

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

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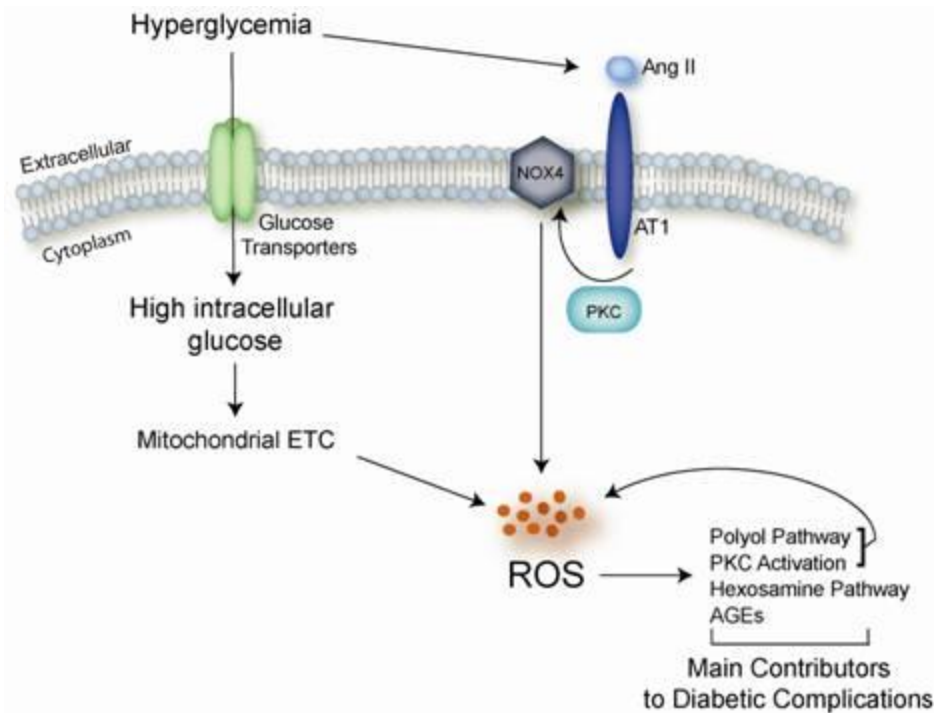
# Disclosure

Within the past 12 months, Dr. Schwartz has received support from the following companies:

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

# Hyperglycemia increases reactive oxygen species (ROS)

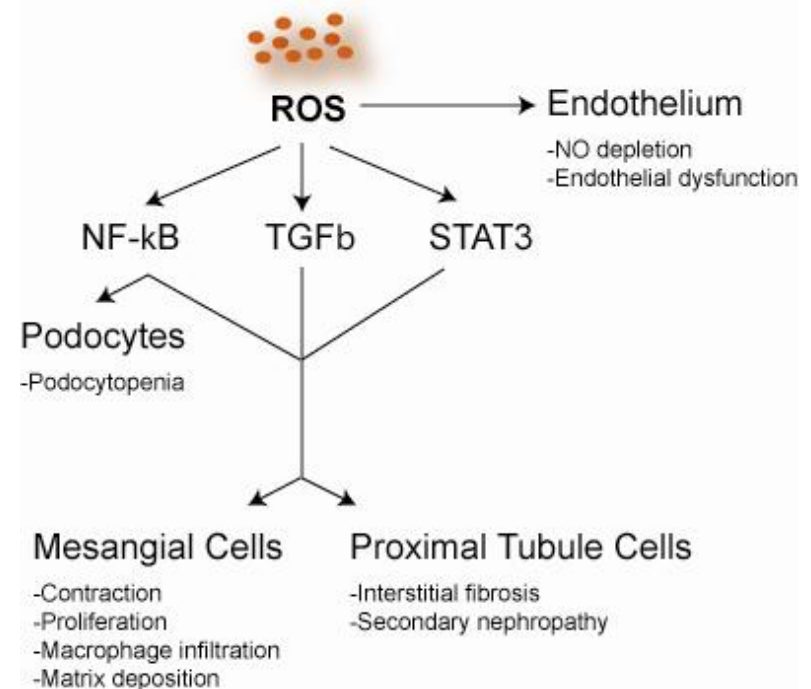
- Hyperglycemia activates pathways that increase ROS
- ROS have been implicated in AGE formation, the Polyol Pathway, and others<sup>1</sup>



<sup>1</sup> Brownlee, Nature (2001)

# ROS stimulate inflammatory promoters responsible for renal injury

- ROS activate NF- $\kappa$ B, TGF- $\beta$ , and STAT3
- These pathways are present in renal tissue and activation results in:<sup>1-2</sup>
  - 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<sup>1,3-4</sup>



<sup>1</sup> Mezzano et al., Nephrol Dial Transplant (2004)

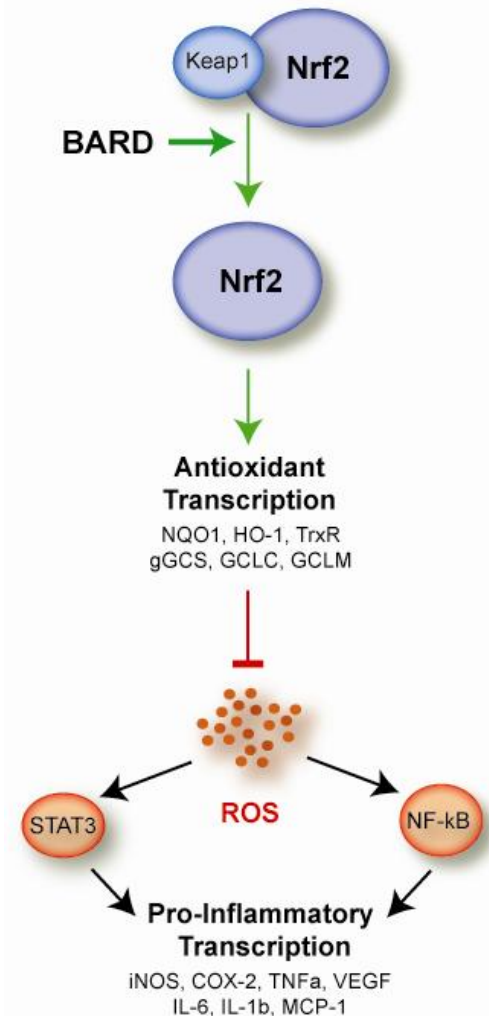
<sup>2</sup> Schmid et al., Diabetes (2006)

<sup>3</sup> Berthier et al., Diabetes (2009)

<sup>4</sup> 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<sup>1-2</sup>
- **Bardoxolone methyl (BARD) is the most potent known inducer of Nrf2<sup>3</sup>**
  - 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



<sup>1</sup> Kensler et al., Annu Rev Pharmacol Toxicol (2007)

<sup>2</sup> Thimmulappa et al., Biochem Biophys Res Commun (2006)

<sup>3</sup> 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	
<b>Primary Efficacy Endpoint</b>	<b>Estimated GFR (eGFR; 4-variable MDRD equation)</b>
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 <sup>2</sup> )	35.6

# Concomitant Medications

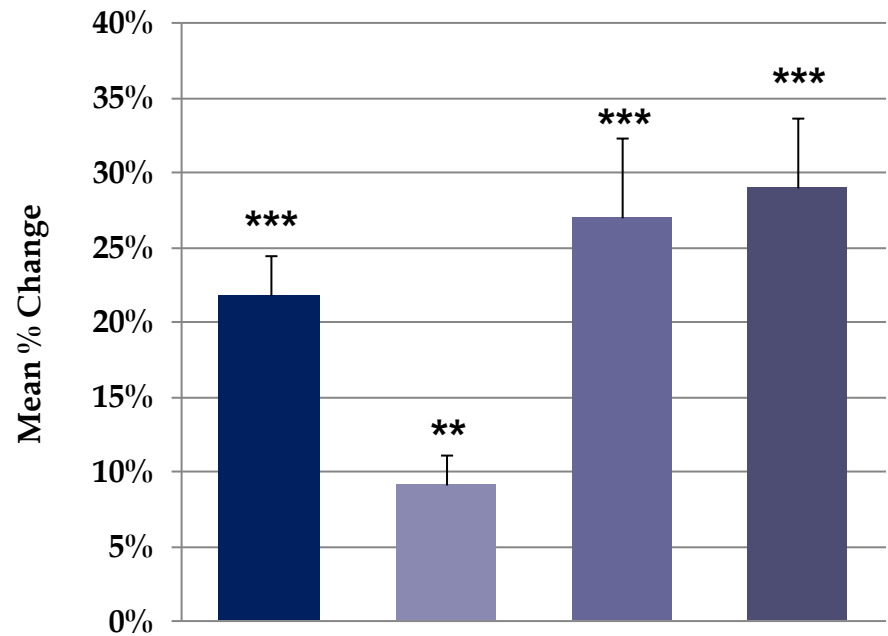
Concomitant Medications (ITT n=60)	
<b>Diabetic medications usage</b>	
Biguanides	3%
Sulfonylureas	25%
GLP-1 analogues	3%
DPP-IV inhibitors	3%
PPAR- $\gamma$ agonists	15%
Insulin Alone	62%
Insulin and/or other diabetes meds	90%
<b>ACE-inhibitors or ARB usage</b>	
ACE-inhibitors	40%
ARBs	42%
ACE-inhibitor 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

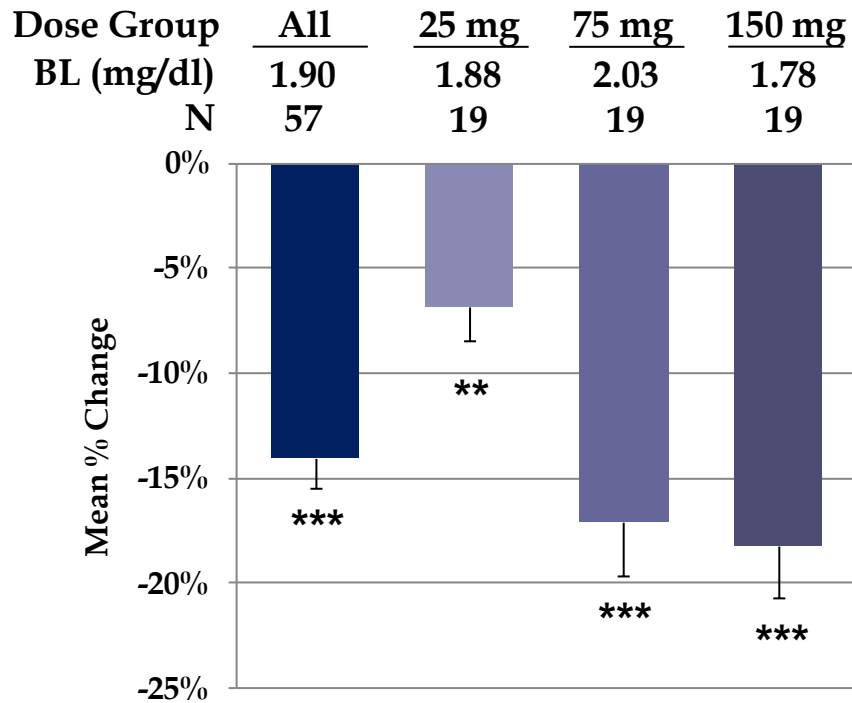
## Change in eGFR



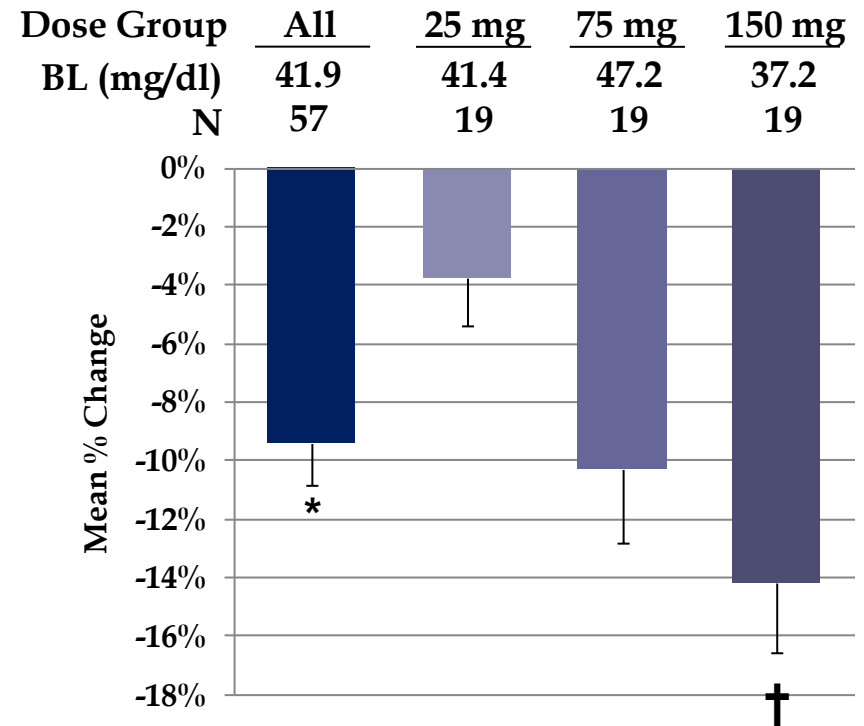
Dose Group	All	25 mg	75 mg	150 mg
BL (ml/min/1.73m <sup>2</sup> )	35.6	37.2	32.8	38.9
N	57	19	19	19

# Improvements in other markers of renal function consistent with eGFR

## Serum Creatinine



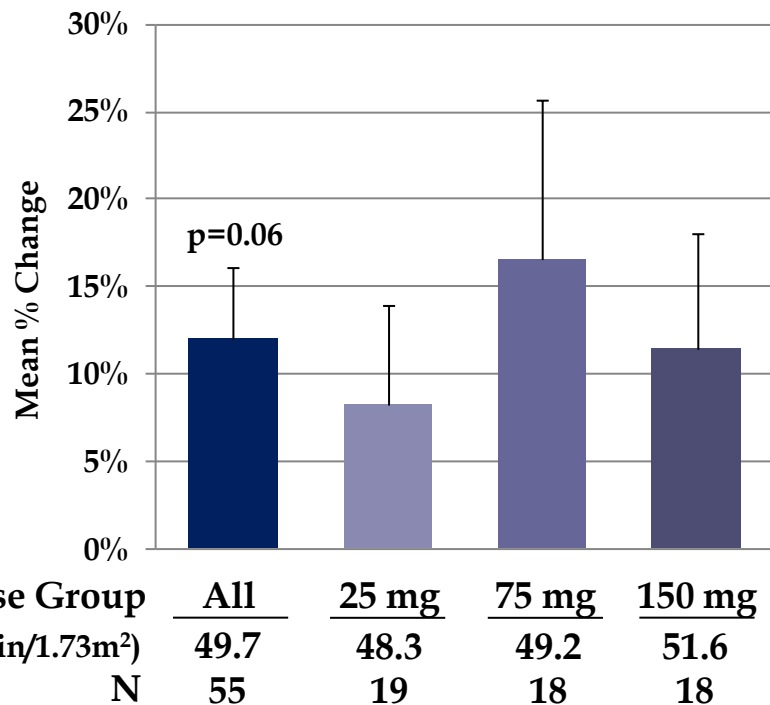
## BUN



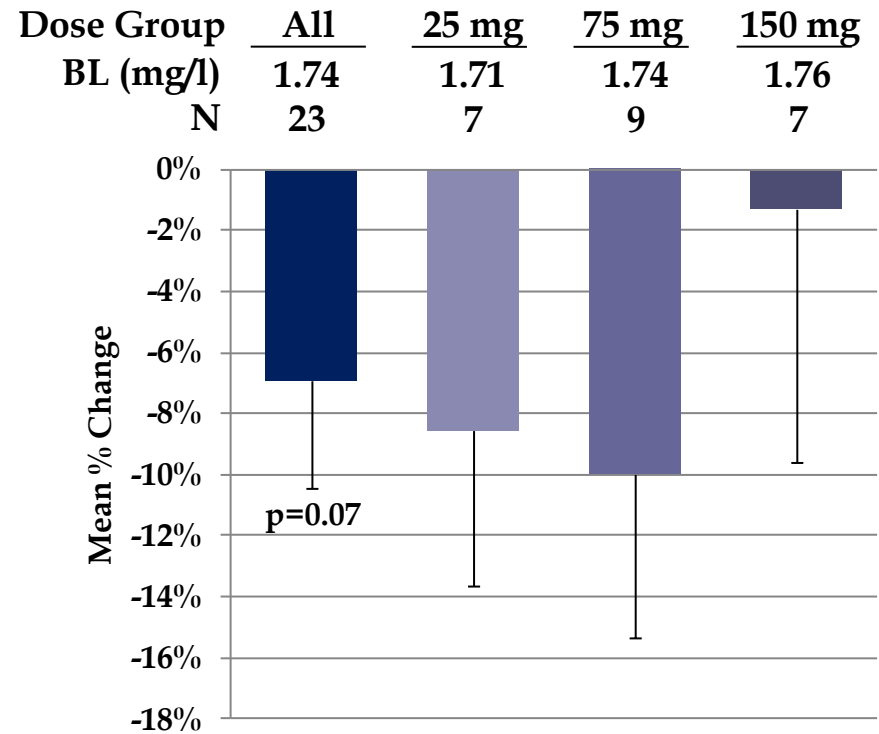
†p<0.05; \*p<0.01; \*\*p<0.001; \*\*\*p<0.0001

# Improvements in other markers of renal function consistent with eGFR

## Creatinine Clearance



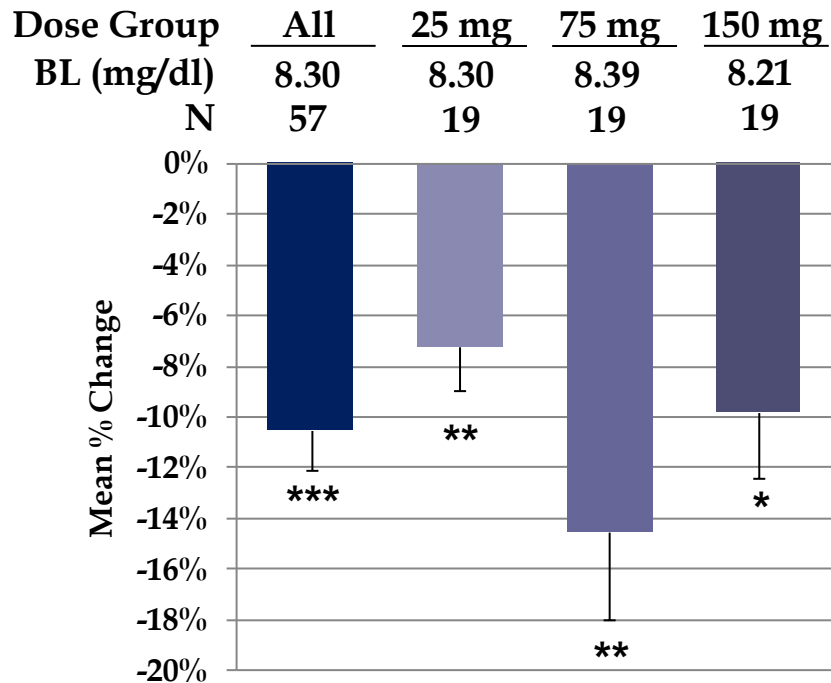
## Cystatin C



# Improvements in renally-excreted uric acid and phosphorus also observed

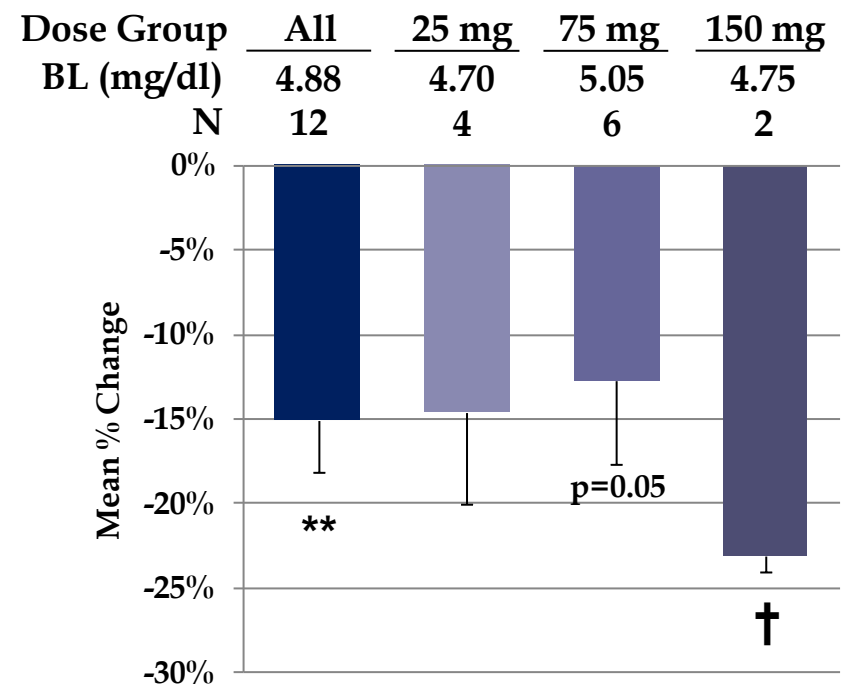
- Phosphorus and uric acid, uremic solutes typically elevated in patients with CKD, both significantly reduced

## Serum Uric Acid



## Serum Phosphorus

patients with baseline  $\geq 4.5$  mg/dl



†p<0.05; \*p<0.01; \*\*p<0.001; \*\*\*p<0.0001

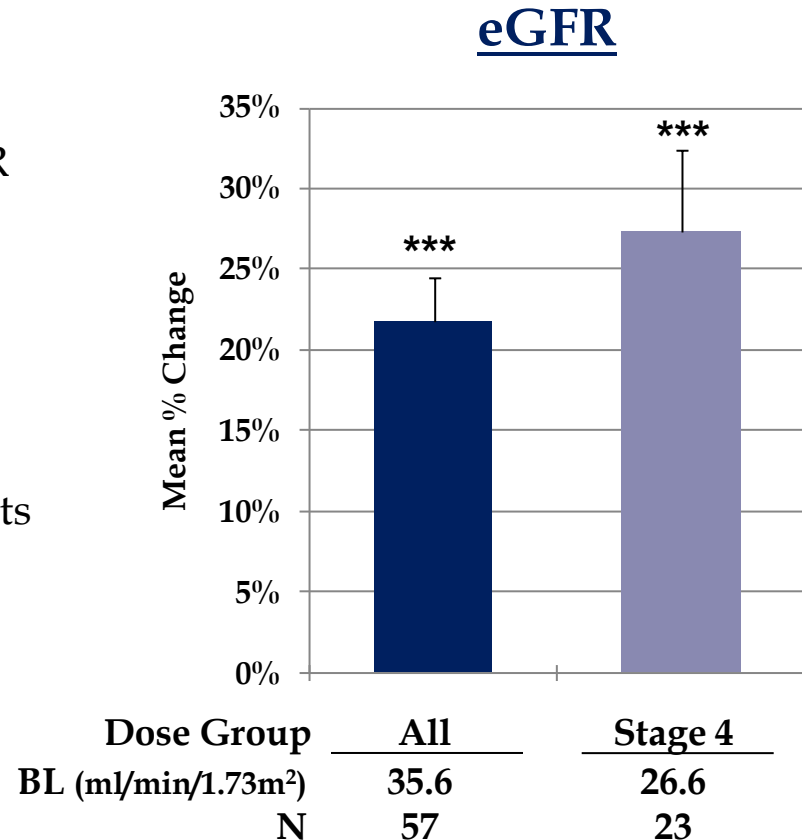
# Urinalysis findings

- 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

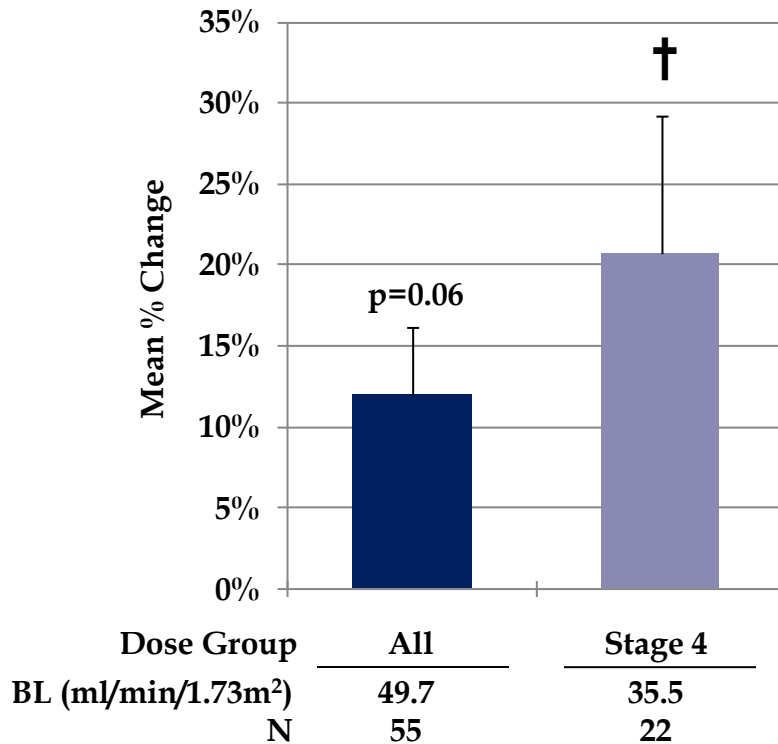
# Stage 4 patients experienced greater improvements on BARD

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



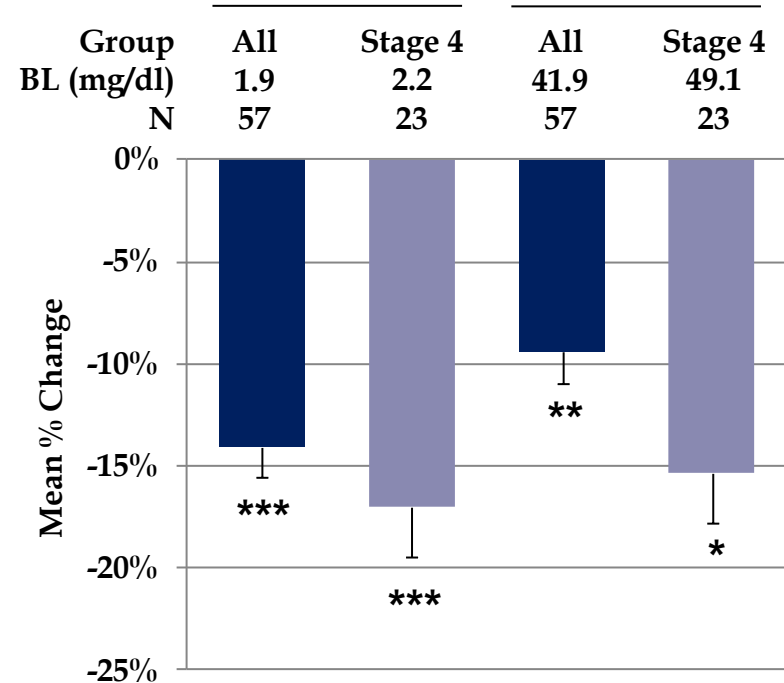
# Stage 4 patients experienced greater improvements on BARD

## Creatinine Clearance



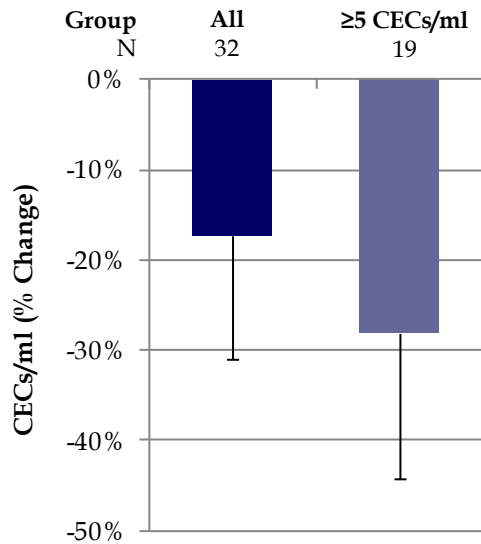
## Serum Creatinine

## BUN

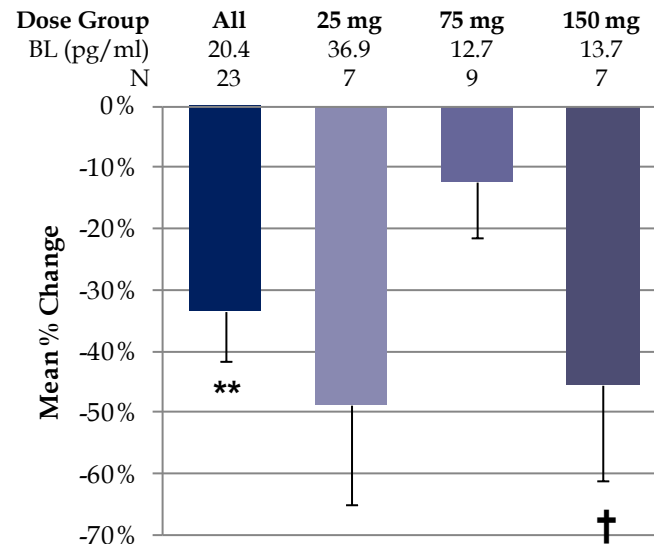


# Improvements also seen in CV markers

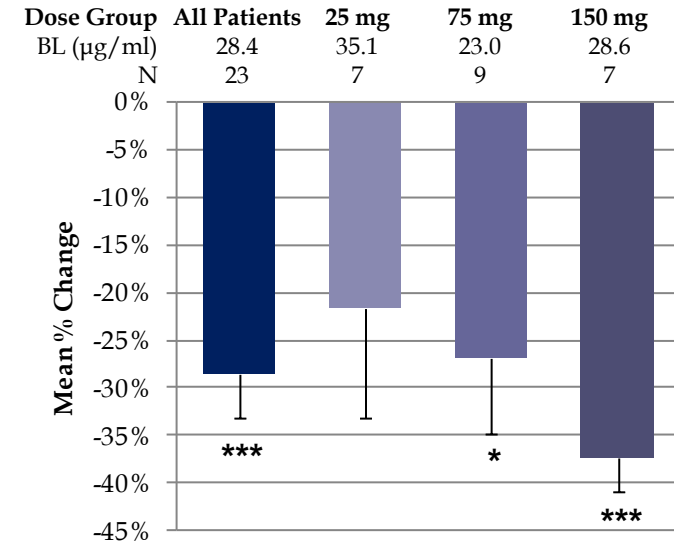
## CECs



## Angiotensin II



## Adiponectin



†p<0.05; \*p<0.01; \*\*p<0.001; \*\*\*p<0.0001



# 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  $\geq 10\%$  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

