Bardoxolone Methyl Improves Renal Function in Patients with Chronic Kidney Disease and Type 2 Diabetes Mellitus

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Disclosure

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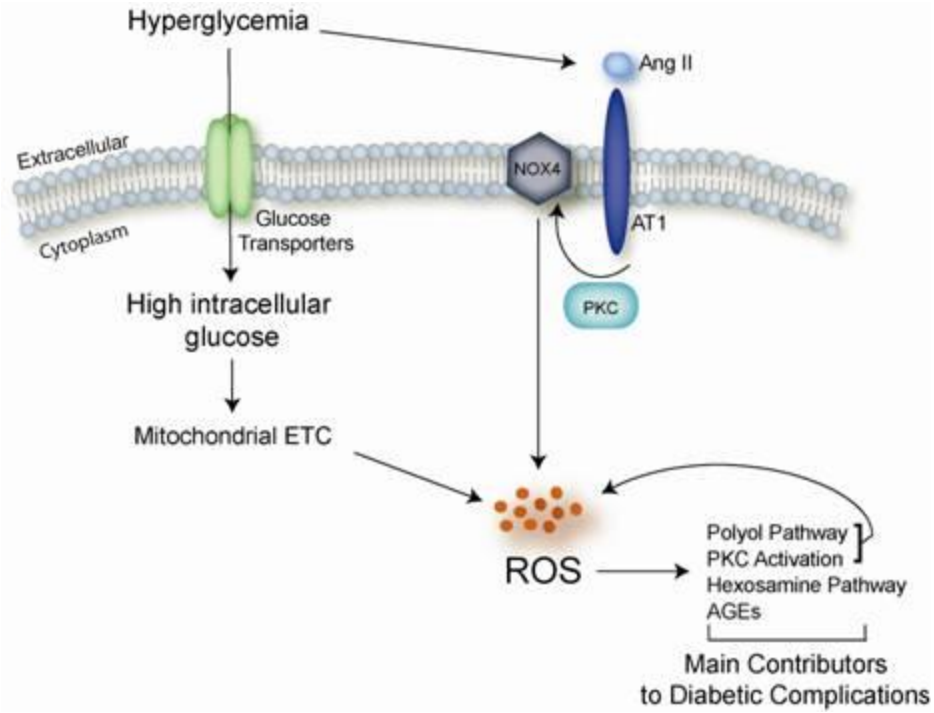
- Speaker's Bureau: Eli Lilly
- Consultant: Biovail, Schering Plough, Eli Lilly and Reata Pharmaceuticals, Inc.

Hyperglyemia increases reactive oxygen species (ROS)

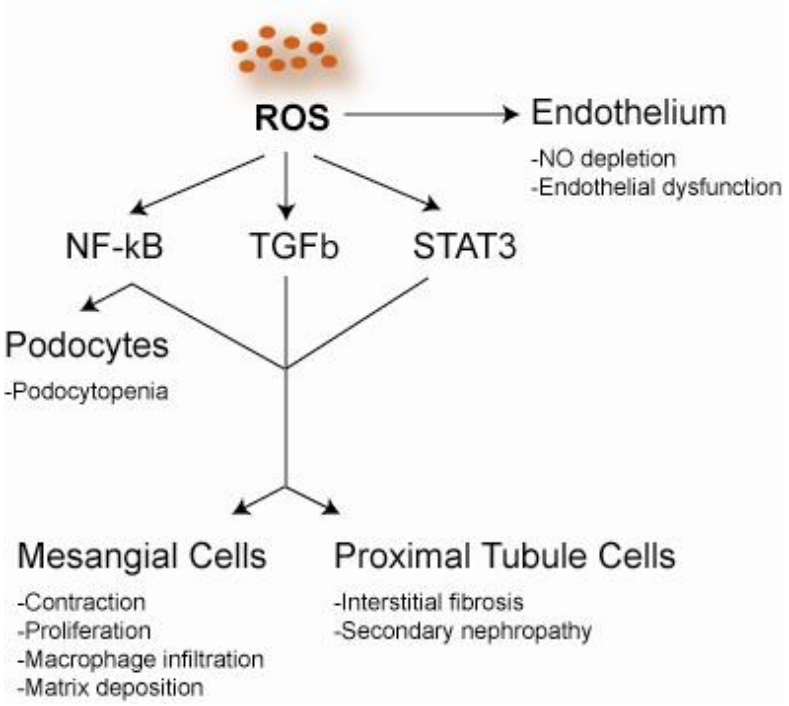
- Hyperglycemia activates pathways that increase ROS
- ROS have been implicated in AGE formation, the Polyol Pathway, and others[1]



[1] Brownlee, Nature (2001)

ROS stimulate inflammatory promoters responsible for renal injury

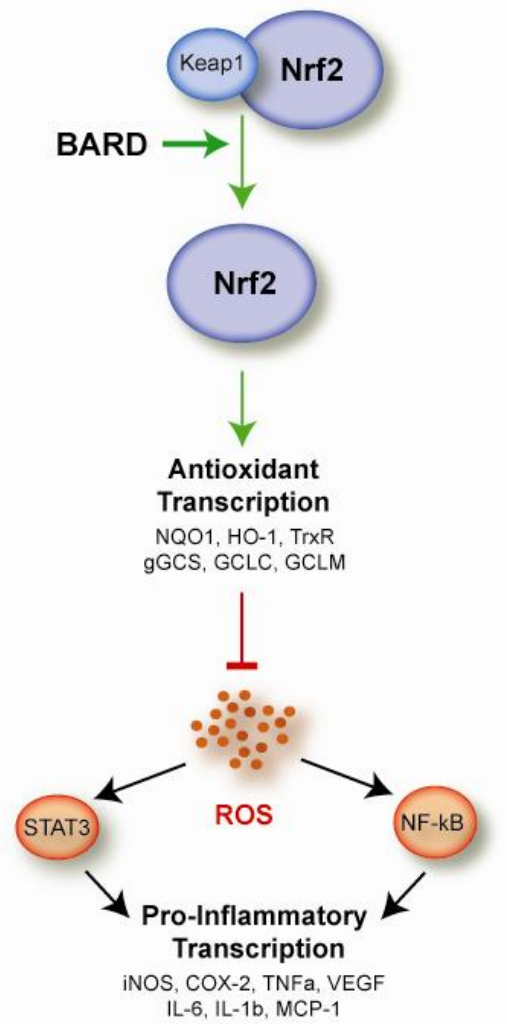
- ROS activate NF-κB, TGF-β, and STAT3
- These pathways are present in renal tissue and activation results in:[1-2]
  - Mesangial cells: contraction, proliferation, inflammatory cell recruitment, ECM-synthesis, and GBM thickening
  - Glomerular endothelial cells: NO depletion and endothelial dysfunction
  - Podocyte and proximal tubule cell injury
- ROS activation correlates with reduced renal function in patients[1,3-4]



[1] Mezzano et al., Nephrol Dial Transplant (2004)
[2] Schmid et al., Diabetes (2006)
[3] Berthier et al., Diabetes (2009)
[4] Arakawa et al., Nephrol Dial Transplant (2008)

Induction of Nrf2 decreases ROS and subsequent renal inflammation and injury

- **Inducing transcription factor Nrf2:**
  - Activates the Phase 2 response and production of over 250 antioxidant and detoxification enzymes
  - Suppresses ROS formation and ROS-driven inflammation[1-2]
- **Bardoxolone methyl (BARD) is the most potent known inducer of Nrf2[3]**
  - Functionally analogous to the endogenous metabolite of PGD2, 15d-PGJ2
  - Previously shown to improve serum creatinine and eGFR in two Phase 1 studies in oncology patients



[1] Kensler et al., Annu Rev Pharmacol Toxicol (2007)
[2] Thimmulappa et al., Biochem Biophys Res Commun (2006)
[3] Dinkova-Kostova et al., PNAS (2005)

Design: Phase 2a study in type 2 diabetics with chronic kidney disease (CKD)

- Entry Criteria:
  - Serum creatinine: 1.5 to 3.0 mg/dl (males) or 1.3 to 3.0 mg/dl (females)
  - Receiving standard of care for diabetes, CKD, CVD
  - Stable doses of medication for hypertension and diabetes required for 6 and 12 weeks, respectively, prior to enrollment
- Treatment:
  - Bardoxolone administered orally, once daily for 28 days
  - 60 patients randomized
    - 20 patients to each of three dose levels: 25mg, 75mg, and 150mg

Study Endpoints and Other Selected Parameters	
Primary Efficacy Endpoint	**Estimated GFR (eGFR; 4-variable MDRD equation)**
Chronic Kidney Disease	Serum Creatinine, Creatinine Clearance, Cystatin C, Phosphorus, Uric Acid, Angiotensin II
Endothelial Dysfunction/ Cardiovascular	Circulating Endothelial Cells
Glycemic Control/Diabetes	Hgb A1c, GDR/Euglycemic Clamp, Fasting Plasma Glucose

Patient Demographics

Baseline Demographics (ITT n=60)	
Mean age, years (range)	62 (37 – 78)
Sex, male	63%
Ethnicity	
Caucasian	35%
Hispanic	57%
African-American	8%
Mean Diabetes Duration, years	19
Neuropathy and/or Retinopathy	70%
Hypertension	98%
Mean Hemoglobin A1c	7.6%
Mean Baseline eGFR (ml/min/1.73m^2)	35.6

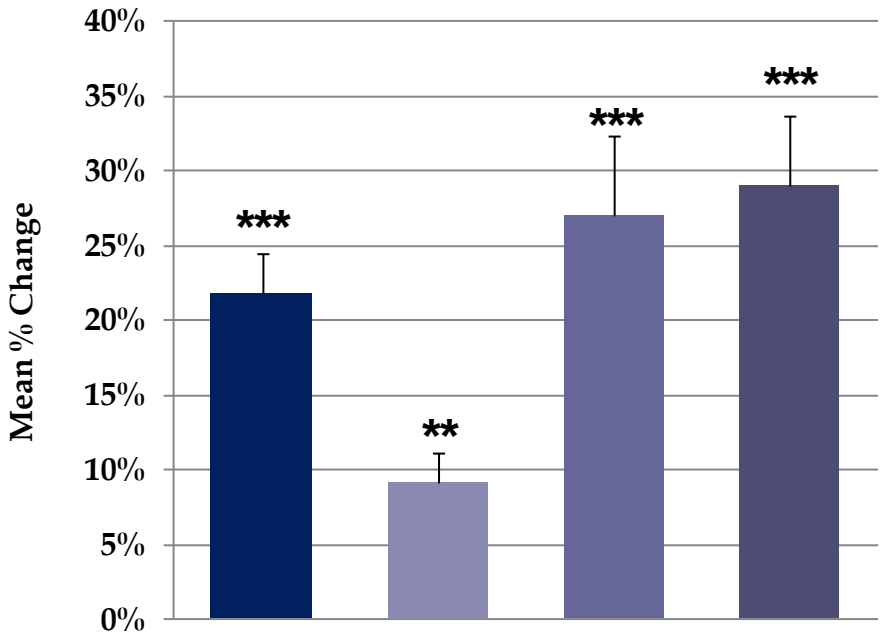
Concomitant Medications

Concomitant Medications (ITT n=60)	
Diabetic medications usage	
Biguanides	3%
Sulfonylureas	25%
GLP-1 analogues	3%
DPP-IV inhibitors	3%
PPAR-γ agonists	15%
Insulin Alone	62%
Insulin and/or other diabetes meds	90%
ACE-inhibitors or ARB usage	
ACE-inhibitors	40%
ARBs	42%
ACE-inhibitor and/or ARB	70%
Calcium Channel Blockers	37%
Statins	83%

Primary endpoint eGFR significantly increases with BARD treatment

- eGFR per MDRD significantly, dose-dependently increased
- 27-29% increase at mid and high dose levels
- 88% response rate
- No weight changes were observed

Change in eGFR

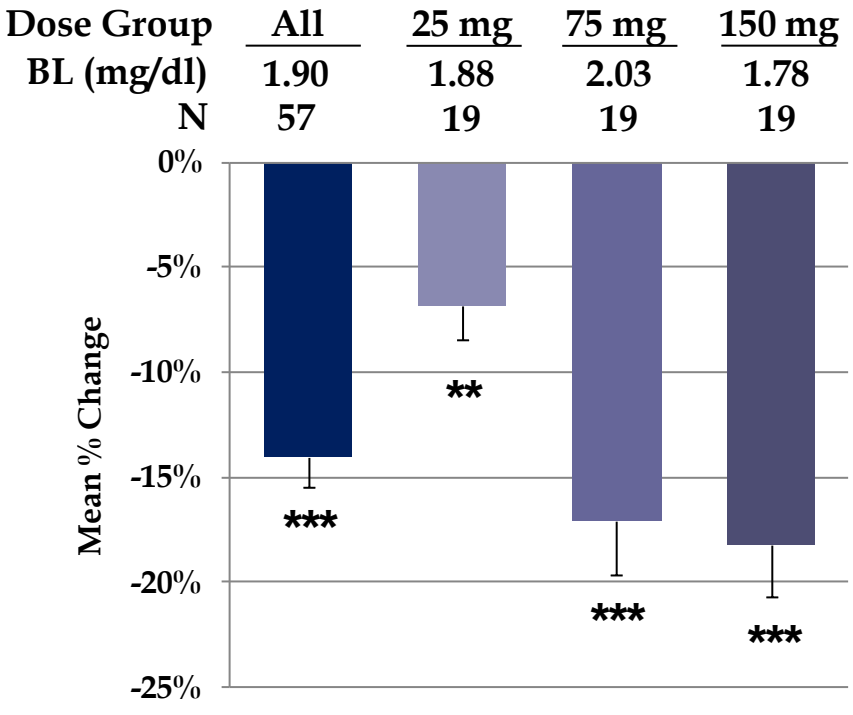


Dose Group	All	25 mg	75 mg	150 mg
BL (ml/min/1.73m^2)	35.6	37.2	32.8	38.9
N	57	19	19	19

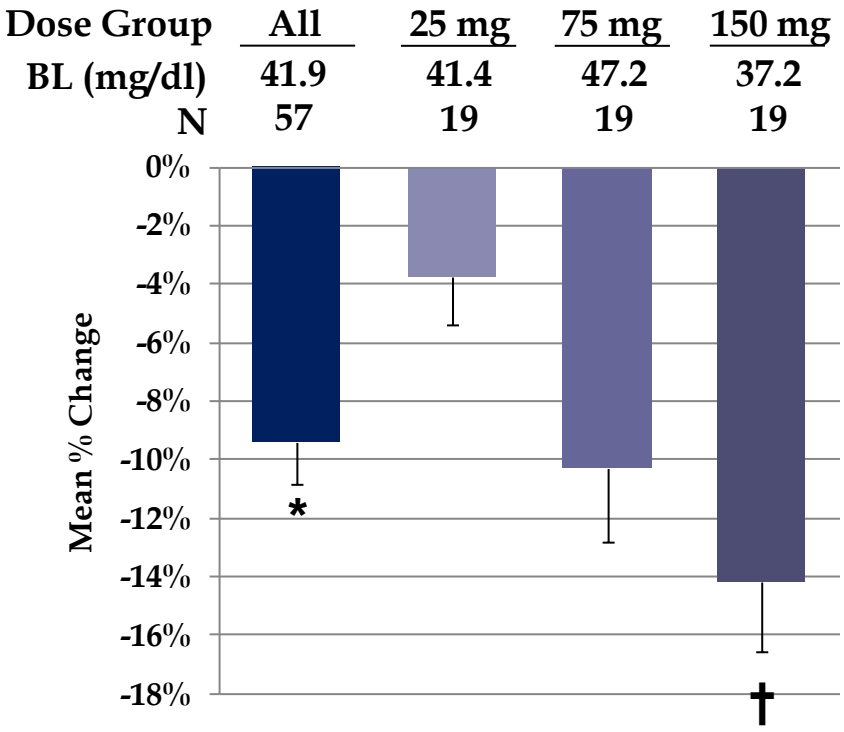
*p<0.01; **p<0.001; ***p<0.0001

Improvements in other markers of renal function consistent with eGFR

Serum Creatinine



BUN



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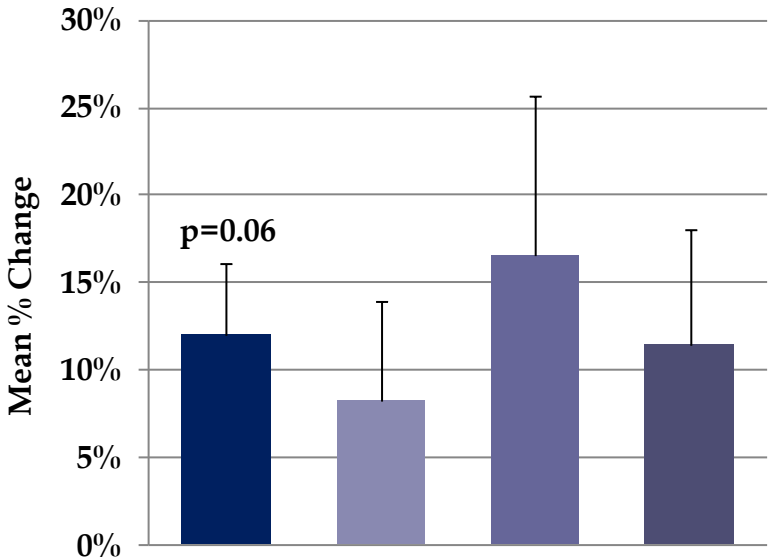
Improvements in other markers of renal function consistent with eGFR

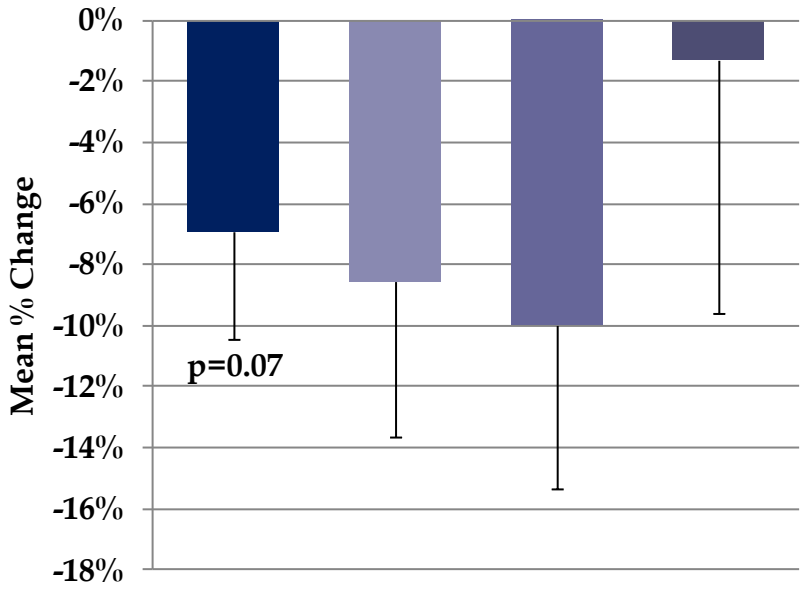
Creatinine Clearance



Dose Group	All	25 mg	75 mg	150 mg
BL (ml/min/1.73m²)	49.7	48.3	49.2	51.6
N	55	19	18	18

Cystatin C

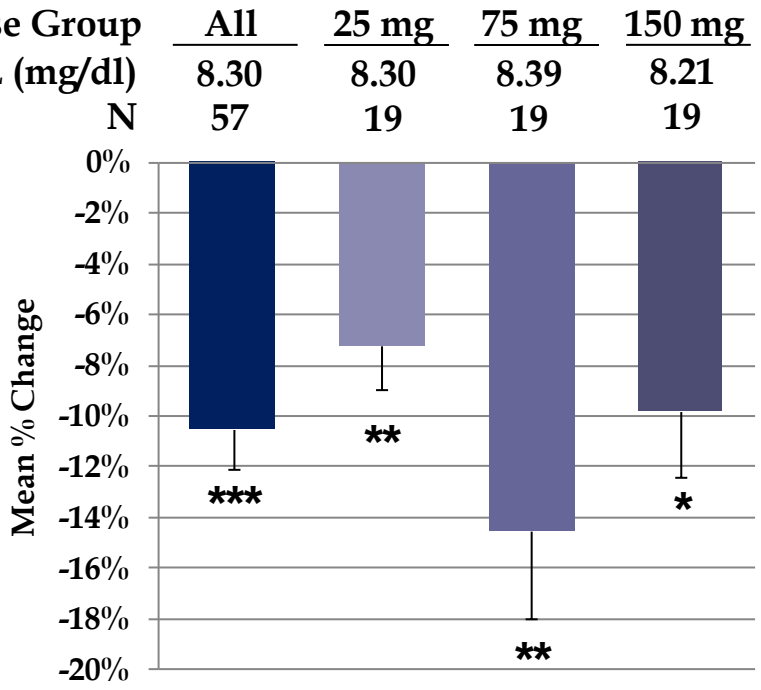
Dose Group	All	25 mg	75 mg	150 mg
BL (mg/l)	1.74	1.71	1.74	1.76
N	23	7	9	7



Improvements in renally-excreted uric acid and phosphorus also observed

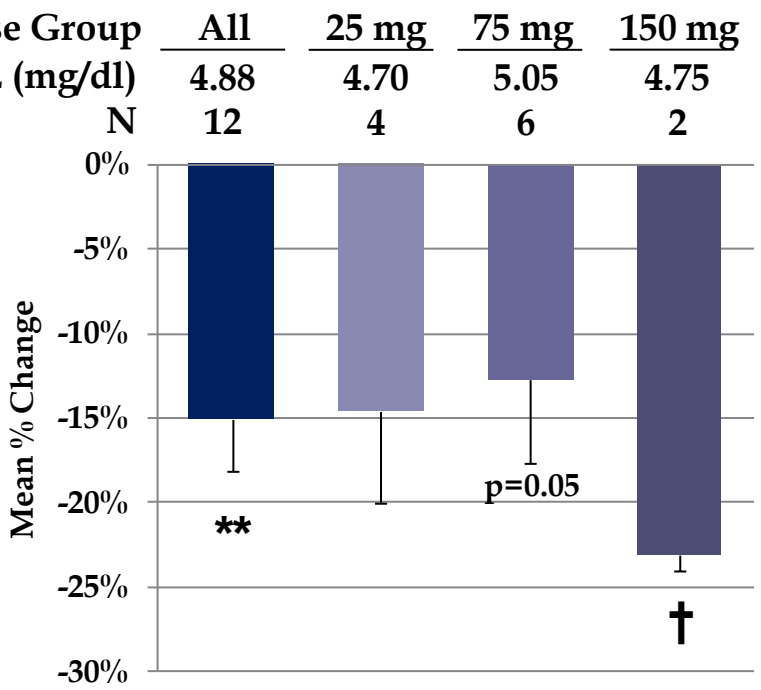
- Phosphorus and uric acid, uremic solutes typically elevated in patients with CKD, both significantly reduced

Serum Uric Acid



Serum Phosphorus

patients with baseline ≥ 4.5 mg/dl



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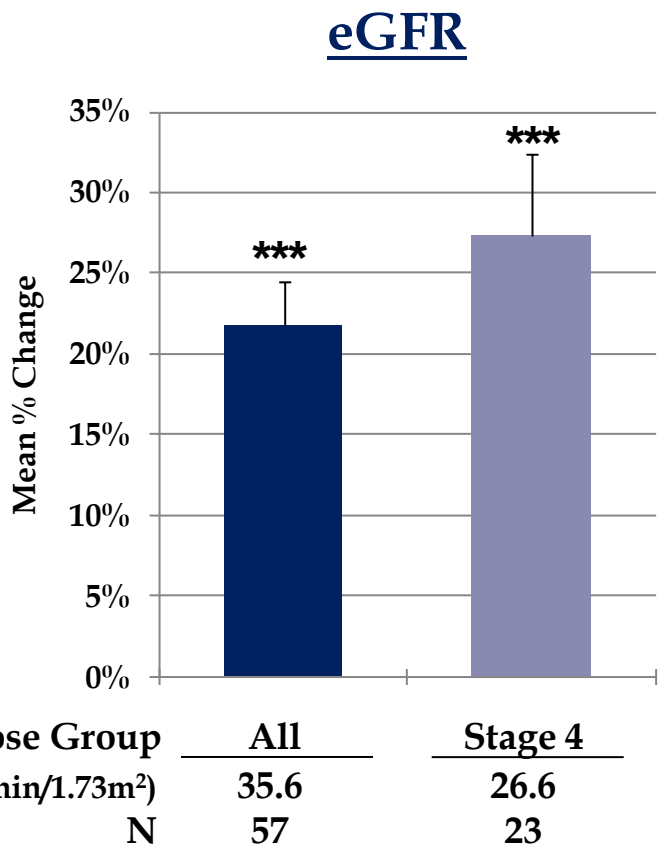
Urinalysis findings

- No changes in markers of injury, NGAL and NAG
- Unable to make reliable inference of treatment effect on ACR
  - Increases prior to dosing with large standard deviations
  - No dose relationship; linear trend contrast p-value equaled 0.99
  - May have been due to in-patient study procedures

Changes in Albumin-to-Creatinine Ratio				
	Pre-treatment		**Post-treatment**	**Change**
	Day -13	**Day -2 or -1**	**Day 27 or 28**	**Day -2 to 27**
25mg (n=15)	696.47 ±839.1	830.26 ±830.26	1289.26 ±1058.94	421.96 ±401.68
75mg (n=18)	1074.09 ±1839.05	1218.24 ±2012.1	1585.02 ±2414.56	326.14 ±556.5
150 mg (n=16)	1368.13 ±2019.24	1404.98 ±2031.51	1939.85 ±2546.67	406.57 ±796.39

Stage 4 patients experienced greater improvements on BARD

- 42% of ITT patients had at least one screening or baseline value for eGFR falling below 30 ml/min/1.73m^2
- 91% response rate
- eGFR increase of approximately 7 ml/min/1.73m^2 in all Stage 4 patients



All patients Stage 4 patients

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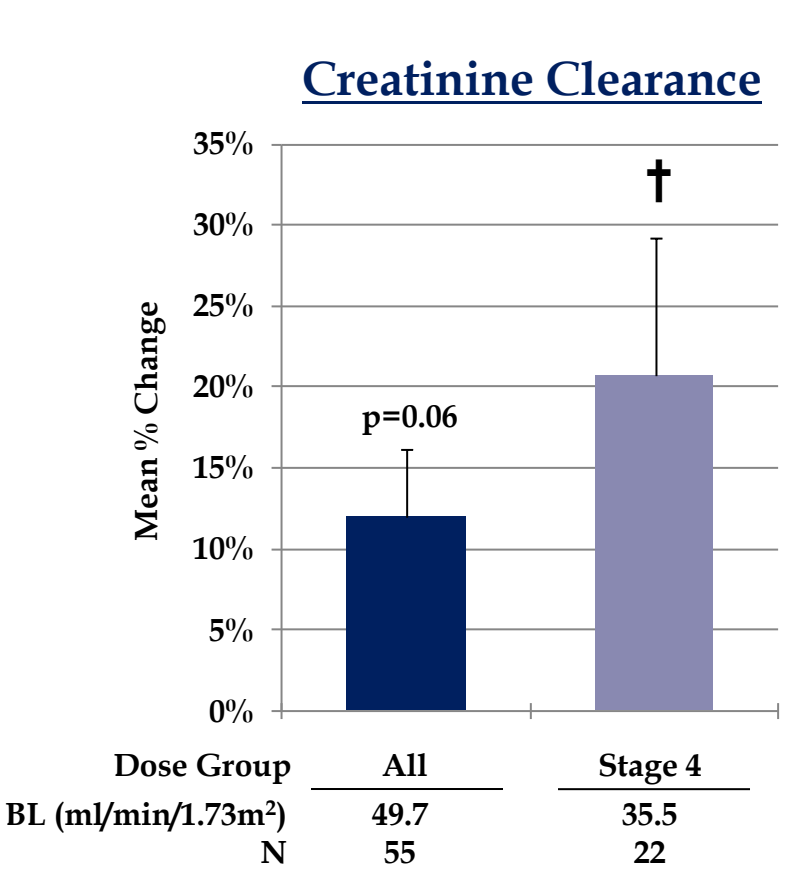

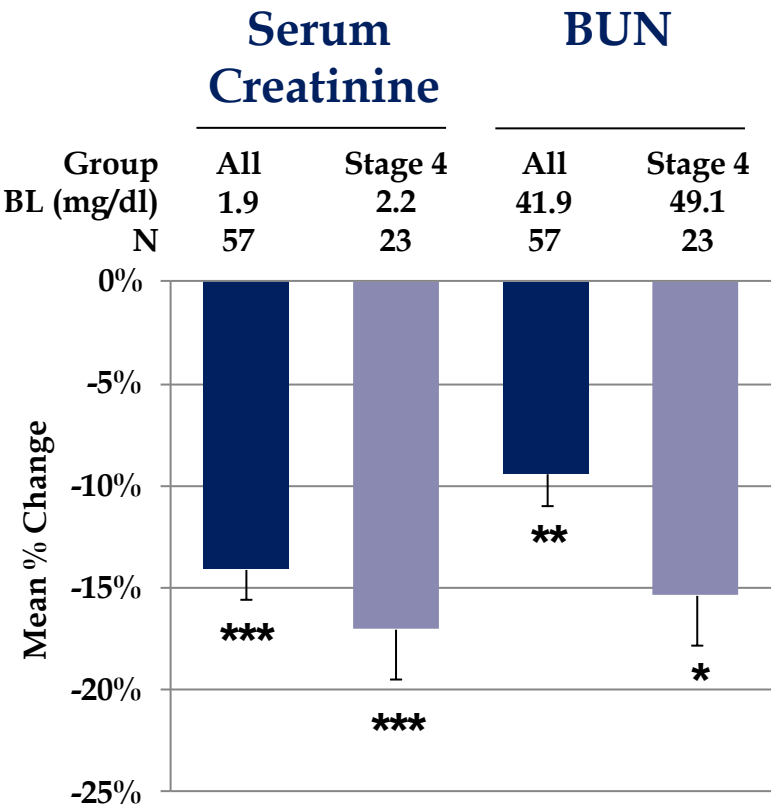

All patients Stage 4 patients

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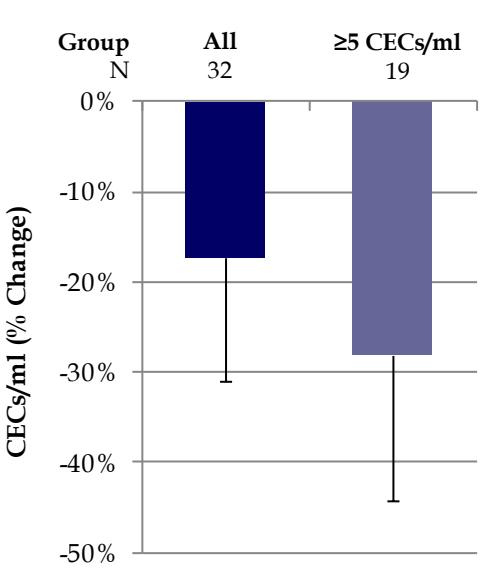
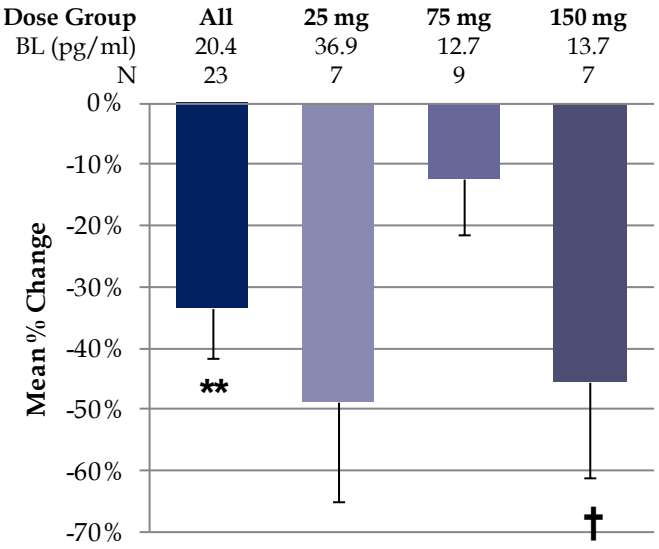
Improvements also seen in CV markers

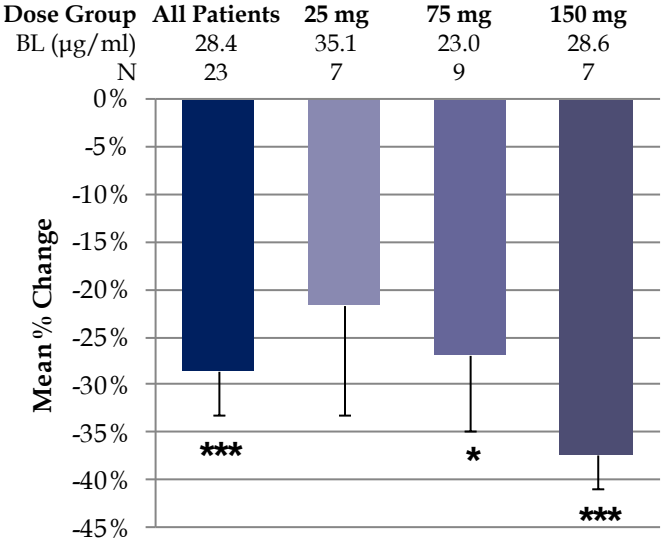
CECs



Angiotensin II



Adiponectin



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Safety

- Generally low frequency of AEs regardless of relationship to BARD
  - Mostly mild severity and consistent with standard symptoms in patients with history of diabetes and chronic kidney disease
  - No apparent dose relationships were observed
  - Occurring in ≥ 10% patients: headache, muscle spasms, dizziness, diarrhea, constipation, and nausea
  - Hypoglycemia detected chemically, but no patients reported hypoglycemic symptoms
- 8 Adverse Events (AEs) attributed to BARD
  - 4/60 (4.6%) patients experienced AEs assessed as possibly or probably related: mild muscle spasms (1), moderate decreased appetite (1), severe increased ALT (1), severe increased AST (1), severe increased ALP (1), and mild hypoglycemia (asymptomatic) (3)
- SAEs: Total of 6, none considered related to study drug:
  - Gastritis/esophagitis, Cellulitis of diabetic foot ulcer, Pancreatitis, Gout, Acute coronary syndrome/Contrast-induced acute renal failure, Acute chest pain

Summary and Conclusions

- This Phase 2 study indicates a beneficial effect of BARD on renal function.
  - BARD significantly improved renal function, as measured by MDRD eGFR
  - Consistent improvements in creatinine clearance, cystatin C, BUN, uric acid, and phosphorus
  - Effects were more pronounced in patients with more severe kidney impairment.
  - Effect on protein excretion are unclear and will need further study.
  - CV markers (CECs, AII and adiponectin) improved as well.
- BARD was well tolerated.
- Further studies that are placebo-controlled and of longer duration are warranted to further profile these effects.
- A 12-month Phase 2b study is underway.

Acknowledgements

Thanks to our patients!

Dr. Pergola's Research Team

Cetero Research

The Sponsor