Initial Results from a Phase 2 Trial of the Safety and Efficacy of Bardoxolone Methyl in Patients with Autosomal Dominant Polycystic Kidney Disease and IgA Nephropathy

FP806

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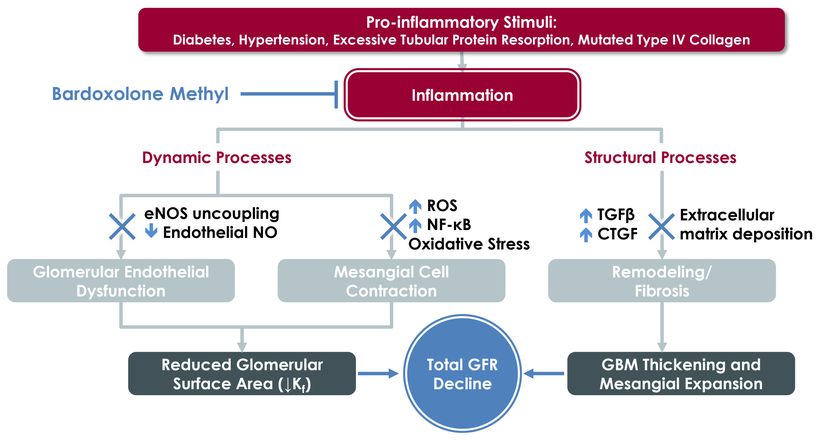
BACKGROUND AND PRECLINICAL RATIONALE

Common pathway of inflammation links diverse etiologies of chronic kidney diseases

- Chronic kidney diseases (CKD) develop due to multiple pathogenic processes that cause injury to cells, disruption of structure, and reduction in function, eventually leading to end-stage renal disease (ESRD)[1-3]
- Despite diverse etiologies, CKDs share a common pathway for tissue damage via prolonged inflammation and oxidative stress, resulting in mesangial expansion, endothelial dysfunction, glomerulosclerosis, reduction in effective glomerular filtration surface area, tubular atrophy, and interstitial fibrosis[1-3]

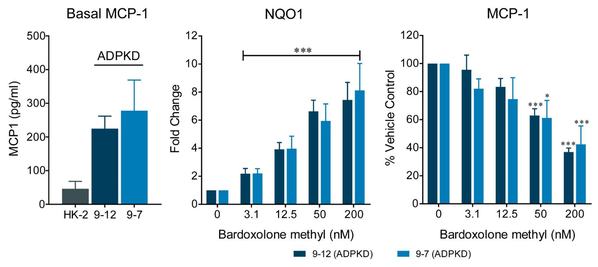


Bardoxolone methyl (BARD) and close analogs improve kidney function and reduce fibrosis in multiple preclinical models

- Through induction of Nrf2 and suppression of NF-κB, BARD targets pro-inflammatory and fibrotic pathways that contribute to GFR loss in CKD[4]
- BARD and close structural analogs improve kidney function and reduce remodeling and fibrosis in multiple models of CKD and AKI
- Markers of inflammation (eg, MCP-1) are higher in the WT 9-7 and WT 9-12 human ADPKD renal cyst cell lines than in the HK-2 normal human proximal tubule cell line and BARD increases Nrf2 activity (NQO1) and suppresses MCP-1 in ADPKD renal cyst cell lines (* P < 0.05; *** P < 0.001)

BARD's Renal Effects Characterized in Multiple Models
Ang II-Induced GFR Decline; *Ding, Kidney Int (2013)*
CKD-Induced Endothelial Dysfunction; *Aminzadeh, Redox Biol (2013)*
5/6 Nephrectomy; *Aminzadeh, Xenobiotica (2014)*
Hypertensive CKD; *Hisamichi, Hypertens Res (2017)*
Hypertensive CKD; *Cuevas, Hypertension (2015)*
Diabetic CKD; *Huang, J Med Chem (2017)*
Diabetic CKD and Atherosclerosis; *Tan, Diabetes (2014)*
High Fat Diet-Induced CKD; *Camer, Chem Biol Interact (2016)*
Lupus Nephritis; *Wu, Arthritis Rheumatol (2014)*
Protein Overload; *Zoja, ASN (2010)*
Ischemic-Reperfusion; *Kocak, Clin Exp Pharm Physiol (2016)*
Ischemic-Reperfusion; *Wu, AJP Renal Physiol (2011)*
Acute Kidney Injury; *Wu, Toxicology (2014)*
FeNTA-Induced Acute Kidney Injury; *Tanaka, Tox Appl Pharm (2008)*
Cisplatin-Induced Acute Kidney Injury; *Aleksunes, JPET (2010)*

BARD Suppresses Inflammation in Renal Cyst Cell Lines



The PHOENIX Phase 2 trial (NCT03366337) was initiated to test the hypothesis that BARD will improve kidney function in patients with CKD due to ADPKD, IgA Nephropathy, Type 1 Diabetes, or FSGS

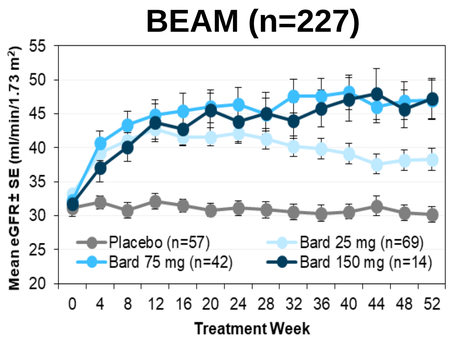
- Multicenter, open-label study, which is targeting enrollment of 25 patients per cohort
- Each cohort is enrolling and will be analyzed separately
- Patients receive once-daily, oral dosing of BARD for 12 weeks titrated from 5 mg to 20 or 30 mg goal dose
- Primary endpoint: change from baseline in eGFR at Week 12

BARDOXOLONE METHYL – CLINICAL TRIALS

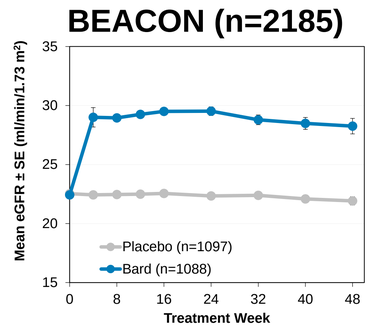
BARD increases measured GFR and eGFR in Phase 2 & 3 studies

- In TSUBAKI, BARD treatment increased inulin clearance compared to placebo[5]
- In the BEAM and BEACON trials, BARD treatment increased eGFR compared to placebo in patients with type 2 diabetes and CKD[6,7]
- In initial data from Phase 2 open-label study CARDINAL, BARD significantly increased eGFR in patients with Alport syndrome through 36 weeks of treatment[8,9]
- Increases in eGFR with BARD in patients with pulmonary arterial hypertension (PAH) in the LARIAT trial are durable for up to two years of treatment
- In BEAM and BEACON, eGFR change at 12 weeks significantly correlated with change at one year
- BARD may target the common pathways contributing to GFR loss in multiple forms of CKD

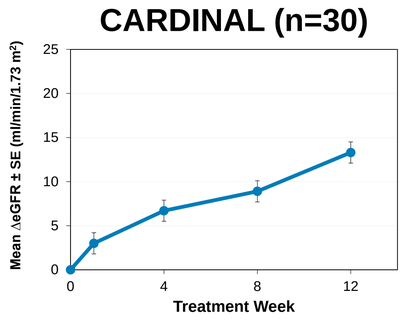
BEAM (n=227)



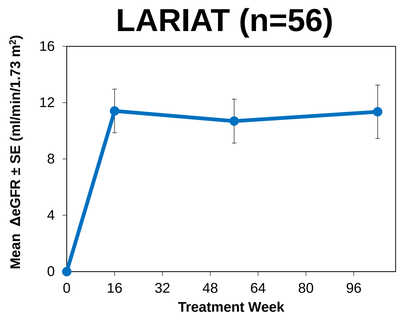
BEACON (n=2185)



CARDINAL (n=30)



LARIAT (n=56)

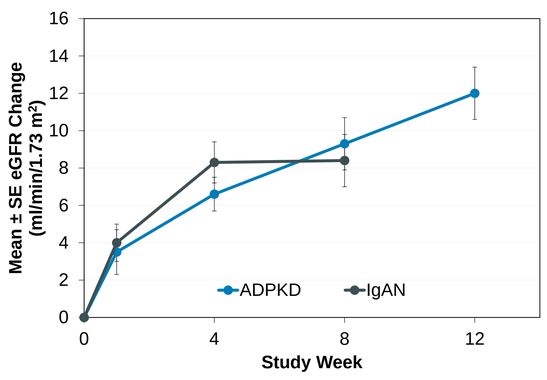


DEMOGRAPHIC AND BASELINE DATA FROM PHOENIX

Characteristic	ADPKD (N=31)	IgAN (N=26)
Age, years (mean, SD)	47.4 ± 9.5	48.5 ± 9.5
Female (n,%)	21 (68%)	11 (42%)
White/Caucasian (n,%)	25 (81%)	22 (85%)
Baseline eGFR, mL/min/1.73 m^2 (mean, SD)	47.7 ± 13.6	46.2 ± 12.6
Baseline ACR, mg/g (geometric mean)	44.4	104.0
Receiving ACEi or ARB (n,%)	25 (81%)	25 (96%)

EFFICACY: CHANGE FROM BASELINE IN eGFR

- Treatment with BARD leads to time-dependent increases in eGFR in patients with ADPKD and IgAN

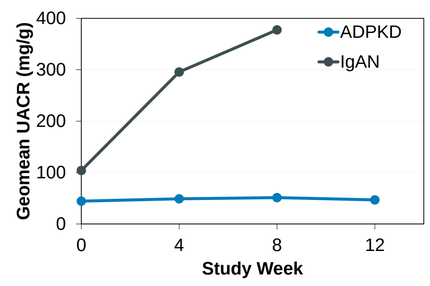


		Baseline eGFR	Change from Baseline in eGFR*			
			WK1	WK4	WK8	WK12
ADPKD	N	31	31	31	15	8
	Mean ± SE	47.7 ± 2.4	3.5 ± 1.2	6.6 ± 0.9	9.3 ± 1.4	12.0 ± 1.4
	p-value		p<0.01	p<0.0001	p<0.0001	p<0.0001
IgAN	N	26	24	16	9	-
	Mean ± SE	46.2 ± 2.5	4.0 ± 1.0	8.3 ± 1.1	8.4 ± 1.4	-
	p-value		p<0.001	p<0.0001	p<0.0001	-

*Available data with > 25% of patients reporting data as of 15 May 2018

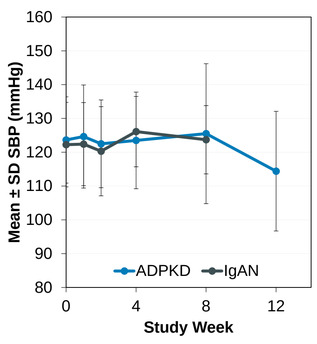
UACR

- UACR unchanged in ADPKD cohort, which generally enrolled patients with lower levels of albuminuria
- UACR increased in IgAN cohort, which enrolled patients with established proteinuria

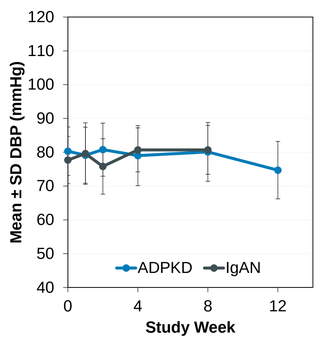


SAFETY: BLOOD PRESSURE, BNP, AND ADVERSE EVENTS

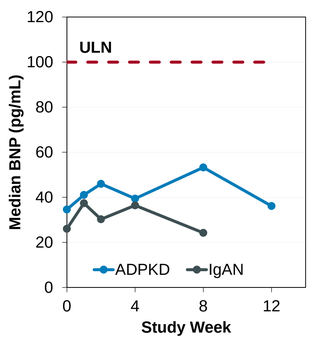
Systolic BP



Diastolic BP



BNP



Vital Signs and BNP

- No significant changes in blood pressure
- No significant change from baseline in BNP

Adverse Events

- No treatment-related serious adverse events to date
- No discontinuations to date
- AEs to date have generally been mild to moderate in intensity
- Most commonly reported AE is muscle spasms, which are associated with CK reductions

Cohort	Adverse Event (Preferred Term)	N (%)
ADPKD (n=31)	Muscle spasms	12 (39%)
	Upper respiratory tract infection	3 (10%)
IgAN (n=26)	Muscle spasms	3 (12%)
	Headache	3 (12%)

AEs occurring in > 2 patients

CONCLUSIONS

- Bardoxolone methyl was generally well-tolerated and significantly increased eGFR in patients with ADPKD and IgA nephropathy
- No treatment-related serious adverse events have been reported to date
- Bardoxolone methyl is currently being evaluated in other forms of chronic kidney disease

DISCLOSURES

PEP, GBA and GAB are consultants to Reata Pharmaceuticals

AA, AR, GBA, LAI, DVR and ALS receive research funding from Reata Pharmaceuticals

MC, AG and CJM are employees of Reata Pharmaceuticals

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