Two-Year Durability of Improvements in eGFR with Bardoxolone Methyl in Patients with Pulmonary Arterial Hypertension: The LARIAT Study

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BACKGROUND

BARDOXOLONE METHYL
• Bardoxolone methyl (BARD) is an oral, once-daily investigational therapy that activates NF-E2 and suppresses NF-κB; in vitro, BARD activates cellular metabolism1
• In prior clinical studies that enrolled over 2,000 patients, BARD increased eGFR2

KIDNEY FUNCTION IN PAH
• Pulmonary arterial hypertension (PAH) is characterized by inflammation and vascular remodeling in the lung as well as impaired mitochondrial function in multiple organs4-9
• CTD implicates management of right heart failure in PAH
• Kidney dysfunction is a powerful poor prognostic factor in PAH especially in those with scleroderma10

LARIAT STUDY
• Phase 2 trial assessing the safety and efficacy of BARD relative to placebo with various etiologies of pulmonary hypertension (PH)
  o Part 1: placebo-controlled study
    • Patients received BARD (2.5, 5, 10, or 20 mg; median 10 mg) or placebo
    • 16-week duration
  o Part 2: Open-label extension study
    • Patients received BARD (up to 20 mg)
• Primary efficacy results of change from baseline in 6-minute walk distance have been previously presented11

This post-hoc analysis investigates the long-term safety and efficacy of BARD on eGFR in cohorts of patients with PAH over a 2-year time period

PATIENT DEMOGRAPHICS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=10)</th>
<th>Bardoxolone Methyl (n=46)</th>
<th>All (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (± SD) Age (yrs)</td>
<td>48.9 ± 10.5</td>
<td>52.2 ± 12.8</td>
<td>51.6 ± 12.4</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>8 (80%)</td>
<td>37 (80%)</td>
<td>45 (80%)</td>
</tr>
<tr>
<td>Mean (± SD) Weight (kg)</td>
<td>75 ± 13.8</td>
<td>80.8 ± 19.1</td>
<td>79.7 ± 18.3</td>
</tr>
<tr>
<td>Mean (± SD) BMI (kg/m²)</td>
<td>27.8 ± 5</td>
<td>30.2 ± 6.1</td>
<td>29.8 ± 5.9</td>
</tr>
<tr>
<td>PH/Potential (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>5 (50%)</td>
<td>24 (52%)</td>
<td>29 (52%)</td>
</tr>
<tr>
<td>CTD</td>
<td>3 (30%)</td>
<td>15 (33%)</td>
<td>18 (32%)</td>
</tr>
<tr>
<td>Anorexia/associated</td>
<td>2 (20%)</td>
<td>4 (9%)</td>
<td>6 (11%)</td>
</tr>
<tr>
<td>Not available</td>
<td>0</td>
<td>2</td>
<td>2 (4%)</td>
</tr>
<tr>
<td>WHO/NYHA Function (n, %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>7 (70%)</td>
<td>36 (78%)</td>
<td>43 (77%)</td>
</tr>
<tr>
<td>Class III</td>
<td>3 (30%)</td>
<td>10 (22%)</td>
<td>13 (23%)</td>
</tr>
<tr>
<td>Mean (± SD) Baseline 6MWD (m)</td>
<td>424 ± 79</td>
<td>427 ± 79</td>
<td>426 ± 87</td>
</tr>
<tr>
<td>Baseline eGFR, mean (± SD)</td>
<td>68.9 ± 17.4</td>
<td>71.7 ± 17.2</td>
<td>75.6 ± 21.1</td>
</tr>
<tr>
<td>eGFR &lt; 60 mL/min/1.73 m² (%)</td>
<td>4 (40%)</td>
<td>7 (15%)</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Mean time (± SD) since PAH diagnosis (yrs)</td>
<td>3.7 ± 2.2</td>
<td>4.6 ± 1.1</td>
<td>4.4 ± 3.8</td>
</tr>
<tr>
<td>Mean PAH Background Therapies</td>
<td>2.1 ± 0.6</td>
<td>1.8 ± 0.5</td>
<td>1.9 ± 0.5</td>
</tr>
<tr>
<td>PDEIS (n, %)</td>
<td>8 (80%)</td>
<td>35 (76%)</td>
<td>43 (77%)</td>
</tr>
<tr>
<td>ERA (n, %)</td>
<td>9 (90%)</td>
<td>37 (80%)</td>
<td>46 (82%)</td>
</tr>
<tr>
<td>Both ERA and PDEIS (n, %)</td>
<td>8 (80%)</td>
<td>27 (59%)</td>
<td>35 (63%)</td>
</tr>
</tbody>
</table>

SAFETY

• Most commonly reported AE was muscle spasms, which are associated with creatine kinase reductions
• No drug-related serious adverse events occurring in > 1 patient treated with BARD for up to 2 years

ADVERSE EVENTS THROUGH 16 WEEKS OF TREATMENT

Preferred Term                                      Number (% of Patients)
Placebo (n=10)                                      Bardoxolone Methyl (n=46)

Muscle Spasms                                       1 (10%)                                          10 (22 %)
Nausea                                              2 (20%)                                          8 (17 %)
Upper Respiratory Tract Infection                   1 (10%)                                          8 (17 %)
Headache                                            2 (20%)                                          7 (15 %)
Diarhoea                                            1 (10%)                                          7 (15 %)
Fatigue                                             1 (10%)                                          6 (13 %)
Decreased Appetite                                  1 (10%)                                          5 (11 %)
Gastrooesophageal Reflux Disease                    0 (0%)                                           5 (11 %)
Urinary Tract Infection                             0 (0%)                                           5 (11 %)
Pain in Extremity                                   0 (0%)                                           5 (11 %)

RESULTS: CHANGE IN eGFR

• Part 1: BARD increased eGFR from baseline and relative to placebo after 16 weeks of treatment (p<0.001)
• Part 2: Increases in eGFR with BARD were durable for up to 2 years of treatment (p<0.001)

CONCLUSION

• Consistent with previous studies of bardoxolone methyl in patients with chronic kidney disease, bardoxolone methyl significantly increased eGFR in patients with PAH
• The increase in eGFR with bardoxolone methyl was sustained through two years of treatment

REFERENCES

3. de Villiers, A in Am Respir Crit Care Med 2014;1:45-47.

DISCLOSURES

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