A Phase 2/3 Study of the Efficacy and Safety of Bardoxolone Methyl in Patients with Alport Syndrome

MP142

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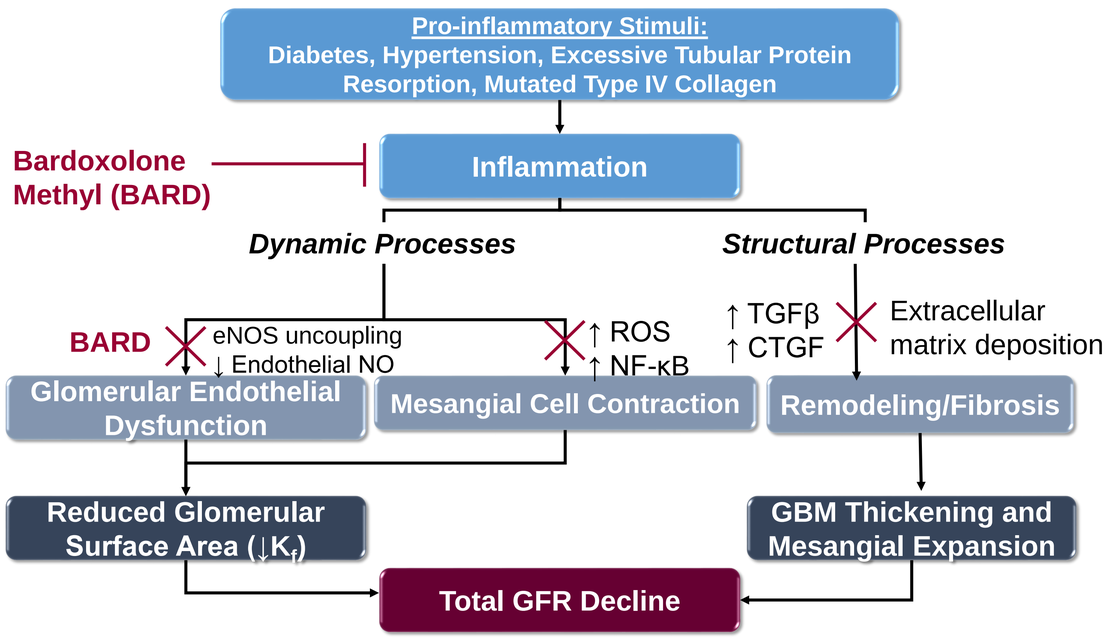
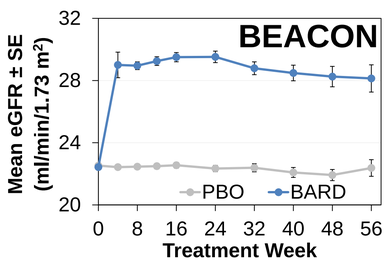
BARDOXOLONE METHYL

- Bardoxolone methyl (BARD) activates Nrf2 and suppresses NF-κB
  - Nrf2 activation is reno-protective in kidney disease models[1,2]
  - BARD increases expression of antioxidant genes to reduce inflammation and pro-proliferative drive[3,4]
- BARD targets inflammatory pathways that contribute to GFR loss in chronic kidney diseases[5-7]



- BARD significantly increases eGFR, inulin clearance, creatinine clearance, and other markers of kidney function across 7 clinical trials in patient with CKD that enrolled over 2,600 patients with CKD[8-11]
- In Phase 2 BEAM and Phase 3 BEAC ON studies[10,11]
  - BARD increased eGFR ($p < 0.0001$)
  - Durable eGFR change through 1 year and retained benefit four weeks after drug cessation, suggesting disease-modifying activity
  - Fewer renal SAEs and ESRD events in BARD vs placebo patients



Number of Patients					
PBO	1093	1023	726	402	125
BARD	1092	958	628	345	103

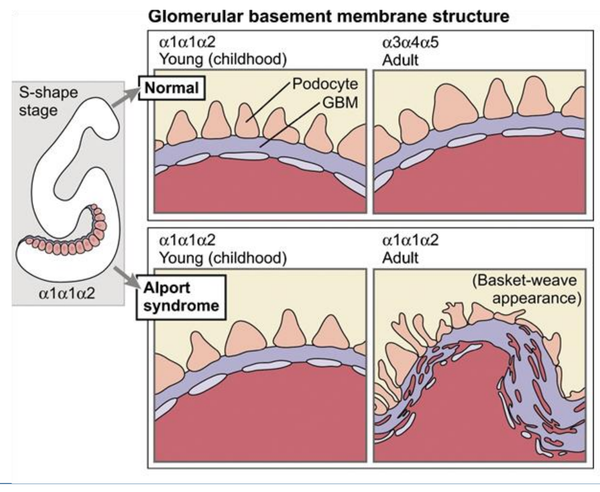
	Baseline eGFR ml/min/ 1.73m²	PBO-Corrected Post-TX ΔeGFR ml/min/ 1.73m²	P-value
BEAM (n=172)			
Low Dose	33	0.6	p>0.05
Mid Dose	32	4.7	p<0.05
High Dose	32	5.0	p<0.05
BEACON (n=498)			
20 mg	23	1.8	p<0.001

- The BEACON study was terminated early due to increased risk for fluid overload hospitalizations within first four weeks. The average age of patients in the study was 68.5±9.6
- Post-hoc analyses identified baseline BNP > 200 pg/ml and prior history of heart failure were risk factors for fluid overload in BEACON[12] and these were used to exclude at-risk patients in subsequent studies
- BARD has potential to prevent kidney function decline and delay or prevent ESRD in patients with Alport syndrome
- Reata has initiated a pivotal Phase 2/3 study (CARDINAL) in patients with Alport syndrome

ALPORT SYNDROME

- Alport syndrome is a hereditary disease caused by mutations in genes that code for type IV collagen
  - Affects approximately 1 in 50,000 in the US[13]
  - Defective glomerular basement membrane leads to:
    - Leakage of proteins
    - Inflammation, glomerular sclerosis, tubular atrophy and interstitial fibrosis [16]
- Like other chronic kidney diseases, progressive eGFR loss (~4 ml/min/1.73 m^2 per year[14]) leads to ESRD
- Median age at onset of ESRD for male hereditary Alport (XLAS) patients is 25[15]
- Standard of care involves off-label ACEi/ARBs, with no approved therapies

Inflammation, fibrosis and mitochondrial dysfunction contribute to GFR loss and decreased kidney function in patients with Alport Syndrome[17-19]



CARDINAL STUDY DESIGN

CARDINAL STUDY (NCT03019185)

- Multicenter, multinational phase 2/3 study
- Patients 12 to 60 years of age with genetic or histologic confirmation of Alport syndrome
- Broad range of kidney function (eGFR between 30-90 mL/min/1.73 m^2) and urine ACR ≤ 3500 mg/g
- Patients with history of cardiovascular disease or baseline risk for increased fluid retention (BNP > 200 pg/ml) will be excluded
- Dose-titration to goal BARD dose of 20 or 30 mg given orally, once daily

Phase 2 Cohort

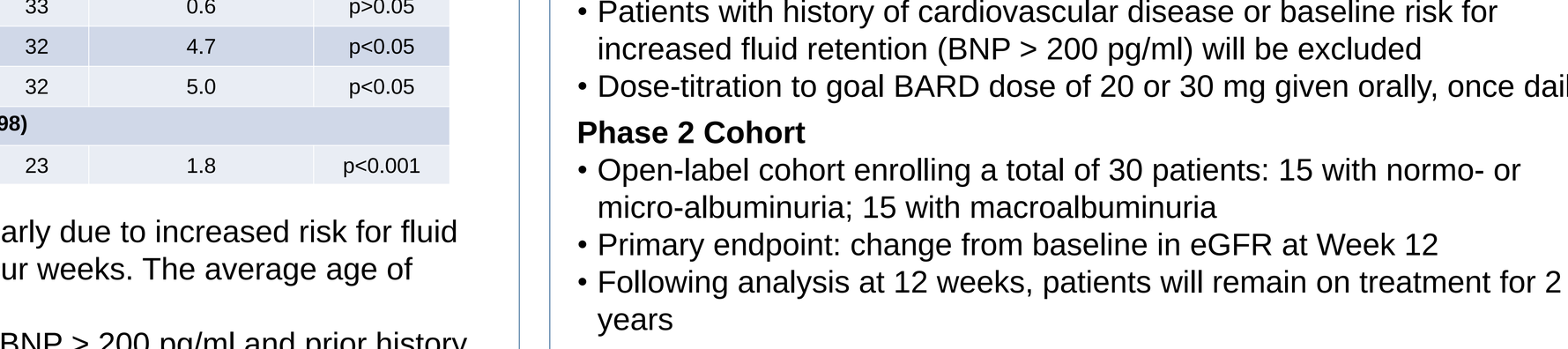
- Open-label cohort enrolling a total of 30 patients: 15 with normo- or micro-albuminuria; 15 with macroalbuminuria
- Primary endpoint: change from baseline in eGFR at Week 12
- Following analysis at 12 weeks, patients will remain on treatment for 2 years

Phase 3 Cohort

- Enroll up to 180 patients for 2 years of treatment
- Placebo-controlled, double-blind, 1:1 randomization
- Primary endpoint - change in eGFR at Week 48
- Key secondary endpoint - change from baseline in eGFR at Week 52 following a 4-week drug withdrawal period

CARDINAL STUDY - SCHEMA AND DOSING SCHEDULE

- ▲ Phase 2 primary efficacy analysis
- ◆ Phase 3 primary efficacy analysis
- O eGFR determination
- T Telephone Contact
- Patients under the age of 18 will receive study drug (BARD or placebo) every other day during Week 1



CONCLUSION

CARDINAL is the first trial to test the hypothesis that BARD will improve kidney function in patients with Alport syndrome.

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DISCLOSURES

CM, MC, AG, MO and KW are employees of Reata Pharmaceuticals
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