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Analyses from a Phase 2 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with IgA Nephropathy: The PHOENIX Study

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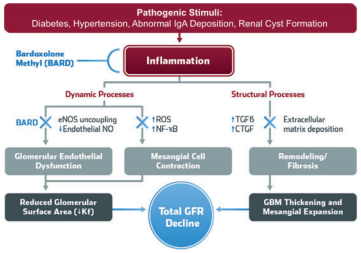
BACKGROUND AND RATIONALE

IgA nephropathy (IgAN)

- IgAN is the most prevalent primary chronic glomerular disease and affects approximately 120,000 patients in the US[1,2]
- Deposition of immunoglobulin complexes in the glomerulus causes inflammation, fibrosis, and progressive loss of kidney function[3]



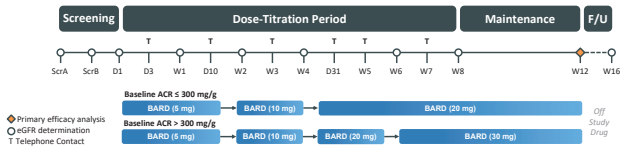
Through induction of Nrf2 and suppression of NF-κB, Bard targets common pro-inflammatory and fibrotic pathways that contribute to GFR loss in CKD[4]

- Despite diverse etiology, inflammation is a common mechanism underlying the development and progression of chronic kidney disease (CKD)[5]
- Bard improves kidney function by increasing filtration surface area and by reducing inflammation, remodeling, and fibrosis in multiple models of CKD and AKI[6-8]
- In 11 clinical trials that enrolled over 2,600 patients, Bard increased eGFR[9-12]
  - eGFR increases verified as true improvement in GFR by inulin clearance[13]
  - eGFR improvements durable for up to two years and partially retained after drug withdrawal[10,11]
  - Bard reduced risk of kidney failure outcomes in patients with type 2 diabetes and stage 4 CKD in BEACON[12]

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

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 m^2; 18-65 years old; biopsy-confirmed IgAN



BASELINE CHARACTERISTICS

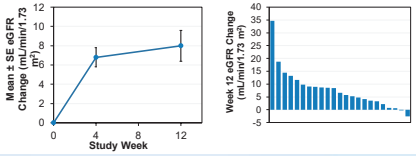
- Enrolled 26 patients and 23 (88%) completed treatment through Week 12
- Historical eGFR data from 3 years prior to enrollment collected for 23/26 patients
- Average annual loss of eGFR of 1.2 mL/min prior to study entry

Characteristic	Total (N=26)
Age, years (mean ± SD)	49 ± 10
Baseline eGFR, ml/min (mean ± SD)	46 ± 13
Baseline ACR, mg/g (geometric mean)	104
ACR ≤ 300 mg/g (n,%)	18 (69%)
ACR > 300 mg/g (n,%)	8 (31%)
Receiving ACEi or ARB (n,%)	25 (96%)
Average yearly historical eGFR decline (mL/min, n=23)	1.2

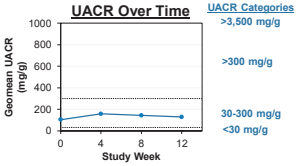
EFFICACY: CHANGE IN eGFR

- Bard treatment resulted in significant eGFR increase of 8.0 mL/min/1.73 m^2 at Week 12
- 21/23 (91%) patients with Week 12 data had increases from baseline in eGFR
- Increase represents recovery of ~6 prior years of loss based on historical data

	Change from Baseline in eGFR	
	WK4	WK12
Mean ± SE	6.8 ± 1.0	8.0 ± 1.6
p-value	p<0.0001	p<0.0001



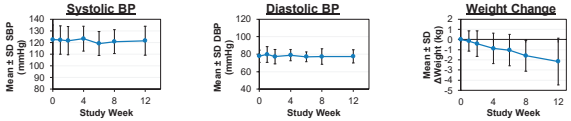
URINARY ALBUMIN TO CREATININE RATIO



- Patients optimized on available therapies upon study entry as evidenced by low urinary protein within international treatment guideline goals (<1,000 mg/g)
- Bard treatment resulted in no significant change in urinary albumin excretion

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[14]



SAFETY: ADVERSE EVENTS

Preferred Term	Total N=26
Muscle spasms	9 (35%)
Headache	5 (19%)
Fatigue	5 (19%)
Transaminases increased	4 (15%)
Hepatic enzyme increased	3 (12%)
Rash	3 (12%)
Myalgia	3 (12%)

*AEs reported in >10% patients

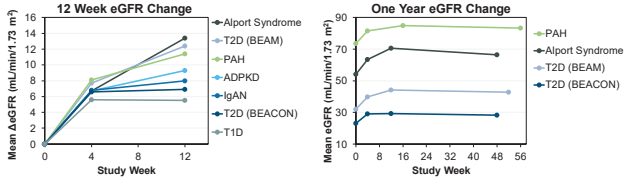
- No treatment-related serious adverse events
- 3 patients (12%) discontinued treatment prematurely due to Bard-related AE (transaminase increase, liver function test abnormal)
  - Transaminase increases are pharmacological effect of Nrf2 activation
  - Not associated with clinical evidence of liver injury
  - No changes in total bilirubin
- AEs were generally mild to moderate in intensity
- Most commonly reported AE is muscle spasms, which were associated with reductions in creatine kinase

CONCLUSION

- Bardoxolone methyl significantly improved eGFR (+8.0 mL/min/1.73 m^2) in patients with IgAN
- No significant change in albuminuria
- 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 IgAN

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 pursue IgAN as commercial indication
- 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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