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Rationale and Design of "CARDINAL": A Phase 2/3 Study of the Efficacy and Safety of Bardoxolone Methyl in Patients with Alport Syndrome

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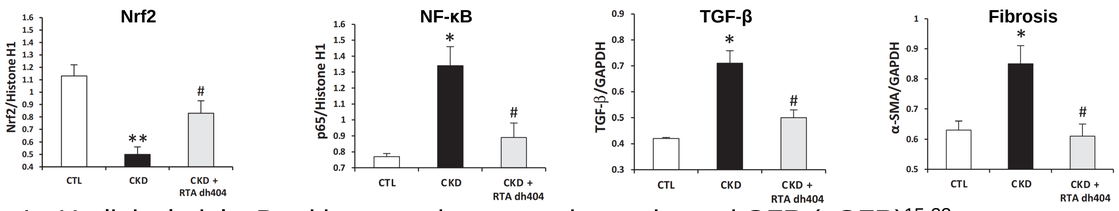
ALPORT SYNDROME

- 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[1]
  - 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 m^2 /year[2]
- Median age at onset of End Stage Kidney Disease (ESKD) for males with X-linked transmission is 25 years[3]
- Standard of care involves ACEi/ARBs, with no AS-specific approved therapies
- **Inflammation, fibrosis and mitochondrial dysfunction contribute to kidney function decline in patients with AS[4-6]**

BARDOXOLONE METHYL

- Bardoxolone methyl (Bard) is an investigational small-molecule drug that, by activation of Nrf2, promotes resolution of inflammation, reduction of oxidative stress, and improved mitochondrial function[7]
- Bard improves GFR acutely by reducing inflammatory signaling and restoring K_f in animal models[8,9]
- Bard improves GFR chronically by reducing remodeling and fibrosis in animal models of hyperfiltration, hypertension, diabetes, lupus, and protein overload[10-14]

Bard Analog RTA dh404 Restored Nrf2 Activation and Suppressed Inflammation, Remodeling, and Fibrosis in 5/6 Nephrectomy Model of Hyperfiltration



- In 11 clinical trials, Bard increased measured or estimated GFR (eGFR)[15-23]
- Bard reduced markers of vascular inflammation and injury, including angiotensin II, circulating endothelial cells (CECs), IFNγ and vascular adhesion molecules[24,25]
- No major safety signals in recent trials enrolling over 600 patients

Bard Reduced Markers of Vascular Inflammation and Injury in CKD Patients

	28 Day Cohort (n=60)		56 Day Cohort (n=18)	
	Baseline	Change	Baseline	Change
Angiotensin II (µg/mL)	12.4	-32.7% (p<0.001)	ND	ND
NGAL (ng/mg creatinine)	ND	ND	79.0	5% (p=0.9)
NAG (IU/g creatinine)	ND	ND	15.7	3% (p=0.8)
CECs/mL	7.4	-17.2%	5.3	-35.8% (p<0.007)
iNOS+ CECs/mL	4.2	-36.0% (p<0.05)	2.9	-34.5% (p<0.001)
IFNγ (pg/mL)	21.9	-62.6% (p<0.05)	ND	ND
E-selectin (pg/mL)	34.3	-13.7% (p<0.01)	35.4	-22.6% (p<0.05)
VCAM (pg/mL)	1170.9	-12.1% (p<0.001)	1250.4	-11.8%

NGAL: Neutrophil gelatinase-associated lipocalin; NAG: N-acetyl beta glucosaminidase; CEC: Circulating Endothelial Cells; iNOS: Inducible nitric oxide synthase; IFN: Interferon; VCAM: vascular cell adhesion molecule; ND: Not done

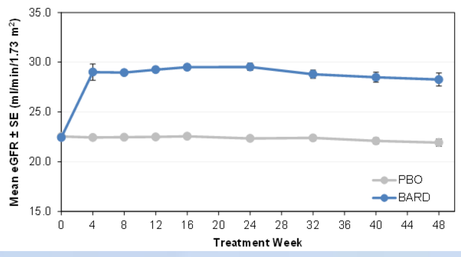
Bard Increased eGFR Across Diverse Types of CKD

Study	Patient Population	eGFR Range (mL/min/1.73 m^2)	N	ΔeGFR (mL/min/1.73 m^2)
Rare CKDs				
CARDINAL	Alport syndrome	30 – 90	30	13.4 (p<0.001)1
PHOENIX	ADPKD	30 – 90	31	9.3 (p<0.001)[1]
PHOENIX	IgAN	30 – 90	26	8.0 (p<0.001)[1]
PHOENIX	FSGS	30 – 90	18	7.7 (p<0.003)[1]
PHOENIX	T1D CKD	30 – 90	28	5.5 (p=0.02)[1]
Type 2 Diabetes				
TSUBAKI	T2D CKD	15 – 59	124	6.6 (p=0.008)[2]
BEACON	T2D CKD	15 – 29	2185	6.4 (p<0.001)[2]
BEAM	T2D CKD	20 – 45	227	8.6 (p<0.001)[2]
402-C-0902	T2D CKD	15 – 45	131	6.5 (p<0.001)[1]

Selected trials listed; [1] Change in eGFR and p-value vs. baseline; [2] Change in eGFR and p-value vs. placebo

- 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[16-20]
- 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

BEACON: eGFR Changes were Maximal 4 Weeks After the Last Increase in Dose



BEACON: Post-treatment eGFR Relatively Stable through 8 Weeks Following Cessation of Bard Treatment

Mean Baseline and Change in eGFR (mL/min/1.73 m^2)	Placebo	Bard
Baseline	22.5	22.4
Change 4 weeks post-last dose	2.1	
Change 8 weeks post-last dose	2.4	

CARDINAL STUDY DESIGN

CARDINAL STUDY (NCT03019185)

- Multicenter, multinational phase 2/3 study
- Patients 12 to 70 years of age with genetic or histologic confirmation of Alport syndrome
- Baseline eGFR between 30-90 mL/min/1.73 m^2 and urine ACR ≤ 3500 mg/g
- Patients received stable ACEi/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
- Following analysis at 12 weeks, patients remained on treatment for 2 years

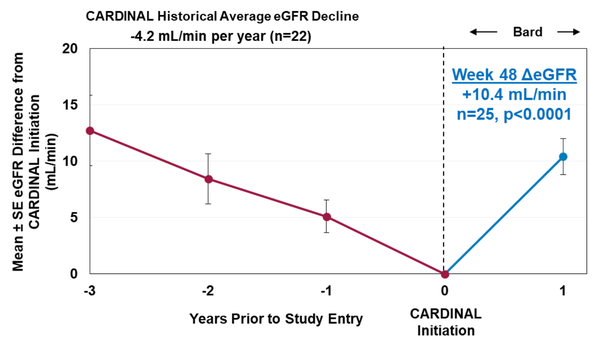
PHASE 3 COHORT

- Enrolled 157 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

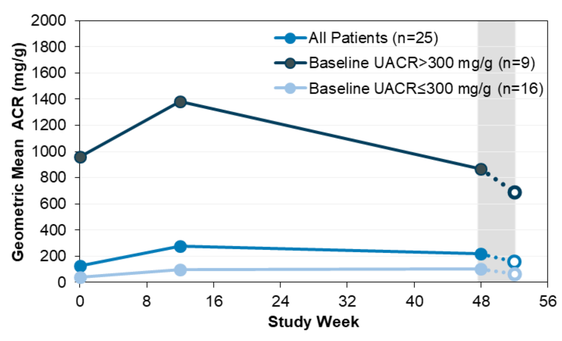
CARDINAL PHASE 2 RESULTS

- Bard treatment improved mean eGFR +10.4 mL/min/1.73 m^2 (p<0.0001) through Week 48, which represents recovery of approximately two years of loss[20]
- Significant retained benefit of 4.1 mL/min/1.73 m^2 4 weeks after Bard withdrawal
- UACR not significantly different from baseline at Weeks 48 or 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 BMI have less weight loss
- No evidence of overt fluid retention

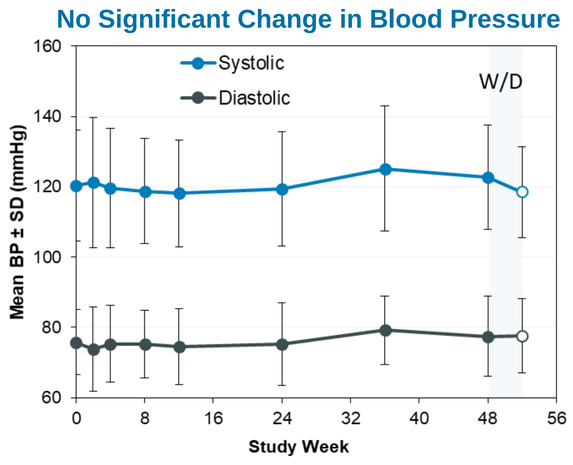
Bard Improved eGFR in Patients That Historically Declined ~4.2 mL/min



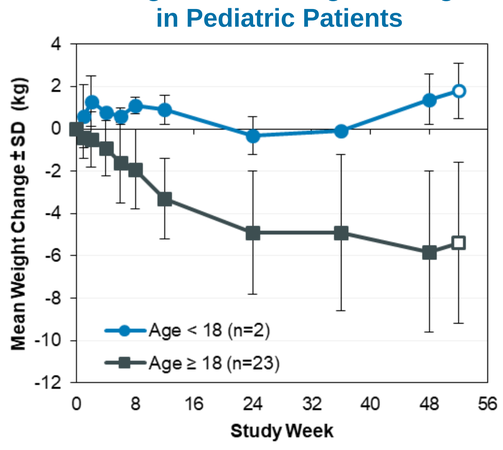
Urinary Albumin Not Significantly Changed at Week 48 or Week 52



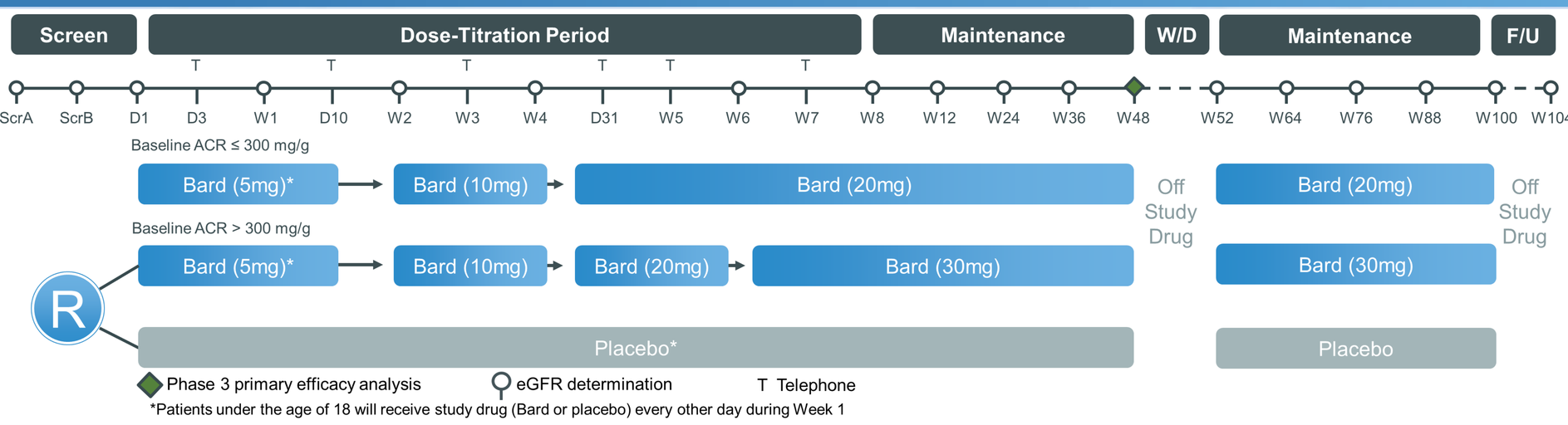
No Significant Change in Blood Pressure



No Significant Change in Weight in Pediatric Patients



CARDINAL PHASE 3 – SCHEMA DOSING SCHEDULE



CONCLUSION

- In the Phase 2 CARDINAL study, Bard treatment was associated with increased eGFR in patients with Alport syndrome
- Phase 3 CARDINAL is the first randomized, placebo-controlled trial testing the long-term efficacy and safety of Bard in patients with Alport syndrome

DISCLOSURES

GAB, CJM, MPC, MOG and AG are employees of Reata Pharmaceuticals.
PEP and SMS are consultants to Reata Pharmaceuticals.
LAI, ALS and SMS receive research funding from Reata Pharmaceuticals.

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Bardoxolone methyl is an investigational drug. Safety and efficacy have not been established by any agency.

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