Efficacy and Safety of Bardoxolone Methyl in Pediatric Patients with Alport Syndrome in CARDINAL Phase 3 Trial

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**ALPORT SYNDROME**

Alport syndrome is a rare, inherited progressive form of chronic kidney disease (CKD) - Affects approximately 30,000 to 60,000 persons in the US41,42 - Type IV collagen mutations cause glomerular basement membrane defects that lead to inflammation, fibrosis, progressive kidney function loss - Annual rate of estimated glomerular filtration rate (eGFR) decline: 4 to 5 mL/min/1.73 m² per year despite management with renin-angiotensin-aldosterone system inhibitors (RAAS)42 - Median age at end-stage kidney disease (ESKD) for X-linked males is 25 years43 - Accounts for 3% of children with kidney failure - No approved therapies specifically for CKD due to Alport syndrome

**BARDOXOLONE METHYL**

- Bardoxolone methyl (Bard) is an investigational drug activating NRF2 and suppressing NF-κB - Bard increases GFR by reducing inflammatory signaling and restoring glomerular function as demonstrated in animal models44,45

**CARDINAL STUDY DESIGN**

**CARDINAL Phase 3 (NCT03019185)**: international, multicenter, double-blind, placebo-controlled, randomized trial46 - Patients 12 to 70 years of age with genetic or histologic confirmation of Alport syndrome - Baseline eGFR between 30-90 mL/min/1.73 m² - Baseline urinary albumin to creatinine ratio (UACR): 3500 mg/g - Primary endpoints: change in eGFR at Week 48 and Week 100 - Key secondary endpoints: change from baseline in UACR at Week 52 and Week 104 following a 4-week drug withdrawal period

**BASELINE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=12)</th>
<th>Bardoxolone Methyl (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), Mean (SD)</td>
<td>15.2 (16.1)</td>
<td>15.4 (12.2)</td>
</tr>
<tr>
<td>Age of Alport Syndrome Diagnosis Age (years), Mean (SD)</td>
<td>10.6 (5.9)</td>
<td>10.5 (4.3)</td>
</tr>
<tr>
<td>Female (%)</td>
<td>3 (25.0%)</td>
<td>1 (9.1%)</td>
</tr>
<tr>
<td>Race: White (n%)</td>
<td>5 (41.7%)</td>
<td>4 (36.4%)</td>
</tr>
<tr>
<td>Mean (SD) eGFR (mL/min/1.73 m²), n (%)</td>
<td>68.2 (16.2)</td>
<td>71.9 (15.0)</td>
</tr>
<tr>
<td>eGFR &gt;=60 mL/min/1.73 m², n (%)</td>
<td>2 (17.6%)</td>
<td>2 (18.2%)</td>
</tr>
<tr>
<td>Geometric Mean (SE) UACR (mg/g)</td>
<td>106.3 (90.0)</td>
<td>109.4 (86.7)</td>
</tr>
<tr>
<td>UACR ≤300 mg/g, n (%)</td>
<td>6 (50.0%)</td>
<td>6 (54.6%)</td>
</tr>
<tr>
<td>UACR &gt;300 mg/g, n (%)</td>
<td>6 (50.0%)</td>
<td>5 (55.6%)</td>
</tr>
<tr>
<td>Genetic Confirmation</td>
<td></td>
<td></td>
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<tr>
<td>X-linked (n%)</td>
<td>8 (66.7%)</td>
<td>6 (54.5%)</td>
</tr>
<tr>
<td>Autosomal (n%)</td>
<td>3 (25.0%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>Histologic Confirmation</td>
<td>3 (25.0%)</td>
<td>3 (27.3%)</td>
</tr>
<tr>
<td>Receiving ACEi or ARB (n%)</td>
<td>8 (66.7%)</td>
<td>9 (81.8%)</td>
</tr>
<tr>
<td>Height (cm), Mean (SD)</td>
<td>166.3 (15.0)</td>
<td>171.7 (6.0)</td>
</tr>
<tr>
<td>Weight (kg), Mean (SD)</td>
<td>57.5 (15.8)</td>
<td>65.1 (10.1)</td>
</tr>
<tr>
<td>Historical rate of eGFR decline (mL/min/1.73 m²), Mean (SE)</td>
<td>-10.7 (1.2)</td>
<td></td>
</tr>
</tbody>
</table>

**ESTIMATED GLOMERULAR FILTRATION RATE**

- **Mean ± SEM eGFR Change (mL/min/1.73 m²)**
  - **Week 100**: Placebo 13.8 ± 5.7 (p=0.017), Bardoxolone Methyl 14.6 ± 5.0 (p=0.0035)
  - **Week 104**: Placebo 14.0 ± 5.7 (p=0.015), Bardoxolone Methyl 14.2 ± 5.0 (p=0.0035)

**URINARY ALBUMIN TO CREATININE RATIO**

- **Fold-Change in UACR Over Time in Pediatric Patients**
  - **UACR remained unchanged vs baseline in pediatric patients**

**WEIGHT AND HEIGHT**

- **Mean changes in weight were minimal in pediatric patients**
- **Pediatric patients generally continued along their baseline growth curves** for height and weight in both treatment groups

**SAFETY: ADVERSE EVENTS**

- **Number of Patients With:**
  - Placebo (n=12): 10 (83.3%), 11 (100%)
  - Bardoxolone Methyl (n=11): 11 (100%)

- **AE leading to permanent treatment discontinuation**
  - Common Adverse Drug Reactions
    - Azanize aminotransferase increased 1 (8.3%), 4 (36.4%)
    - Hypokalemia 1 (8.3%), 3 (27.3%)
    - Cough 0
    - Aspartate aminotransferase increased 1 (8.3%), 1 (9.1%)
    - Brain natriuretic peptide increased 0
    - Weight decreased 0
    - Diarrhea 0

- **AE profile in pediatric patients similar to overall study population**
- **No severe adverse events in Bard patients**
- **No AE leading to permanent treatment discontinuation in Bard patients**

**CONCLUSION**

In CARDINAL, the addition of Bard to RAAS in pediatric patients with CKD due to Alport syndrome appeared to preserve kidney function and was generally well-tolerated.

**DISCLOSURES**

- **REATA Pharmaceuticals.**
- **SA, RG, and KL have nothing to disclose.**

**REFERENCES**


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