dose n, (%)</th>
<th>Patient Same Dose n, (%)</th>
<th>Patient Same Dose n, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 Year</td>
<td>2 Years</td>
<td>3 Years</td>
<td></td>
</tr>
<tr>
<td>2.5 mg</td>
<td>96</td>
<td>81</td>
<td>70 (86)</td>
<td>69</td>
</tr>
<tr>
<td>5 mg</td>
<td>190</td>
<td>152</td>
<td>129 (85)</td>
<td>124</td>
</tr>
<tr>
<td>10 mg</td>
<td>97</td>
<td>81</td>
<td>78 (96)</td>
<td>66</td>
</tr>
</tbody>
</table>

*Same dose = Patients remaining at same randomized dose at 1, 2 and 3 years

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**Figure 4.** 6-minute Walk Distance—Change from Baseline by Randomized Dose (LOCF).

**Figure 5.** 6-minute Walk Distance—Change from Baseline by Randomized Dose (Observed Case).

**Figure 6.** WHO Functional Class—Change from Baseline by Randomized Dose (LOCF).

After 1 year of ambrisentan treatment, improvements in 6MWD compared to baseline were observed for all dose groups.

After 2 and 3 years of ambrisentan treatment, improvements compared to baseline in 6MWD were maintained for the randomized 5 mg and 10 mg dose groups.

Maintenance of treatment-effect over 3 years for the randomized 2.5 mg dose group was not sustained despite uptitration to 5 mg and 10 mg.

Similar to 6MWD, there appears to be maintenance of the treatment effect with BDI over 3 years in the 5 mg and 10 mg dose groups.

- Change from baseline BDI score at 2 years (LOCF).
  - 5 mg dose group: -0.33 (95% CI: -0.68 to 0.03).
  - 10 mg dose group: -0.65 (95% CI: -1.12 to -0.18)

- Change from baseline BDI score at 3 years (LOCF).
  - 5 mg dose group: -0.14 (95% CI: -0.51 to 0.22).
  - 10 mg dose group: -0.48 (95% CI: -0.93 to -0.03).

Approximately 80% of patients either improved or maintained their WHO functional class through 3 years of ambrisentan treatment.

Mean ± 95% confidence interval; Observed Case

Mean ± 95% confidence interval
Last observation carried forward for missing data
The majority of patients were free of clinical worsening events through 3 years of ambrisentan treatment.

*Kaplan-Meier estimates (95% CI); randomized dataset: Clinical worsening was defined as:

- Time from initiation of ambrisentan to first occurrence of death, lung transplantation, hospitalization for PAH, atrial septostomy, addition of prostanoid therapy, or study withdrawal due to addition of other PAH therapy.

**Figure 7. Time to Clinical Worsening.**

At 3 years, 74% of the PAH patients taking first line ambrisentan therapy were still alive.

**Figure 8. Post-study Outcome Status—Patient Disposition.**

At 3 years, the Kaplan-Meier survival rate was 79% for PAH patients randomized to ambrisentan.

**Figure 9. Post-Study Outcome—Long-Term Survival.**

**Figure 10. Hepatic Safety Monitoring—Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) Plot – Peak Bilirubin vs. ALT Levels per Subject Through 3 Years.**
Adverse Events Through 3 Years

The 3-year safety profile was similar to the 2-year safety profile (JACC 2009).

The most frequent AEs were:
– Peripheral edema, Headache, Upper respiratory tract infection, Cough, Right Ventricular Failure, Dizziness, Arthralgia.

Most AEs of peripheral edema were mild or moderate with only 6 (1.6%) AEs considered severe and 1 (0.3%) AE leading to discontinuation of study.

Most frequent AEs leading to discontinuation were consistent with worsening PH.

Estimated risk of developing serum aminotransferase abnormalities (ALT/AST >3X ULN) was:
– 1.8% (95% CI: 0.8% to 3.9%) at 1 year
– 3.9% (95% CI: 2.2% to 6.8%) at 2 years
– 4.8% (95% CI: 2.8% to 8%) over 3 years for an annualized risk of approximately 1.6%

CONCLUSIONS

ARIES 3-Year Data

Long-term ambrisentan treatment was associated with:
– Sustained improvements for the 5 mg and 10 mg randomized dose groups.
– Exercise ability and dyspnea.

– Majority of the patients in ARIES-E remained on ambrisentan monotherapy.
– Maintained or improved WHO functional class for the majority of patients.
– A low risk of clinical worsening and death
  – Majority of patients free of clinical worsening events through 3 years of ambrisentan treatment
  – At 3 years, the Kaplan-Meier survival rate was 79% for PAH patients taking first line ambrisentan therapy.
– A 3-year ambrisentan safety profile consistent with previous ambrisentan 2-year data
– Low risk of aminotransferase abnormalities with an annualized incidence rate of 1.6% - a rate similar to that of placebo rates.

These data support the long-term use of ambrisentan in the treatment of PAH.

REFERENCES


DISCLOSURES AND ACKNOWLEDGEMENTS

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Da consegnare unitamente all’RCP Volbris (ambrisotan)