



BARDOXOLONE METHYL OVERVIEW

Topics Addressed

- Overview of bardoxolone methyl (Bard)
- How does Bard target pathogenic pathways in CKD?
- How does Bard affect kidney function in diabetic CKD?
- What happened in BEACON?
- How can the risk for fluid overload be mitigated?
- Are the increases in eGFR with Bard reflective of true increases in GFR?
- Is the increase in eGFR due to hyperfiltration?
- How does Bard affect proteinuria?
- What are some other pharmacological effects of Bard?
- Why is Bard being studied in Alport syndrome?
- How does Bard affect kidney function in patients with Alport syndrome?
- Is Bard being studied in other forms of chronic kidney disease?

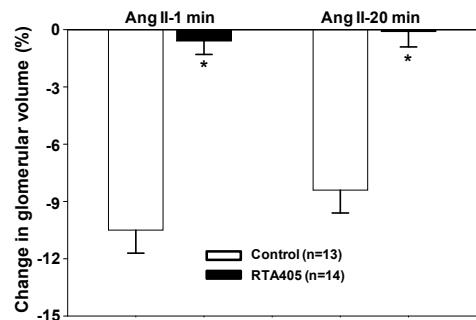
Overview of Bardoxolone Methyl and Reata

- Reata is developing small-molecule drugs for serious and life threatening diseases
- Bardoxolone methyl is our lead program and it was developed to prevent tissue injury from chronic inflammation
 - Bard invented at Dartmouth by scientist who co-discovered TGF β , Dr. Michael Sporn
 - Bard activates Nrf2, which promotes resolution of inflammation, and suppresses NF- κ B
 - Bard restores mitochondrial function and suppresses tissue remodeling and fibrosis in animal models
- Mitochondrial dysfunction, oxidative stress, and chronic, unresolved inflammation are features of many diseases and our drugs have many potential applications
 - Bard is in a Phase 3 trial for connective tissue disease-associated pulmonary arterial hypertension with data expected 2H 2018
 - Bard analog, Omav, is in a pivotal Phase 2 trial in severe genetic form of ataxia called Friedreich's ataxia with data expected in 2H 2019
- Bard is in a Phase 3 trial in severe genetic form of CKD caused by Alport syndrome with data expected 2H 2019
- Reata is initiating the PHOENIX Phase 2 trial to study Bard in four additional rare kidney indications with data expected from 2H 2018 through 2019

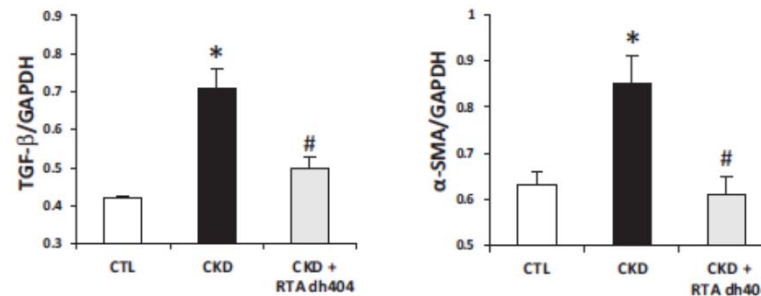
Bardoxolone Methyl Targets Pathways Contributing to Chronic Kidney Disease Progression

- Reata observed unprecedented increases in kidney function in early clinical trials in cancer patients
- Reata and collaborators extensively characterized Bard effects on kidney (150+ published papers)
- Both acute and chronic kidney disease, regardless of initiating cause (infection, diabetes, hypertension, autoimmunity), have inflammation and immune activation in common¹
 - Bard targets these common inflammatory pathways that are implicated in CKD
 - Bard protects structure and function of kidney in many animal models of kidney disease, including 5/6 nephrectomy model of hyperfiltration², diabetic nephropathy³, hypertension-induced CKD⁴, protein-overload nephropathy⁵, and lupus nephritis⁶
 - To acutely improve kidney function, Bard reduces inflammatory angiotensin II-induced intraglomerular endothelial and mesangial cell dysfunction, restoring K_f and GFR in animal models⁷⁻⁹
 - Bard does not affect blood pressure, renal plasma flow, or hydrostatic pressure in animals⁹

Regulation of GFR in Animals: Increased Glomerular Volume



5/6 Nephrectomy Model: Reduced TGF- β , Fibrosis, and Histological Injury



Reata and Collaborators Conducted Battery of Phase 2 Studies in Diabetic CKD Patients

- Consistently showed unprecedented increases in kidney function
- Culminated in a large Phase 2b study (BEAM) that demonstrated durable increases in kidney function for one year
- Data published in the New England Journal of Medicine¹

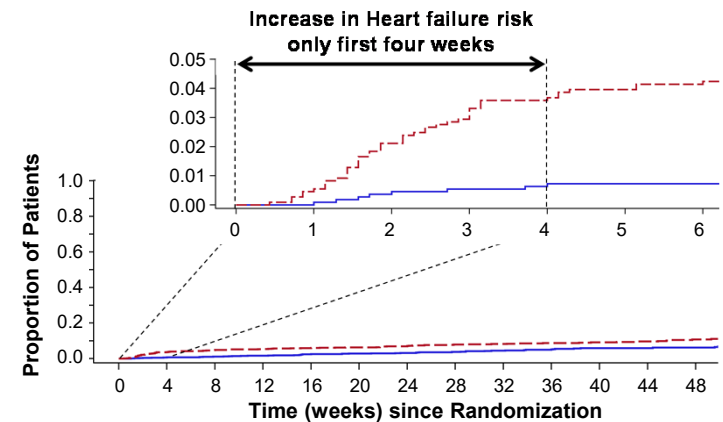
Study	Phase/ Country	Patient Population	N	BL eGFR (mL/min/1.73m ²)	ΔeGFR (mL/min/1.73m ²)
402-C-0804 (BEAM)	2/US	CKD/Diabetes	227	32.7	8.6 (p<0.001 vs PBO)
402-C-0902	2/US	CKD/Diabetes	131	32.2	6.5 (p<0.001)
402-C-0801 (Stratum 1)	2a/US	CKD/Diabetes	60	35.6	6.7 (p<0.001)
402-C-0801 (Stratum 2)	2b/US	CKD/Diabetes	20	30.3	7.2 (p<0.001)
402-C-1102	1/US	CKD/Diabetes	24	29.7	9.0 (p<0.05)

- For regulatory approval, FDA required outcomes trial with primary composite endpoint of only ESRD and CV death
- Large Phase 3 study (BEACON) designed to meet FDA requirement conducted in only Stage 4 patients since earlier stage patients would not have contributed to ESRD endpoint²
 - Enrolled 2,185 diabetic Stage 4 CKD patients (eGFR 15 to 29 ml/min/1.73 m²)
 - Study was terminated in 2012 when DSMB detected an increase in risk of fluid overload related heart failure hospitalizations (8.8% in Bard vs 5% in placebo) with unknown etiology at time study was terminated

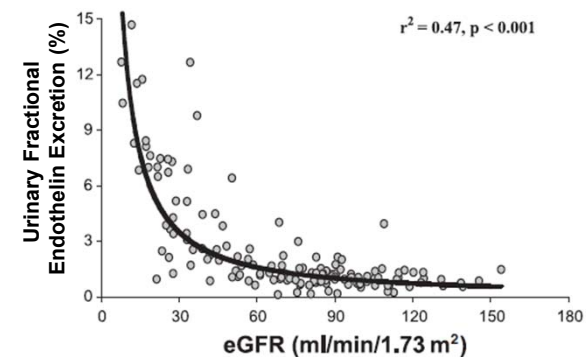
BEACON Safety Finding: Acute Fluid Overload in Patients with Prior HF or Elevated BNP in First Four Weeks

- Patients in heart failure prior to randomization (mean baseline BNP 550 pg/mL) presented with acute fluid retention during first 4 weeks^{1,2}
- Investigators in the ASCEND trial noted that fluid overload timing and pattern in BEACON similar to ASCEND³
 - ASCEND study tested an ERA (avosentan) in diabetic CKD
 - Suppression of endothelin pathway likely precipitated acute fluid retention in both trials
 - Urinary protein induces endothelin signaling and subsequent vasoconstriction in Stage 4 and 5 CKD patients⁴
 - Bard suppresses the endothelin pathway, likely through suppression of NF- κ B²
 - Urinary data from phase 2 study showed Na⁺ and volume retention in Stage 4 CKD but not Stage 3b CKD patients²
 - Cardiac function was preserved with no evidence of cardiotoxicity

Heart Failure Risk in BEACON



Endothelin Dysregulation in Late-Stage CKD



Exclusion of At-Risk Patients in BEACON Appears to Improve Risk-Benefit Profile of Bard

- Post-hoc analysis identified risk factors for fluid overload
 - BNP > 200 pg/mL
 - Prior HF history
- Risk of fluid overload same (2%) for Bard and placebo patients without these factors
- Exclusion of at-risk BEACON patients improves distribution of ESRD, primary composite events, and SAEs in BEACON
- Can easily monitor and treat subclinical fluid retention with diuretics before it becomes severe
- Exclusion of at-risk patients and careful monitoring have been used in all subsequent trials that have enrolled > 500 patients
 - No concerns by DSMBs or safety committees
 - Analyses reviewed by FDA and Japanese PMDA

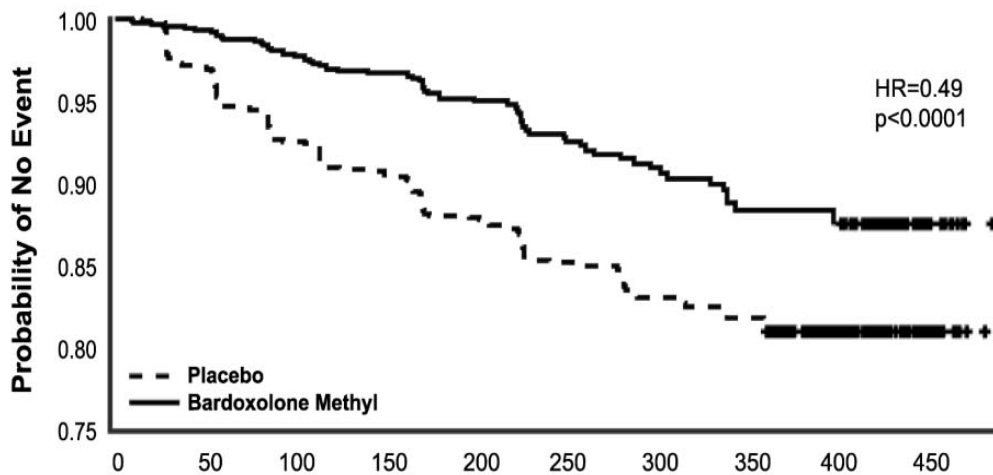
Exclusion of At-Risk Patients in BEACON

Treatment	PBO (n = 557)	BARD (n = 519)
Primary Composite	25 (5%)	15 (3%)
ESRD	20 (4%)	8 (2%)
CV Death	6 (1%)	7 (1%)
Secondary Endpoints		
Heart Failure	10 (2%)	12 (2%)
MI	6 (1%)	6 (1%)
Stroke	5 (1%)	2 (<1%)

Despite Study Termination, Bard Increased eGFR and Reduced Kidney Failure Outcomes in BEACON

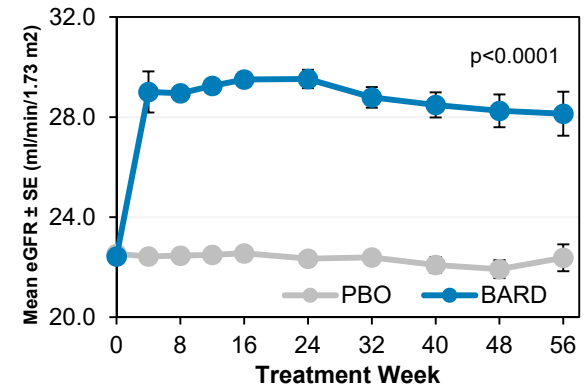
- Bard significantly increased eGFR ($p < 0.0001$) and increases were durable through at least one year
- Reduced ESRD and renal SAE events
- Significantly reduced likelihood of kidney failure outcomes, including composite of adjudicated ESRD, 30% decline, or eGFR < 15 events ($HR = 0.49$; $p < 0.0001$)

ESRD, 30% Decline or eGFR < 15 mL/min/1.73 m²



PBO	n=1093	n=1037	n=855	n=732	n=568	n=427	n=316	n=215	n=91	n=13
BARD	n=1092	n=994	n=826	n=689	n=540	n=392	n=305	n=186	n=92	n=11

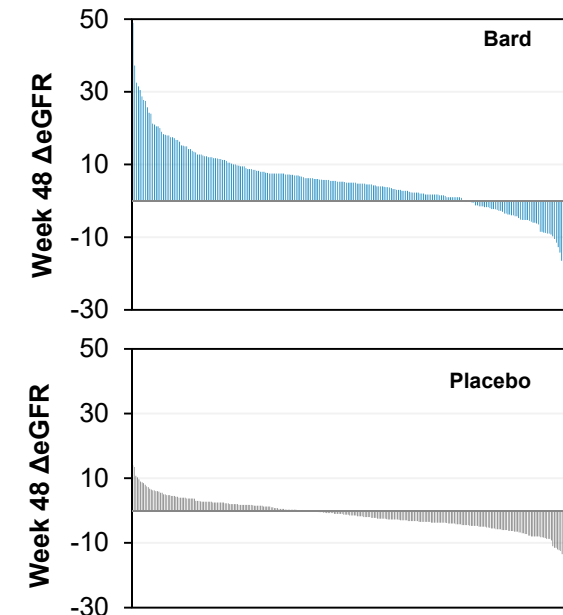
eGFR Over Time



Number of Patients

PBO	1093	1023	885	726	547	402	281	125
BARD	1092	958	795	628	461	345	241	103

Distribution of eGFR Changes



Kidney Function Partially Retained After Withdrawal of Bard

- Kidney function increased after one year of treatment followed by washout
 - eGFR assessed after one year of treatment followed by 4 week withdrawal
 - Four week withdrawal corresponds to three weeks after loss of pharmacologic activity
 - In BEAM and BEACON, significant placebo-corrected increase in eGFR 4 weeks after withdrawal
 - Data suggest Bard may affect kidney remodeling and fibrosis in humans as is observed in CKD animal models
- Acute eGFR increases positively correlate with durable increase through one year and retained eGFR increase post-withdrawal
 - Acute eGFR increases are not associated with clinical evidence of injury or harm
 - One year of on- and off-treatment data differentiate Bard from amlodipine and pressure-mediated hyperfiltration

Withdrawal Analysis

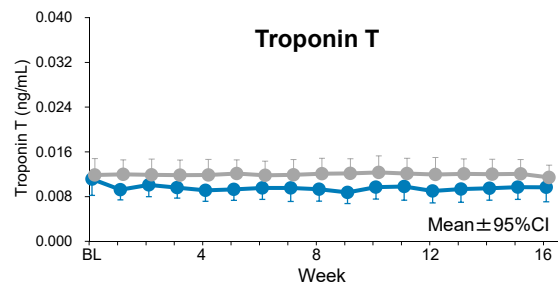
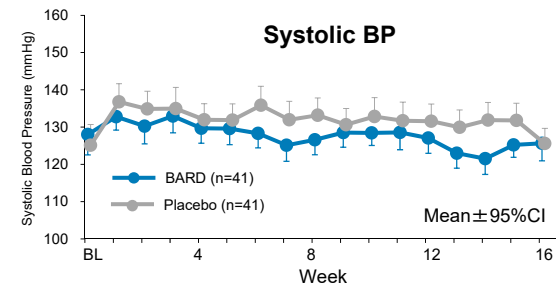
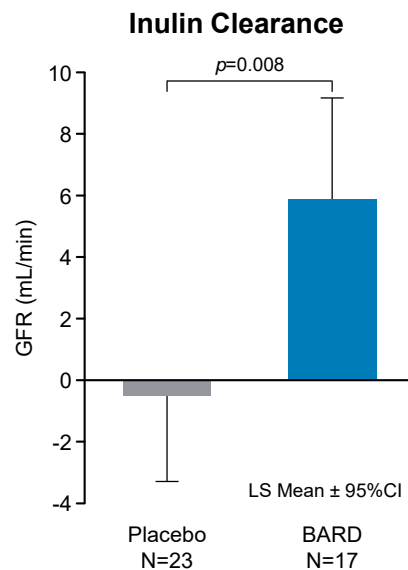
	Baseline eGFR	Placebo-Corrected Δ eGFR Post-Withdrawal	P-value
BEAM (n=172)			
Mid Dose	32	4.7	p<0.05
High Dose	32	5.0	p<0.05
BEACON (n=498)			
20 mg	23	1.8	p<0.001

Correlation Analysis

		Correlation	
	N	Week 12/ One Year	Week 12/ 4WK Post-treatment
BEAM	129	0.52 (p<0.0001)	0.42 (p<0.0001)
BEACON	219	0.48 (p<0.0001)	0.43 (p<0.0001)

KHK Demonstrated Bard eGFR Increases Reflect True Increases in GFR Using Inulin Clearance Method

- Japanese partner KHK conducted TSUBAKI to measure GFR using “Gold Standard” inulin clearance method
 - Enrolled diabetic CKD patients and treated with Bard or placebo for 16 weeks
 - Placebo-corrected change in inulin GFR at Week 16 was 6.64 mL/min/1.73 m² (p=0.008)



- Bard well tolerated and no major safety concerns in Stage 3 or 4 CKD patients
 - Volume status well controlled with unchanged BP and no urinary Na⁺ or volume retention
 - No fluid overload-related hospitalizations
 - Bard not associated with evidence of cardiotoxicity, as assessed by Troponin T

Increases in eGFR with Bard are not due to Changes in Creatinine Metabolism

- Serum creatinine used to estimate kidney function in calculation of eGFR
 - Creatinine is produced in the muscle and is removed from the blood via glomerular filtration
 - Increased serum creatinine reflects decreased glomerular filtration
- Bardoxolone methyl does not affect creatinine metabolism
 - Loss of muscle mass would decrease creatinine production and therefore decrease urinary creatinine
 - Bard did not change 24-hr urinary creatinine excretion in four different clinical studies¹⁻³
- Weight loss does not affect estimate of kidney function using creatinine-based eGFR
 - eGFR increases observed in patients with and without weight loss⁴
 - eGFR change happens much earlier than weight loss in patients who experience weight loss
 - Inulin clearance data also demonstrate that increases in eGFR reflect true increases in GFR

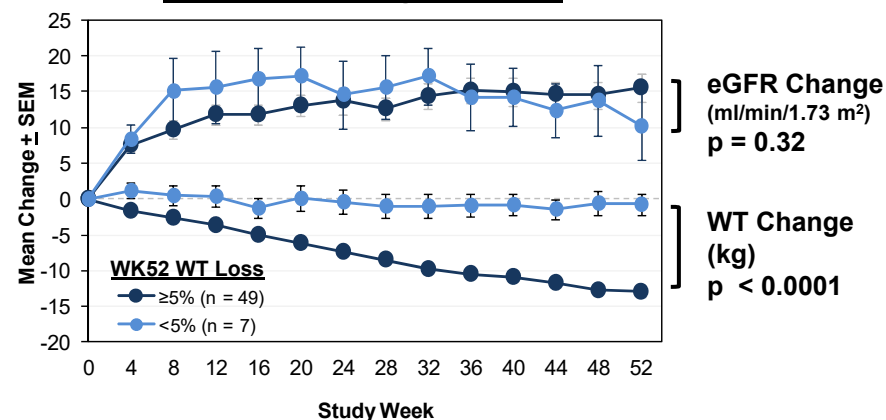
24-hr Urinary Creatinine Excretion

Study	Design	N	P-value
402-C-0903 (BEACON)	PBO-controlled	134	NS ^{a,b}
RTA402-002 (TSUBAKI)	PBO-controlled	44	NS ^{a,b}
402-C-1102	Open-label	15	NS ^a
402-C-0801	Open-label	18	NS ^a

^a p-value versus baseline

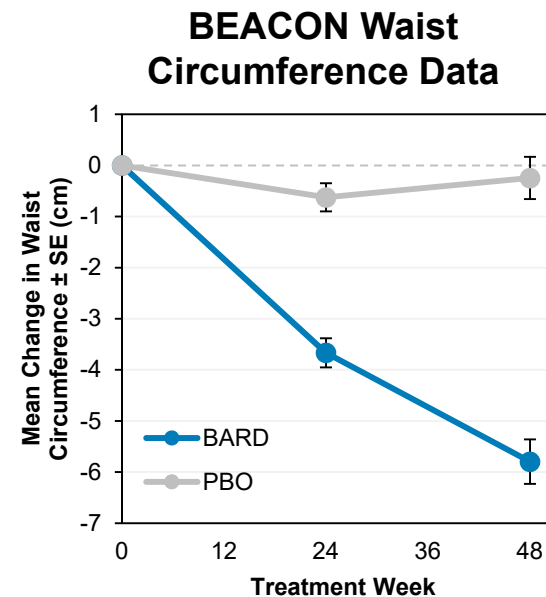
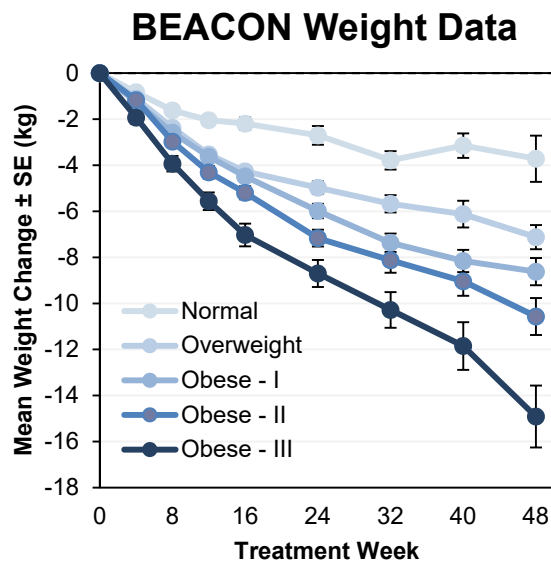
^b p-value versus placebo

BEAM: eGFR and Weight Changes at Mid and High Doses



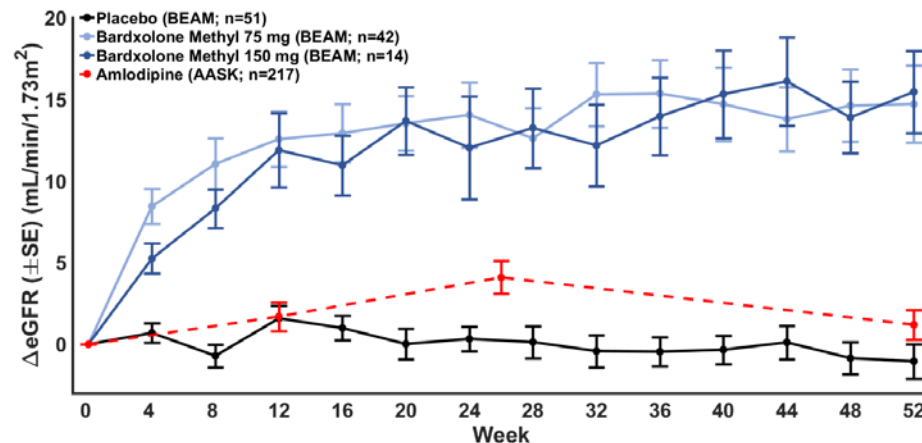
Weight Loss with Bard Associated with Improved Metabolism and Not Muscle Loss

- Preclinical studies demonstrate that Bard improves metabolism, reduces lipid synthesis, increases beta-oxidation of fat, and reduces fat mass¹⁻³
 - No reduction in lean muscle mass, including muscle
 - In one year non-human primate toxicology study, no adverse effect on muscle
- Decreased weight with Bard due to reduction in fat mass, not muscle
 - Weight loss is more pronounced in patients with higher BMI
 - Significant decreases in waist circumference, a measure of adiposity
 - Unchanged 24-hr urinary creatinine indicate muscle mass not decreased⁴⁻⁶



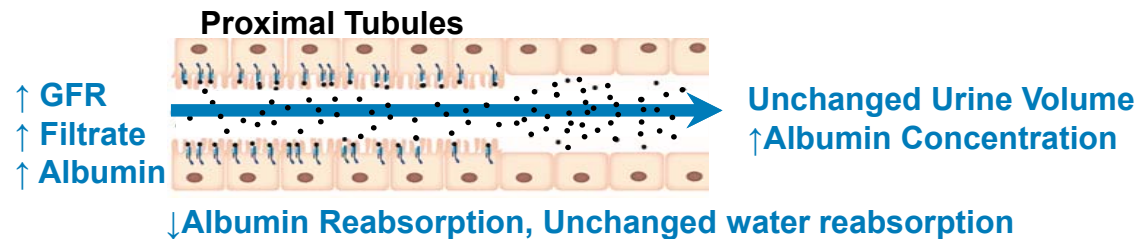
Profile of Bard is Inconsistent with Pressure-Mediated Hyperfiltration

- Hydrostatic pressure-mediated hyperfiltration due to systemic hypertension or certain types of calcium channel blockers, such as amlodipine, can be deleterious¹⁻⁵
 - Demonstrated preclinically using 5/6 nephrectomy model of hyperfiltration⁵
 - Demonstrated clinically in the AASK trial that studied amlodipine in hypertensive CKD patients^{1,2}
- Bard preclinical profile inconsistent with pressure-mediated hyperfiltration
 - GFR increases due to increased glomerular surface area ($\uparrow K_f$, not hydrostatic pressure)⁶
 - Reduces fibrosis and preserves renal function in 5/6 nephrectomy and hypertensive CKD models^{7,8}
- Bard clinical profile inconsistent with pressure-mediated hyperfiltration
 - In AASK, eGFR increase of ~10% (~ 4 mL/min/1.73 m²) with amlodipine was sufficient to result in loss of effect after 6 months¹
 - In BEAM, eGFR increased ~50% at mid and high dose (~15 mL/min/1.73 m²) but eGFR was sustained through 12 months⁹
 - Withdrawal data showing increased eGFR from baseline and placebo after one year of treatment rule out injury⁹

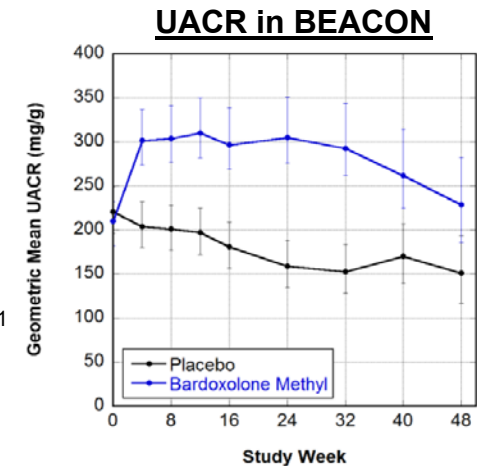


Increases in Urinary Protein are Consistent with Increases in GFR and not Injury

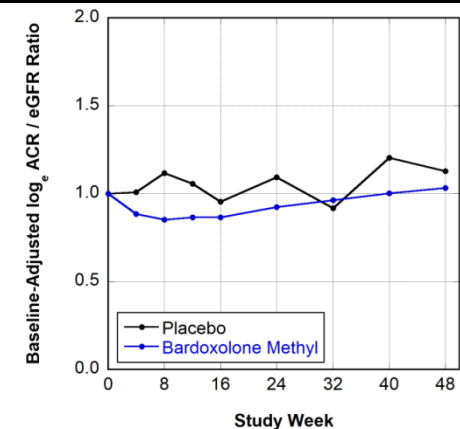
- In CKD, damage to the glomerular filtration barrier results in loss of selectivity, increased filtration of protein and subsequent proteinuria
- When GFR increases, increased urinary protein results from increased filtrate flow, not further loss of filtration selectivity¹
 - Increased flow delivers more albumin to proximal tubules
 - Increased flow decreases protein reabsorption in tubules
 - Most water is reabsorbed and urine volume is generally constant
 - Increased GFR shunts more protein to same urinary volume increasing concentration¹



- Increases in urinary protein with Bard are consistent with increases in filtration (↑ GFR) and inconsistent with increased glomerular injury
 - Increases in proteinuria (UACR) significantly correlate with eGFR increases in BEAM and BEACON^{2,3}
 - Increase in UACR is modest and does not continue to increase over time^{2,3}
 - UACR adjusted for eGFR show UACR/eGFR ratios unchanged^{2,3}
 - UACR returns to baseline 4 weeks post treatment-withdrawal
 - Bard associated with durable increase in eGFR on- and off-treatment after one year



Log ACR/eGFR Ratios in BEACON



Have Extensively Characterized Other Clinical and Pharmacological Effects

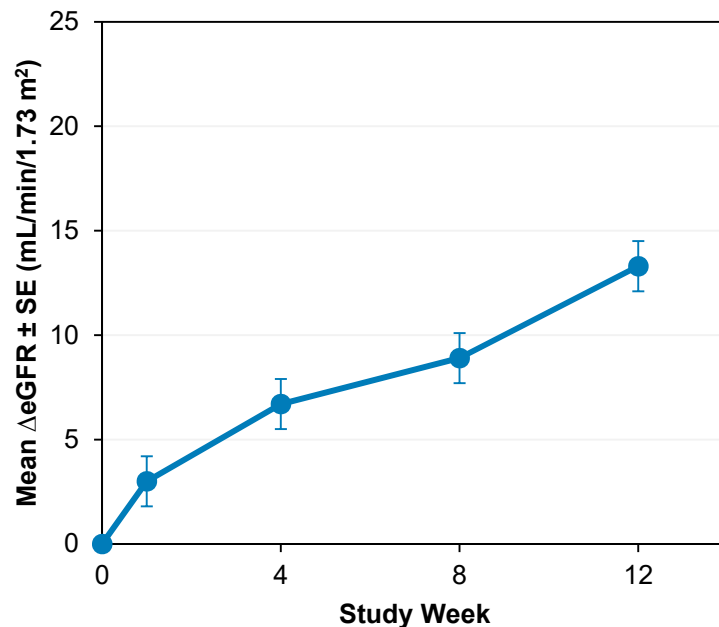
- Analysis of collective CKD data from clinical and preclinical studies has further elucidated other key pharmacological effects of Bard
- Bard pharmacologically regulates transaminases through Nrf2
 - Nrf2 regulates cellular production of transaminases, which function to support metabolism
 - Increases not associated with other signs or symptoms of liver injury
 - No evidence of liver injury or Hy's Law cases in >2000 patients who have been exposed
- Bard promotes re-distribution of magnesium and not renal loss
 - Cellular re-distribution to accommodate increased metabolism and energy production¹
 - Total body Mg depletion does not occur and intracellular Mg unchanged¹
 - Associated with reduced fractional excretion with no evidence of tubular injury or increased QTc^{1,2}
- Bard-induced muscle spasms likely pharmacologic and not toxic
 - Presents as “Charley horse” muscle cramp, not isolated pain
 - Possibly due to metabolic effects in muscle and not associated with changes in Mg
 - Associated with reduction of CK, not increase, suggesting that it is pharmacologic and not toxic

Transition to Alport Syndrome

- Alport syndrome is a rare kidney disease in which chronic inflammation drives progression to ESRD
 - Protein overload from collagen mutation drives chronic inflammation in glomerulus and renal interstitium
 - Median age of ESRD in males with the most common form is 25 years
 - Severe form of CKD with no approved therapies
 - Patients normally do not have risk factors for fluid overload
- FDA agreed that change in eGFR could support registration in Alport syndrome
 - Accelerated approval would be supported by a retained improvement in eGFR following 48 weeks of treatment and 4 weeks off drug
 - Full approval would be supported by a retained improvement in eGFR following 100 weeks of treatment and 4 weeks off drug
- CARDINAL study design leverages data from 2,700 CKD patients
 - BEAM and BEACON on- and off-treatment eGFR data extensively modeled to design and conservatively power CARDINAL
 - Based on BEAM and BEACON, Phase 2 primary efficacy endpoint at Week 12 should be predictive of longer-term and off-treatment response
 - Phase 3 portion of CARDINAL powered to detect off-treatment change in eGFR
 - Employs risk mitigation features to minimize potential for fluid overload observed in late-stage diabetic CKD

CARDINAL Phase 2 Primary Efficacy Analysis

- All patients completed treatment through Week 12
- eGFR data show time-dependent increases through Week 12
- Changes consistent with Bard treatment in prior diabetic CKD studies



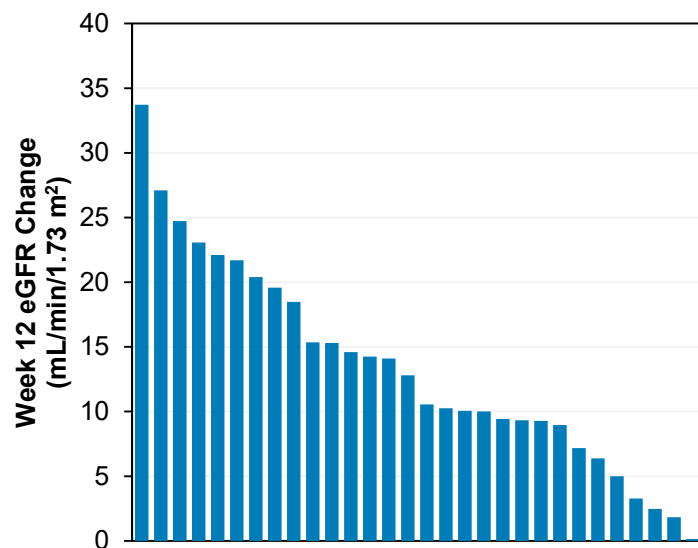
Change from Baseline in eGFR				
	Week 1	Week 4	Week 8	Week 12
N	30	30	30	30
Mean ± SE	3.0 ± 0.7	6.7 ± 1.3	8.9 ± 1.3	13.4 ± 1.4
95% CI	(1.6, 4.4)	(4.1, 9.3)	(6.2, 11.6)	(10.5, 16.3)
p-value	0.0001	<0.0001	<0.000001	<0.000000001

LS mean eGFR change from baseline at each visit is compared to zero using a mixed-model repeated measures analysis using baseline eGFR and log-transformed ACR as continuous covariates.

CARDINAL Distribution of eGFR Changes

- All patients demonstrated eGFR increases from baseline
 - 87% of patients demonstrated increases of at least 4 ml/min/1.73 m²
 - 63% of patients demonstrated increases of at least 10 ml/min/1.73 m²
- 22/30 (73%) of patients had an improvement in CKD stage and none worsened

eGFR Changes for All Patients



Baseline CKD Stage		Week 12 CKD Stage				
	N	Stage 4	Stage 3b	Stage 3a	Stage 2	Stage 1
Stage 4 (eGFR <30)	5	1	4	-	-	-
Stage 3b (eGFR 30 to 44)	11	-	4	7	-	-
Stage 3a (eGFR 45 to 59)	2	-	-	0	2	-
Stage 2 (eGFR 60 to 89)	10	-	-	-	1	9
Stage 1 (eGFR >90)	2	-	-	-	-	2

Improved CKD Stage →

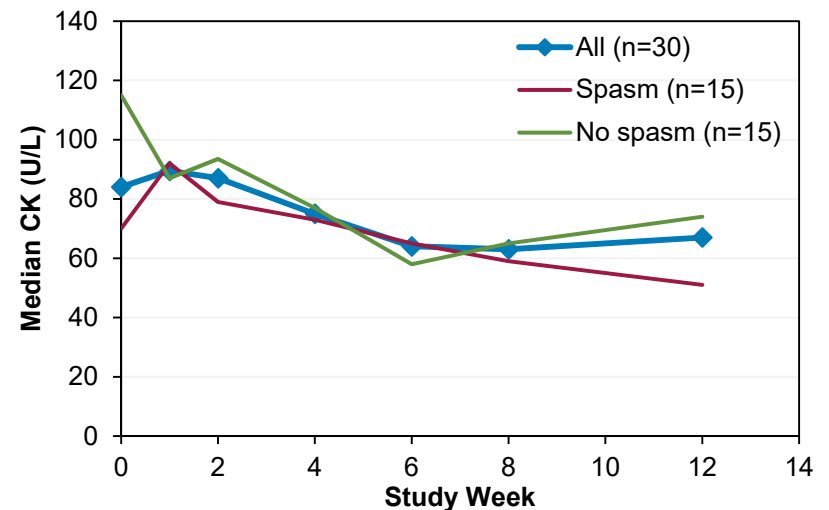
CARDINAL Summary of Safety through Week 12

- No discontinuations and no serious adverse events
- AEs to date have generally been mild to moderate in intensity
- No reports of fluid overload
- No consistent AEs yet, except muscle spasms
 - Also observed in prior diabetic CKD trials
 - Present as contraction, usually in the lower extremity, and similar to exercise-induced cramps
 - Usually transient; occur in first month and resolve a few weeks after titration is completed
 - Not associated with evidence of muscle toxicity as assessed by CK

Number of Patients Reporting AEs	27 (90%)
Number of AEs	87
Preferred Term	Number (%) of Patients*
Muscle spasms	15 (50%)
Nausea	4 (13%)
Fatigue	4 (13%)
Headache	4 (13%)
Hyperkalemia	3 (10%)

*AEs reported in >2 patients

Creatine Kinase



Expanded Rare Kidney Disease Program Underway

- Novel anti-inflammatory MOA and clinical activity in Alport syndrome and diabetic CKD encourage study of Bard in additional, rare kidney diseases
- PHOENIX Phase 2 trial to study Bard in four additional rare kidney indications:
 - Autosomal Dominant Polycystic Kidney Disease (genetically confirmed PKD1 mutations)
 - IgA Nephropathy (biopsy confirmed)
 - Type 1 Diabetic CKD
 - FSGS (biopsy confirmed idiopathic and genetic causes)
- Similar to CARDINAL Phase 2 design:
 - 12 weeks of open-label treatment, titration to goal dose of 20 or 30 mg of Bard orally, once daily
 - Key eligibility criteria similar to CARDINAL design
 - Stable doses of background meds (ACEi, ARB, insulin, prednisone, etc.)
 - Will enroll 20-30 patients per indication powered to detect a change of 3.4 mL/min/1.73 m²
- Site activations are underway and data will be available from 2H 2018 through 2019

Upcoming Key CKD Program Milestones

- Phase 3 portion of the CARDINAL trial began enrollment during August 2017 and one year data are expected 2H 2019
- Site activations in PHOENIX Phase 2 trial to study Bard in four additional rare kidney indications are underway
 - Enrolling patients with Autosomal Dominant Polycystic Kidney Disease, IgA nephropathy, type 1 diabetic CKD, and FSGS
 - Data will be available from 2H 2018 through 2019
- If positive data from PHOENIX, will plan to rapidly initiate additional Phase 3 trial(s)
- KHK is planning to initiate a large Phase 3 trial in diabetic CKD patients in Japan to further evaluate safety and efficacy in 2018

Glossary

ACEi	Angiotensin converting enzyme inhibitors
Ang II	Angiotensin II
ARB	Angiotensin receptor blockers
Bard	Bardoxolone methyl
BNP	B-type natriuretic peptide
CK	Creatine kinase
ERA	Endothelin receptor antagonist
ESRD	End-stage renal disease
FA	Friedrich's Ataxia
GFR	Glomerular filtration rate
K_f	Ultrafiltration coefficient
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B-cells
Nrf2	Nuclear factor (erythroid-derived 2)-related factor 2
UACR	Urinary albumin to creatinine ratio

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