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Efficacy and Safety of Bardoxolone Methyl in Pediatric Patients with Alport Syndrome in CARDINAL Phase 3 Trial

Bradley A. Warady

Sharon Andreol

Vimal Chadha

Melanie Chin

Rasheed Gbadegesin

See next page for additional authors

Authors

Bradley A. Warady, Sharon Andreol, Vimal Chadha, Melanie Chin, Rasheed Gbadegesin, Keisha Gibson, Debbie Gipson, Angie Goldsberry, Kenneth Lieberman, Colin Meyer, Kevin Meyers, Nozu Kandai, Megan O'Grady, Michelle Rheault, and Clifford Kashtan

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Warady, Bradley, MD; Andreoli, Sharon, MD; Chadha, Vimal, MD; Chin, Melanie P, PhD.; Gbadegesin, Rasheed, MD; Gibson, Keisha L, MD.; Gipson, Debbie S, MD.; Goldsberry, Angie, MS; Lieberman, Kenneth V, MD.; Meyer, Colin J, MD.; Meyers, Kevin E, MD.; Nozu, Kandai, MD; O'Grady, Megan, PhD; Rheault, Michelle, MD; Kashtan, Clifford, MD

ALPORT SYNDROME

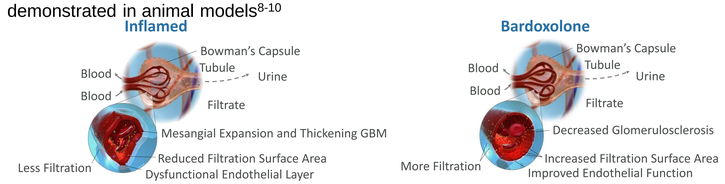
Alport syndrome is a rare, inherited progressive form of chronic kidney disease (CKD)

- Affects approximately 30,000 – 60,000 persons in the US[1]
- Type IV collagen mutations cause glomerular basement membrane defects that lead to inflammation, fibrosis, progressive kidney function loss
- Annual rate of estimated glomerular filtration rate (eGFR) decline: 4 to 5 mL/min/1.73 m^2 per year despite management with renin-angiotensin-aldosterone system inhibitors (RAASi)[2,3]
- Median age at end-stage kidney disease (ESKD) for X-linked males is 25 years[4]
- Accounts for 3% of children with kidney failure
- No approved therapies specifically for CKD due to Alport syndrome

Inflammation, fibrosis and mitochondrial dysfunction contribute to GFR loss and decreased kidney function in patients with Alport Syndrome[5-7]

BARDOXOLONE METHYL

- Bardoxolone methyl (Bard) is an investigational drug activating Nrf2 and suppressing NF-κB
- Bard increases GFR by reducing inflammatory signaling and restoring glomerular function as demonstrated in animal models[8-10]



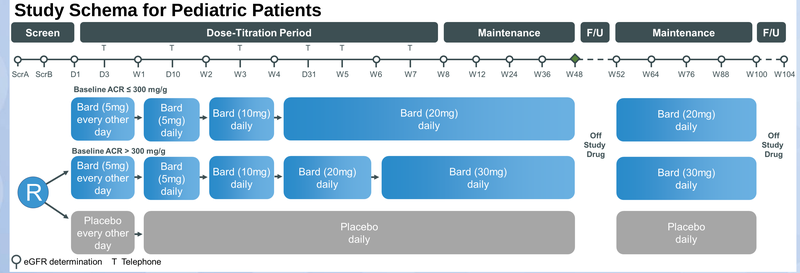
- In 11 clinical trials, Bard increased eGFR
  - — Increases in eGFR reflect true improvements in kidney function, as supported by increases in inulin and creatinine clearance[11,12]
  - — Kidney function improvements have been durable for up to two years, have been shown to reduce the risk of a composite kidney endpoint, and are partially retained following drug withdrawal[12-15]
  - — Improvements in kidney function observed in Alport syndrome, diabetic CKD, FSGS, IgAN, and ADPKD[12,13,16,17]

CARDINAL STUDY DESIGN

CARDINAL Phase 3 (NCT03019185): international, multicenter, double-blind, placebo-controlled, randomized trial[3]

- 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
- Baseline urinary albumin to creatinine ratio (UACR)≤ 3500 mg/g
- Primary endpoints: change in eGFR at Week 48 and Week 100
- Key secondary endpoints: change from baseline in eGFR at Week 52 and Week 104 following a 4-week drug withdrawal period

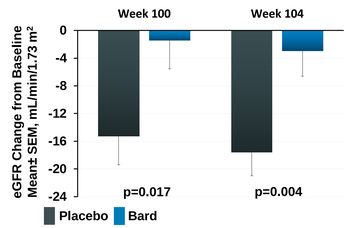
Study Schema for Pediatric Patients



BASELINE CHARACTERISTICS

Characteristic	Placebo (n=12)	Bardoxolone Methyl (n=11)
Age (years), Mean (SD)	15.2 (1.6)	15.4 (1.2)
Age of Alport Syndrome Diagnosis Age (years), Mean (SD)	10.6 (5.9)	10.5 (4.3)
Female (n,%)	3 (25.0%)	1 (9.1%)
Race: White (n%)	5 (41.7%)	4 (36.4%)
Mean (SD) eGFR (mL/min/1.73m^2)	68.2 (16.2)	71.9 (15.0)
eGFR ≤60 mL/min/1.73 m^2, n (%)	2 (16.7%)	2 (18.2%)
eGFR >60 mL/min/1.73 m^2, n (%)	10 (83.3%)	9 (81.8%)
Geometric Mean (SE) UACR (mg/g)	136.6 (90.0)	409.4 (187.0)
UACR ≤ 300 mg/g, n (%)	6 (50.0%)	4 (36.4%)
UACR >300 mg/g, n (%)	6 (50.0%)	7 (63.6%)
Genetic Confirmation		
X-linked (n,%)	8 (66.7%)	6 (54.5%)
Autosomal (n,%)	3 (25.0%)	3 (27.3%)
Histologic Confirmation	3 (25.0%)	3 (27.3%)
Receiving ACEi or ARB (n,%)	8 (66.7%)	9 (81.8%)
Height (cm), Mean (SD)	166.3 (15.0)	171.7 (6.0)
Weight (kg), Mean (SD)	57.5 (15.8)	65.1 (10.1)
Historical rate of eGFR decline (mL/min/1.73m^2), Mean (SE)	-10.7 (1.2)	

ESTIMATED GLOMERULAR FILTRATION RATE

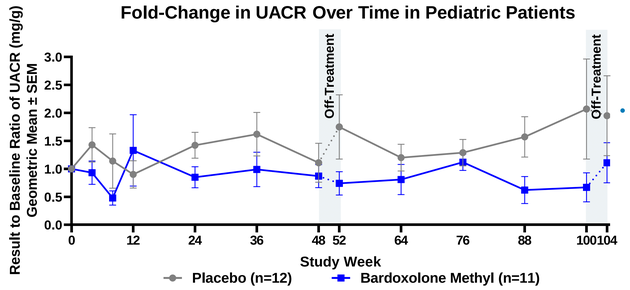


Mean ± SEM eGFR Change (mL/min/1.73 m^2)

	Difference (Bard – Placebo)
Week 100	13.8 ± 5.7 (p=0.017)
Week 104	14.6 ± 5.0 (p=0.0035)

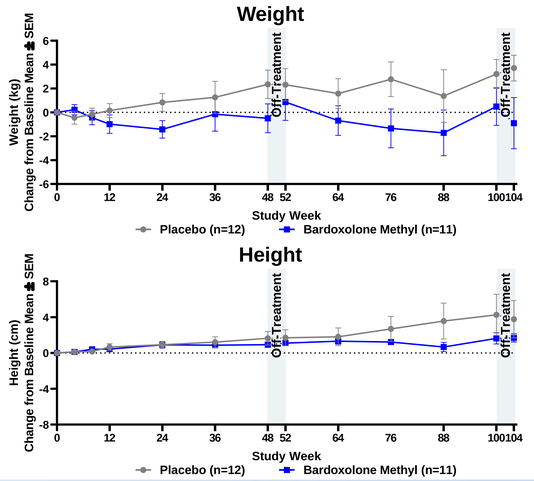
- Significant on- and off-treatment eGFR improvements vs placebo

URINARY ALBUMIN TO CREATININE RATIO



- UACR remained unchanged vs baseline in pediatric patients

WEIGHT AND HEIGHT



- Mean changes in weight were minimal in pediatric patients
- Pediatric patients generally continued along their baseline growth curves* for height and weight in both treatment groups

**Based on CDC clinical growth charts (https://www.cdc.gov/growthcharts/percentile_data_files.htm)*

SAFETY: ADVERSE EVENTS

Number of Patients With:	Placebo (n=12)	Bardoxolone Methyl (n=11)
AE	10 (83.3%)	11 (100%)
Serious AE	2 (16.7%)	0
AE leading to permanent treatment discontinuation	1 (8.3%)	0
Common Adverse Drug Reactions		
Alanine aminotransferase increased	1 (8.3%)	4 (36.4%)
Hyperkalemia	1 (8.3%)	3 (27.3%)
Cough	0	2 (18.2%)
Aspartate aminotransferase increased	1 (8.3%)	1 (9.1%)
Brain natriuretic peptide increased	0	1 (9.1%)
Weight decreased	0	1 (9.1%)
Diarrhoea	0	1 (9.1%)

- AE profile in pediatric patients similar to overall study population
- No severe adverse events in Bard patients
- No AE leading to permanent treatment discontinuation in Bard patients

CONCLUSION

In CARDINAL, the addition of Bard to RAASi in pediatric patients with CKD due to Alport syndrome appeared to preserve kidney function and was generally well-tolerated.

DISCLOSURES

BW, KG, and MR are consultants to Reata. CK receives current or recent research funding from Reata. KN receives funds from KKC. MPC, AG, CJM, and MO are employees of Reata Pharmaceuticals. SA, RG, and KL have nothing to disclose.

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