Analyses from a Phase 2 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease: The PHOENIX Study

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BACKGROUND AND RATIONALE

Through induction of Nrf2 and suppression of NF-κB, Bard targets common pro-inflammatory and fibrotic pathways that contribute to GFR loss in CKD8

• Despite diverse etiologies, inflammation is a common mechanism underlying the development and progression of chronic kidney disease (CKD)8

• Bard improves kidney function by increasing filtration surface area and by reducing inflammation, remodeling, and fibrosis in multiple models of CKD and ADPKD8

• In 12 clinical trials that enrolled over 2,600 patients, Bard increased eGFR8-11

• Bard reduced risk of kidney failure outcomes in patients with type 2 diabetes and stage 4 CKD in BEACON11

Role of Bard in autosomal dominant polycystic kidney disease (ADPKD)

• ADPKD affects approximately 400,000 people and is leading inheritable cause of kidney failure in the US12

• Cyst formation and growth trigger pro-inflammatory and pro-fibrotic pathways, resulting in progressive loss of kidney function13

• Markers of inflammation (e.g., MCP-1) are higher in human ADPKD renal cyst cell lines (WT 9-7, WT 9-12) than in normal HK-2 human proximal tubule cell line. Bard increases Nrf2 activity (NQO1) and suppresses MCP-1 in ADPKD renal cyst cell lines (∗ p < 0.05; *** p < 0.001)

Phase 2 PHOENIX trial was initiated to determine whether Bard improves kidney function in patients with ADPKD

PHOENIX STUDY DESIGN

• Phase 2, open-label, multi-center, US-only trial (NCT03366337)

• Four separate cohorts of patients with ADPKD, IgAN, T1D CKD, or FSGS

• Targeted enrollment of 25 to 30 patients per cohort

• Primary endpoint: change in eGFR from baseline at Week 12

• Key eligibility: eGFR ≥ 30 to ≤ 90 mL/min/1.73 m2, 18-65 years old; genetic confirmation of PKD1 mutation

BASELINE CHARACTERISTICS

- Enrolled 31 patients and 28 (90%) completed treatment through Week 12
- Historical eGFR data from 3 years prior to enrollment collected for 2931 patients
- Average annual loss of eGFR of 4.8 mL/min per study entry
- Bard treatment resulted in significant eGFR increase of 9.3 mL/min/1.73 m2 at Week 12
- Average increase represents recovery of two prior years of loss based on historical data

Efficacy: Change in eGFR

• Bard treatment resulted in significant eGFR increase of 9.3 mL/min/1.73 m2 at Week 12
• 27/28 (96%) patients with Week 12 data had increases from baseline in eGFR

UACR to Creatinine Ratio

• Patients had normal to near-normal levels of UACR at baseline
• Bard did not change urinary albumin despite the large increase in eGFR

SAFETY: ADVERSE EVENTS

• No treatment-related serious adverse events
• 1 patient (3%) discontinued prematurely due to Bard-related AE (fatigue)
• AEs were generally mild to moderate in intensity
• Most commonly reported AE was muscle spasms, which were associated with reductions in creatinine kinase

CONCLUSION

• Bardoxolone methyl significantly improved eGFR (+9.3 mL/min/1.73 m2) in patients with ADPKD that historically declined −4.8 mL/min/1.73 m2 annually

• Profile of unchanged albuminuria is inconsistent with injury due to increased intraglomerular pressure

• Bard was well-tolerated without any drug-related SAEs, changes in blood pressure, or evidence of fluid overload

FUTURE DIRECTIONS

• Increases in eGFR observed in six distinct patient populations following Bard treatment
• Long-term eGFR increases of one to two years observed in three patient populations
• eGFR improvement post-withdrawal observed in two patient populations
• Acute changes in eGFR correlate with durable response and retained eGFR benefit
• Planning to advance ADPKD program into pivotal Phase 3 study in 2019

• Bard is also currently being studied in:
  - CARDINAL: Phase 2b study in patients with Alport syndrome
  - AVAYME: Phase 3 outcomes study in Japanese patients with diabetic CKD

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DISCLOSURES

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