**ALPORT SYNDROME**

- Alport syndrome (AS) is the second most common hereditary form of CKD and is caused by mutations in genes that encode type IV collagen.
- Estimated to affect approximately 30,000 – 60,000 people in the US.
- Defective filtration barrier leads to:
  - Proteinuria
  - Inflammation, interstitial fibrosis, tubular atrophy, and glomerular sclerosis
  - Average decline in kidney function is estimated to be ~4 mL/min/1.73 m²/year
  - Median age at onset of ESKD: 31 years
- Standard of care involves ACE/ARBs, with no AS-specific approved therapies.
- Inflammation, fibrosis, and mitochondrial dysfunction contribute to kidney function decline in patients with AS.

**BARDOXOLONE METHYL**

- Bardoxolone methyl (Bard) is an investigational small-molecule drug that, by activation of Nrf2, promises resolution of inflammation, reduction of oxidative stress, and improved mitochondrial function.
- Bard improves GFR acutely by reducing inflammatory signaling and restoring K+ in animal models.
- Bard improves GFR chronically by reducing remodeling and fibrosis in animal models of hyperfiltration, hypertension, diabetes, lupus, and protein overload.
- No major safety signals in recent trials enrolling over 600 patients.

**CARDINAL SYNDROME**

- Significant retained benefit of 4.1 mL/min/1.73 m².
- 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 and urine ACR ≤ 3500 mg/g.
- Patients received stable ACE/ARB therapy if indicated.
- Patients with history of cardiovascular disease or BNP > 200 pg/mL at baseline are excluded.
- Dose titration to goal Bard dose of 20 or 30 mg given orally, once daily.

**PHASE 2 COHORT**

- Open-label cohort enrolled a total of 30 patients.
- Primary endpoint: change from baseline in eGFR at Week 12.
- Follow-up analysis at 12 weeks, patients remained on treatment for 2 years.

**CARDINAL SYNDROME 2019**

- Multicenter, multinational phase 2/3 study.
- Patients 12 to 70 years of age with genotypic or histologic confirmation of Alport syndrome.
- Baseline eGFR between 30-90 mL/min/1.73 m² and urine ACR ≤ 3500 mg/g.
- Patients received stable ACE/ARB therapy if indicated.
- Patients with history of cardiovascular disease or BNP > 200 pg/mL at baseline are excluded.
- Dose titration to goal Bard dose of 20 or 30 mg given orally, once daily.

**PHASE 2 RESULTS**

- Bard treatment improved mean eGFR 10.4 mL/min/1.73 m² (p=0.0001) through Week 48, which represents recovery of approximately two years of loss.
- Significant retained benefit of 4.1 mL/min/1.73 m² 74% after Bard withdrawal.
- UACR not significantly different from baseline at Week 48 and 52.
- Bard has been generally well-tolerated without any safety concerns noted by the Data Monitoring Committee.
- Most commonly reported AE is muscle spasms, which are not associated with markers of muscle toxicity such as creatine kinase.
- Blood pressure (BP) stable and within normal limits during treatment.
- Consistent with prior studies, patients with lower baseline Bili have less weight loss.

**No evidence of fluid retention.

**CARDINAL PHASE 2 RESULTS**

- Increases in eGFR have been durable for up to two years on treatment and improvements post-withdrawal have been observed for up to 8 weeks after withdrawal.
- Bard’s maximal effect on eGFR after initiation of dosing occurred within 2-4 weeks after the last increase in dose, and plasma levels of Bard are undetectable within 2 weeks of cessation of dosing.
- No significant change in blood pressure.

**No Significant Change in Blood Pressure**

**CARDINAL PHASE 3 - SCHEMA DOSING SCHEDULE**

- Baseline ACR ≥ 30 mg/g.
- No patients with history of cardiovascular disease or BNP > 200 pg/mL at baseline are excluded.
- Patients received stable ACE/ARB therapy if indicated.
- Patients with history of cardiovascular disease or BNP > 200 pg/mL at baseline are excluded.
- Dose titration to goal Bard dose of 20 or 30 mg given orally, once daily.

**DISCLOSURES**

- No patients with history of cardiovascular disease or BNP > 200 pg/mL at baseline are excluded.
- Patients received stable ACE/ARB therapy if indicated.
- Patients with history of cardiovascular disease or BNP > 200 pg/mL at baseline are excluded.
- Dose titration to goal Bard dose of 20 or 30 mg given orally, once daily.

**REFERENCES**

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