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MANAGEMENT CALL TO DISCUSS LONGER-TERM IMPROVEMENTS IN KIDNEY FUNCTION WITH BARDOXOLONE

Introduction

- Substantial body of prior CKD clinical data characterizes Bard's unique profile
  - Bard has demonstrated improved kidney function in multiple trials across diverse causes of CKD, which were durable for one year in BEAM and BEACON
  - In BEACON, improvements in eGFR were associated with significantly reduced risk of adverse renal events validated to predict kidney failure outcomes
  - Statistically significant retained eGFR benefit post-withdrawal in BEAM and BEACON
  - 12-week on-treatment eGFR change correlates with retained benefit at one year
- CARDINAL trial in Alport syndrome is lead study for Bard rare CKD program
  - Accelerated approval based on retained increase in eGFR post-withdrawal after one year
  - Full approval based on two-year withdrawal data
- In LARIAT trial of Bard in PAH, patients upon study entry on average had impaired kidney function and were followed beyond one year
  - Progressive loss of kidney function is a prevalent and critical complication for PAH patients
  - eGFR loss is a validated predictor of mortality even in PAH patients with normal kidney function
- LARIAT data showed that Bard increased eGFR and increases were sustained for 2 years

Multiple PAH Studies Demonstrate that CKD is Associated with Reduced Survival

- CKD or progressive loss of kidney function is a key contributor to several pathophysiologic processes, which amplify the adverse effects of PAH
- Several recently published PAH studies demonstrate increased mortality with progressive loss of kidney function
- Analyses of largest PAH registry, REVEAL[1], demonstrate that 10% loss of kidney function in one year is associated with:
  - HR of 1.66 ($p<0.0001$) for survival
  - HR of 1.33 for death or all-cause hospitalization ($p=0.002$)
  - Findings independent of baseline eGFR, 6MWD, and WHO functional class

Study	N	Patient Population	HR of CKD on Survival
Benza et al.	2716	47% IPAH; 23.9% CTD-PAH	3.3
Chakinala et al.	2368	45% IPAH; 28% CTD-PAH; 10% PAH-CHD; 17% other	1.66 per 10% decline
O'Leary et al.	840	Etiology not reported	1.4
Navaneethan et al.	552	Etiology not reported	1.7
Shah et al.	500	57% IPAH, 11% CHD, 31% CTD, 11% Other	2.54 if SCr > 1.4 mg/dL
Campo et al.	76	100% SSc	2.6

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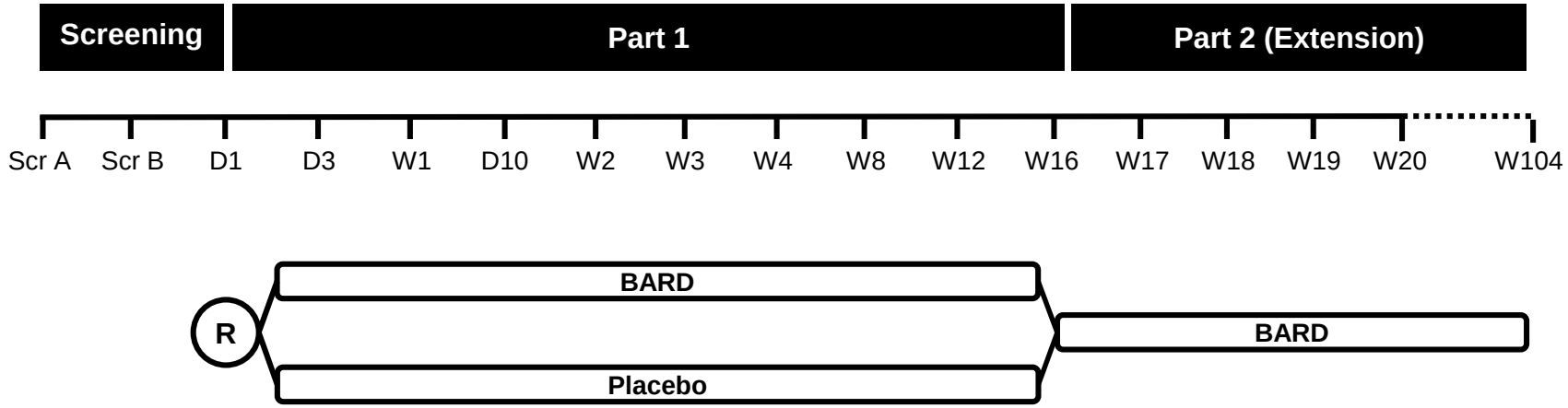
[1]*Chakinala et al., J Heart Lung Transplant (2017)*

LARIAT Design

- LARIAT is a two-part Phase 2 trial that enrolled patients with pulmonary hypertension
  - Included a 16-week placebo-controlled phase
  - Dose-ranging and titration cohorts were studied
  - After initial 16 weeks, all patients were given the opportunity to be provided Bard and followed longer-term in an open-label extension phase of the trial
- Analyses in this presentation include all PAH patients enrolled in LARIAT across dose-ranging and titration cohorts (n=101)
  - 71 received Bard during 16-week placebo-controlled phase
  - 30 received placebo initially and were then given Bard and followed during the extension phase

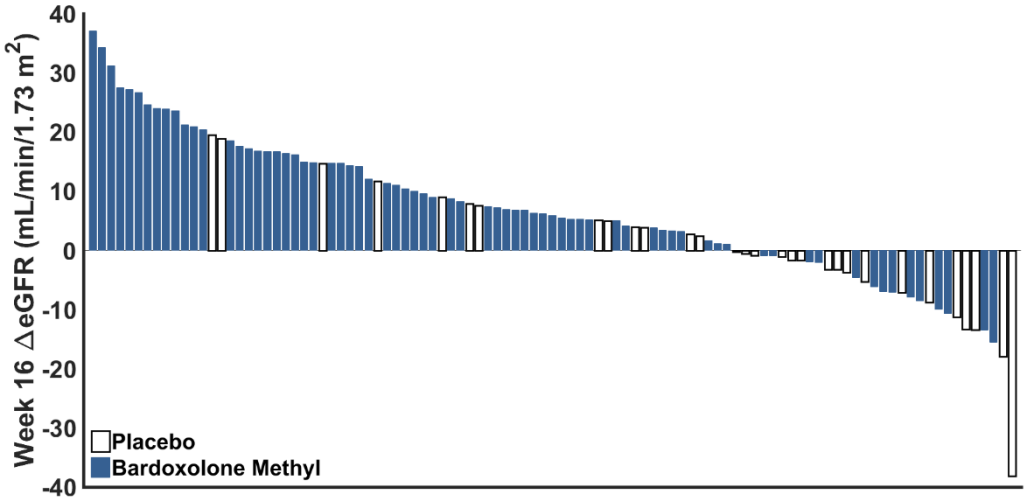


Bard Significantly Improves eGFR

- LARIAT patients had impaired kidney function upon study entry
- During 16-week placebo-controlled phase of trial, Bard improved eGFR 10.6 mL/min/ 1.73 m^2 versus placebo
- High proportion of Bard responders

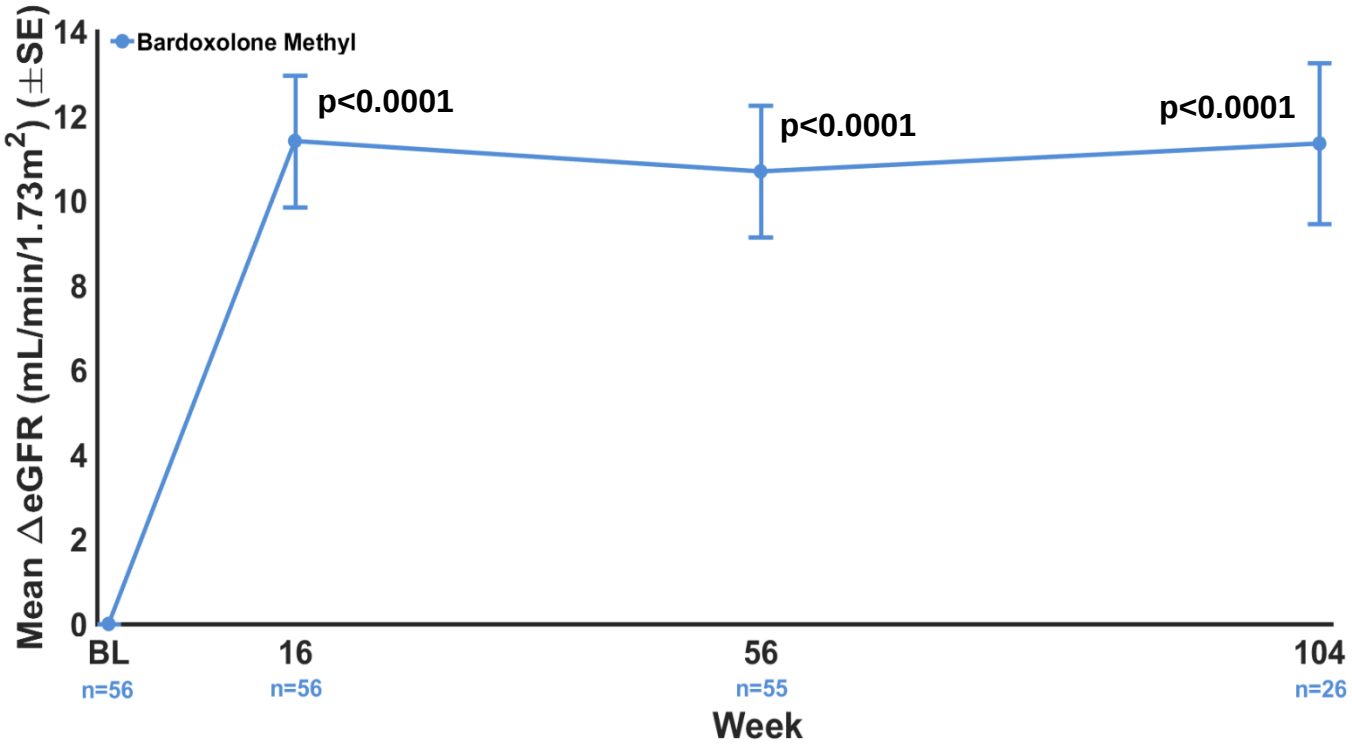
Treatment	N	Baseline eGFR (±SD)	Week 16 ΔeGFR	
			Mean Change from Baseline[a]	Placebo-corrected
Placebo	30	78.1 ± 21.3	-1.1 ± 2.1 p = 0.60	-
Bardoxolone methyl	71	74.7 ± 20.2	9.4 ± 1.4 p < 0.0001	10.6 ± 2.6 p < 0.0001

All eGFR measurements are mL/min/1.73 m^2

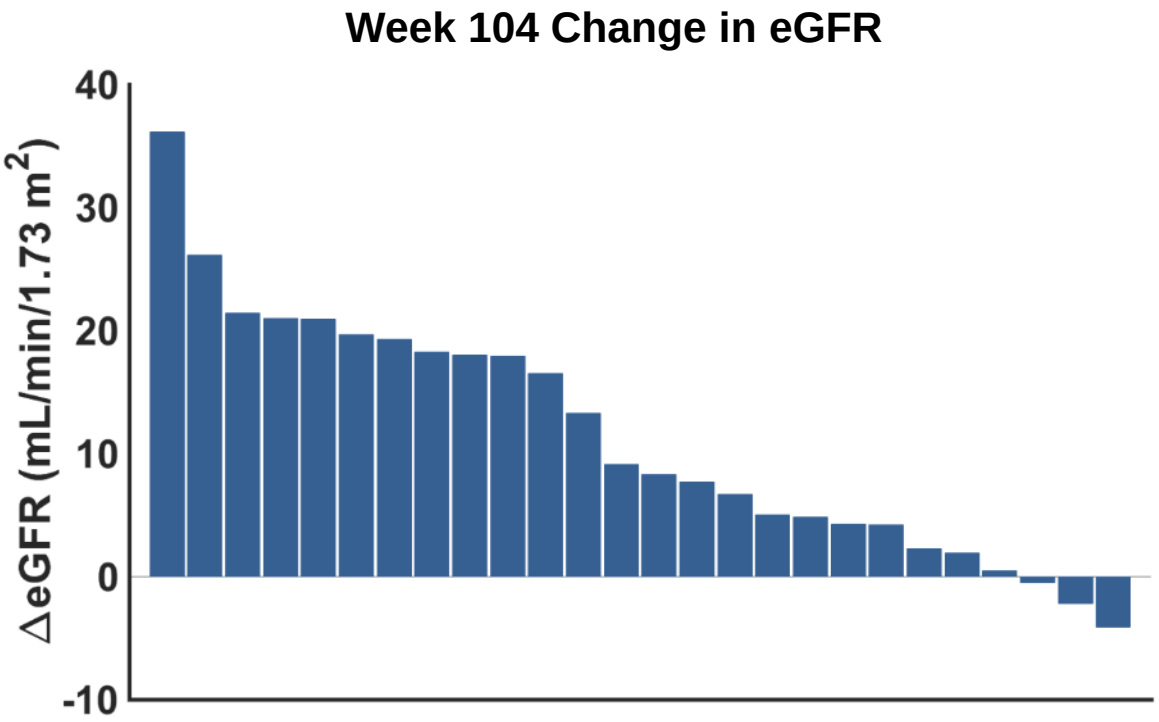


Kidney Function Improvements Durable for Two Years

- After 16-week placebo-controlled period, placebo patients in LARIAT were converted to Bard and followed in a longer-term extension trial
- Patients included in analysis below were those treated for at least one year (n=56)



A High Proportion of Patients Have Durable Increases in eGFR after Two Years of Treatment



LARIAT Safety

- Formal safety monitoring committee met regularly to review unblinded safety data
- Across all 101 PAH patients, the median duration of treatment was 66 weeks
  - No deaths
  - No safety concerns were raised by the safety monitoring committee
- In informal comparisons, patients in LARIAT had a reduced rate of hospitalization and death compared to:
  - Recent PAH outcomes studies
  - The REVEAL registry, which is the largest PAH registry[1]
- Data suggest that improvements in kidney function are not associated with adverse long-term outcomes

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[1]*Burger CD et al., Characterization of first-time hospitalizations in patients with newly diagnosed pulmonary arterial hypertension in the REVEAL registry. Chest. 2014 Nov;146:1263-1273.*

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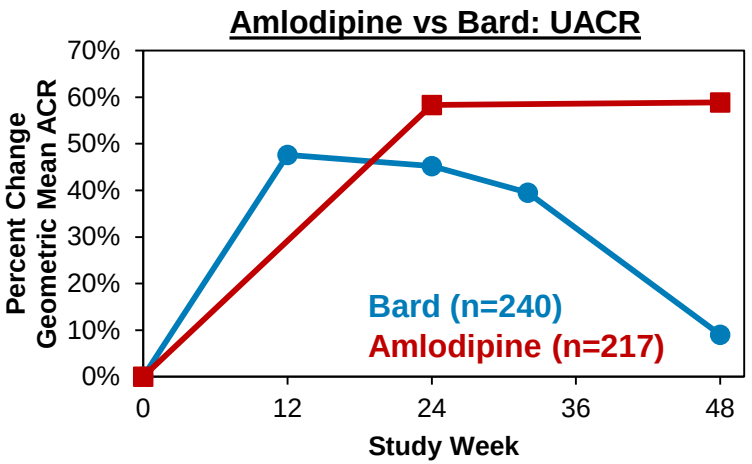
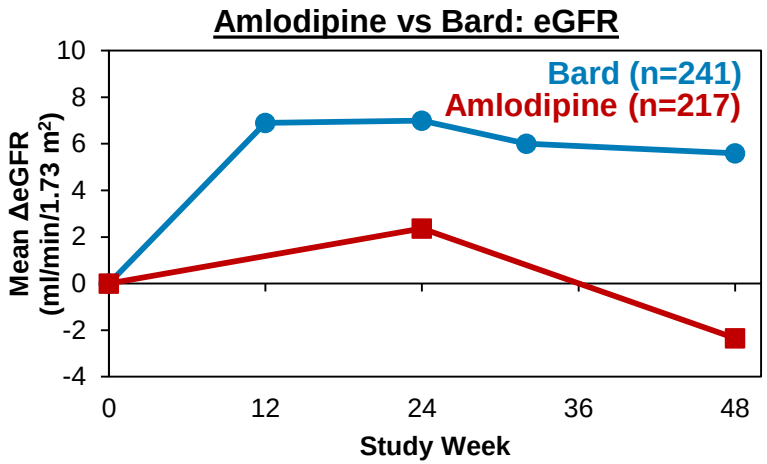
Q&A

Clinical Profile of Bard Distinct from Amlodipine and Hyperfiltration

- Pressure-mediated hyperfiltration due to increased systemic blood pressure or certain calcium channel blockers, like amlodipine, can increase blood pressure in the kidney, causing injury and:
  - Increased rate of eGFR decline after a modest, transitory increase[1-5]
  - Increased proteinuria out of proportion to eGFR increases due to further loss of glomerular integrity
- Bard and close analogs preserve kidney function and reduce fibrosis in multiple preclinical models of hyperfiltration
- Bard's clinical profile is also distinct from primary precedent of hyperfiltration (amlodipine; AASK trial[2,5])





- By contrast, Bard increases in UACR:
  - Are modest and decline over time[6,7]
  - Significantly correlate with eGFR increases[6,7]
  - Return towards baseline 4 weeks after withdrawal of Bard

- Further, Bard eGFR increases:
  - Are large and persist for at least two years
  - Are significantly increased vs. placebo for at least one year
  - Significantly reduce adverse renal events validated to predict kidney failure

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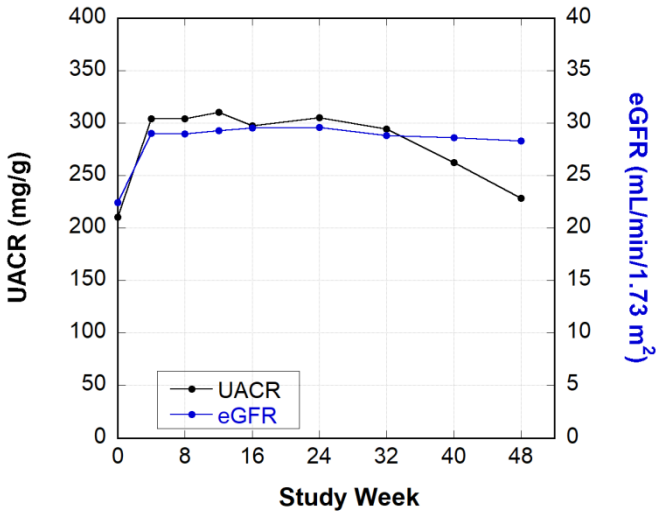
[1]Appel, N Engl J Med (2010); [2]Agodoa, JAMA (2001); [3]Delles, Am J Hypertens (2003); [4]Iñigo, J Am Soc Nephrol (2001); [5]Wright, JAMA (2002); [6]Pergola, N Engl J Med (2011); [7]de Zeeuw, N Engl J Med (2014)

Changes in Albuminuria are a Pharmacological Effect of Bard due to Increased GFR and Profile is Inconsistent with Injury

- Bard works differently than RAAS blockers and has a different effect on albuminuria
- Increased surface area→ GFR increase→ increased filtrate flow→ increased urinary albumin[1]
  - Albuminuria not due to damage to the glomerular filtration barrier
- Bard urinary albumin increases correlate significantly with eGFR increases[2,3]
- After initial increase, albuminuria plateaus and then trends towards baseline
- Large, early increases in albuminuria associated with increases in eGFR on and off drug after 48 weeks of treatment

BEACON Bard ACR and eGFR



eGFR Change at One Year by Quartile of Week 12 UACR Change

Quartile	N	Baseline ACR	Week 12 ACR	Week 12 ACR % Change	Mean eGFR Change ± SD	
					Week 48	4 Weeks Post-Withdrawal
1	59	115	48	-58%	6.4 ± 7.8	1.5 ± 5.9
2	60	216	252	16%	4.4 ± 6.1	0.3 ± 6.3
3	60	194	392	102%	4.0 ± 8.9	0.6 ± 4.5
4	60	56	304	440%	7.8 ± 10.9	1.7 ± 8.4

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[1]*Lazzara, AJP Renal Physiol (2007);* [2]*Rossing, ASN Poster (2012);* [3]*Manuscript in preparation*

Bard Produced Retained eGFR Benefit After Drug Withdrawal Indicating Disease-Modifying Effect

- To determine if a drug's long-term profile is beneficial or harmful to the kidney, FDA has requested sponsors to withdraw study drug after one year of treatment and compare retained eGFR to placebo
  - eGFR less than placebo indicates drug is injurious and may accelerate kidney failure outcomes
  - eGFR no different than placebo indicates a transient, non-disease modifying effect
  - eGFR better than placebo indicates disease-modifying effect that would reduce risk of kidney failure outcomes
- Statistically significant retained increases in eGFR were observed in longer-term diabetic CKD trials of Bard (BEAM and BEACON)
- Week 12 eGFR changes in BEAM and BEACON correlated with changes post-withdrawal

Post-Withdrawal eGFR Benefit in BEAM and BEACON

	Baseline eGFR	Week 12 ΔeGFR	Post-Week 48 Withdrawal ΔeGFR	P-value*	WK12/ Post-Withdrawal Correlation
BEAM (Mid/High Dose)	32	11.4	4.8	p<0.05	r=0.53 (p<0.001)
BEACON	23	6.0	1.8	p<0.001	r=0.43 (p<0.001)

- FDA requested withdrawal endpoint for Otsuka's PKD trial of tolvaptan (REPRISE), which showed a 1.27 ml/min/1.73 m^2 off-treatment improvement versus placebo
- FDA is requiring this withdrawal analysis at one year for accelerated approval and at two years for full approval of Bard in Alport syndrome

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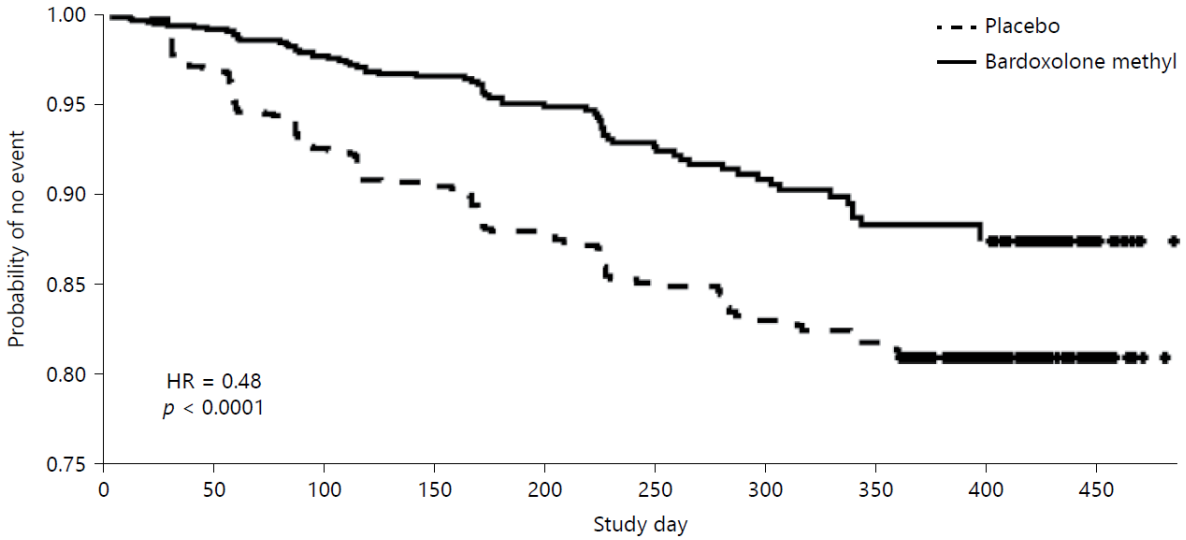
Bard eGFR Increases Associated with Reduced CKD Progression

- Conducted an intent-to-treat analysis of BEACON data using an outcomes composite endpoint that was recently validated by a joint National Kidney Foundation, FDA, and EMA working group
- Bard significantly reduced likelihood of kidney failure outcomes, including composite of adjudicated ESRD, 30% eGFR decline, or eGFR < 15 events (HR=0.48; p<0.0001)

Composite of ESRD, ≥30% eGFR Decline, and eGFR < 15 ml/min/1.73 m^2



- KHK is planning to use a similar endpoint in their Japanese diabetic CKD outcomes trial that they are planning to initiate in 2018

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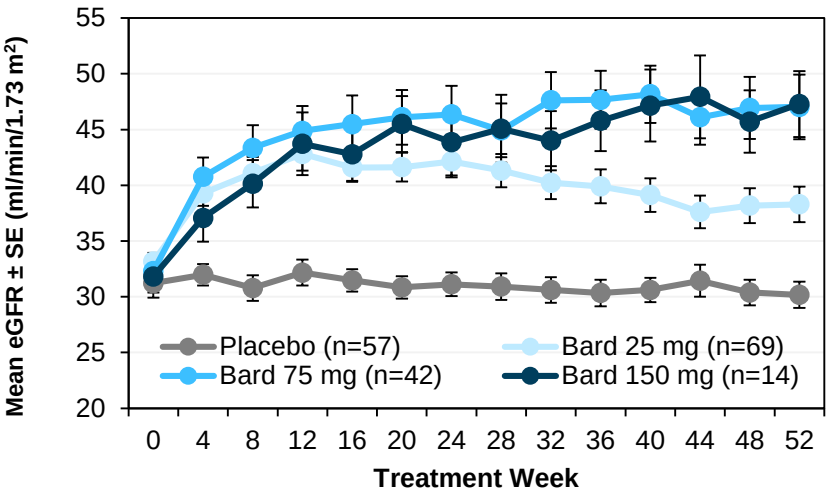
Chin et al, AJN 2018

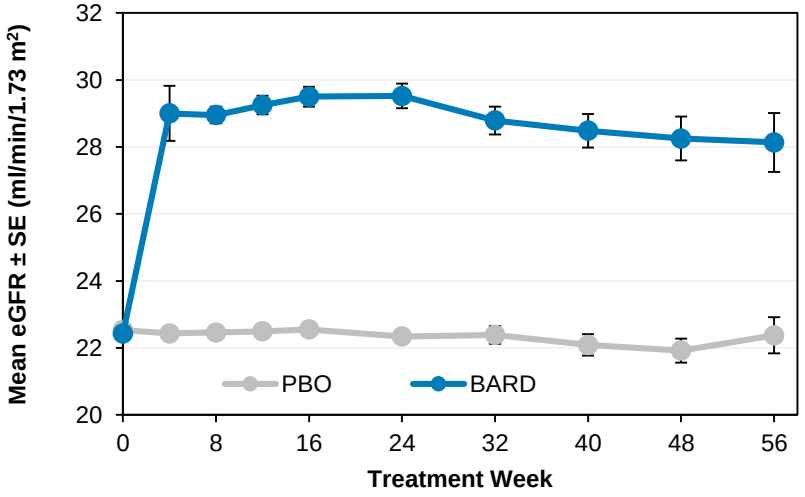
Patients with Chronic Kidney Disease and Type 2 Diabetes Show Durable Renal Function Improvement

- Bard significantly increased eGFR ($p<0.0001$) in BEAM and BEACON
- Change was durable through one year, the longest duration tested
- Changes were associated with fewer renal SAEs and ESRD events

BEAM (Stage 3b/4CKD)



BEACON (Stage 4 CKD)



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Pergola et al., NEJM (2011); De Zeeuw et al., NEJM (2013)