FR-PO241

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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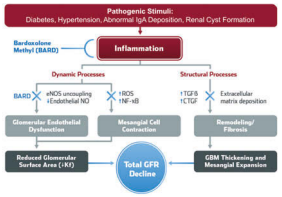
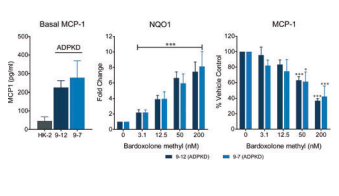
BACKGROUND AND RATIONALE

Through induction of Nrf2 and suppression of NF-κB, Bard targets common pro-inflammatory and fibrotic pathways that contribute to GFR loss in CKD[1]

- Despite diverse etiologies, inflammation is a common mechanism underlying the development and progression of chronic kidney disease (CKD)[2-4]
- Bard improves kidney function by increasing filtration surface area and by reducing inflammation, remodeling, and fibrosis in multiple models of CKD and AKI[5-7]
- In 11 clinical trials that enrolled over 2,600 patients, Bard increased eGFR[8-11]
  - eGFR increases verified as true improvement in GFR by inulin clearance[12]
  - eGFR improvements durable for up to two years and partially retained after drug withdrawal[9,10]
  - Bard reduced risk of kidney failure outcomes in patients with type 2 diabetes and stage 4 CKD in BEACON[11]





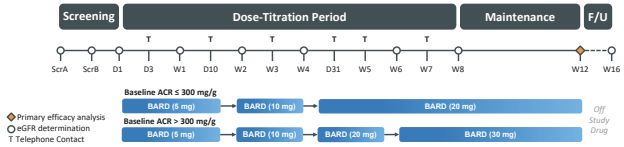
Role of Bard in autosomal dominant polycystic kidney disease (ADPKD)

- ADPKD affects approximately 400,000 people and is leading inheritable cause of kidney failure in the US[13]
- Cyst formation and growth trigger pro-inflammatory and pro-fibrotic pathways, resulting in progressive loss of kidney function[14]
- Markers of inflammation (eg, 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

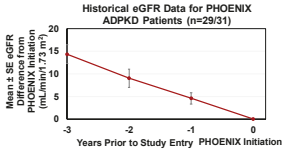
- Phase 2, open-label, multi-center, US-only trial (NCT03366337)
  - Four separate cohorts of patients with ADPKD, IgAN, T1D CKD, or FSGS
  - Targeted enrollment of 25 to 30 patients per cohort
- Primary endpoint: change in eGFR from baseline at Week 12
- Key eligibility: eGFR ≥ 30 to ≤ 90 mL/min/1.73 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 29/31 patients
- Average annual loss of eGFR of 4.8 mL/min prior to study entry

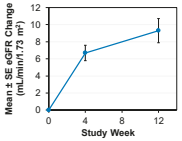
Characteristic	Total (N=31)
Age, years (mean ± SD)	47 ± 9
Baseline eGFR, ml/min (mean ± SD)	48 ± 14
Baseline ACR, mg/g (geometric mean)	44.4
ACR ≤ 300 mg/g (n,%)	28 (90%)
ACR > 300 mg/g (n,%)	3 (10%)
Receiving ACEi or ARB (n,%)	25 (81%)

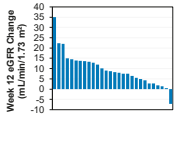


EFFICACY: CHANGE IN eGFR

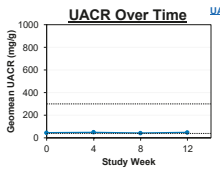
- Bard treatment resulted in significant eGFR increase of 9.3 mL/min/1.73 m² at Week 12
- 27/28 (96%) patients with Week 12 data had increases from baseline in eGFR
- Average increase represents recovery of two prior years of loss based on historical data

	Change from Baseline in eGFR	
	WK4	WK12
Mean ± SE	6.7 ± 0.9	9.3 ± 1.4
p-value	p<0.0001	p<0.0001





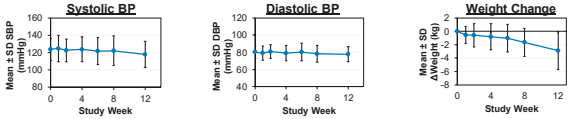
URINARY ALBUMIN TO CREATININE RATIO



- Patients had normal to near-normal levels of UACR at baseline
- Bard did not change urinary albumin despite the large increase in eGFR
- Profile is inconsistent with injury due to increased intraglomerular pressure

VITAL SIGNS

- Blood pressure (BP) stable and within normal limits during treatment
- No evidence of overt fluid retention and no significant weight increases during study
- Consistent with prior studies, slight decreases in weight observed[15]



SAFETY: ADVERSE EVENTS

Preferred Term	Total N=31
Muscle spasms	17 (55%)
Upper respiratory tract infection	4 (13%)
Hypertension	4 (13%)

*AEs reported in >10% patients

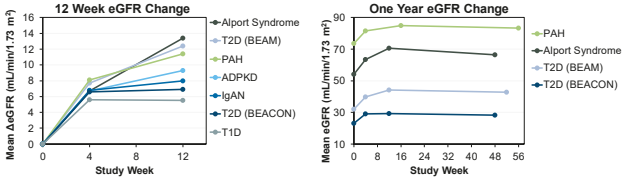
- No treatment-related serious adverse events
- 1 patient (3%) discontinued prematurely due to Bard-related AE (fatigue)
- AEs were generally mild to moderate in intensity
- Most commonly reported AE was muscle spasms, which were associated with reductions in creatine kinase

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
- Data suggest that long-term eGFR improvements and retained eGFR benefit observed in other forms of CKD may translate to patients with ADPKD

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 2/3 study in patients with Alport syndrome
  - AYAME: Phase 3 outcomes study in Japanese patients with diabetic CKD



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DISCLOSURES

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