Investigation of Serious Adverse Events in Bardoxolone Methyl Patients in BEACON

Colin Meyer[1], George Bakris[2], Melanie Chin[1], Dick de Zeeuw[3], Angie Goldsberry[1], Peter Linde[4], Peter A. McCullough[5], John McMurray[6], Megan O'Grady[1], David Packham[7], Scott Reisman[1], Nosratola Vaziri[8], David G. Warnock[9]

1. Reata Pharmaceuticals, Irving, TX, USA
2. The University of Chicago Medicine, Chicago, IL, USA
3. Department of Clinical Pharmacology, University of Groningen University Medical Center, Groningen, The Netherlands,
4. AbbVie, North Chicago, IL, USA
5. Baylor University Medical Center, Dallas, TX, Baylor Heart and Vascular Institute, Baylor Jack and Jane Hamilton Heart and Vascular Hospital, The Heart Hospital, Plano, TX, USA
6. BHF Cardiovascular Research Centre, University of Glasgow, Glasgow, UK
7. Melbourne Renal Research Group and Department of Nephrology, Royal Melbourne Hospital and Medicine, University of Melbourne, Melbourne, Australia
8. University of California, Irvine, CA, USA
9. Department of Medicine, University of Alabama at Birmingham, Birmingham, AL, USA

BEACON Study Rationale

- Bardoxolone methyl (BARD) and analogs activate the antioxidative Nrf2 pathway and suppress NF-κB
  - 250+ publications of BARD and analogs show activity in numerous animal models, including kidney disease and diabetes
  - In several phase 2 clinical trials, bardoxolone methyl improved markers of renal function, including serum creatinine, creatinine clearance, BUN, and uric acid
- These data plus regulatory guidance informed the design and initiation of BEACON
  - Regulatory agencies required a primary endpoint that included only ESRD and CV death
  - Did not allow other renal endpoints (i.e. serum creatinine or eGFR change) as part of primary endpoint
  - Since stage 3 CKD patients have low near-term risk for ESRD and death, study was limited to stage 4 CKD patients
  - Enrolled 2185 patients with type 2 diabetes and stage 4 CKD to receive BARD (20 mg) or placebo

Selected Preclinical Studies

Model	Citation
Inulin clearance	Ding et al., Kidney Int (2013)
Endothelial dysfunction	Aminzadeh et al., Redox Biol (2013)
Protein overload	Zoja et al., ASN (2010)
Megalin suppression	Reisman et al., J Am Soc Nephrol (2012)
5/6 Nephrectomy	Aminzadeh et al., Xenobiotica (2013)
Diabetes (HFD and Lepr$^{db/db}$)	Saha et al., J Biol Chem (2010)
Diabetes-associated atherosclerosis (Apo E$^{-/-}$)	Tan et al., Diabetes (2014)
Type II diabetes/obesity (ZDF)	Chin et al., AJP Renal Physiol (2014)
FeNTA-Induced AKI	Tanaka et al., Tox Appl Pharmacol (2008)
Cisplatin-Induced AKI	Aleksunes et al., JPET (2010)
Ischemic AKI	Wu et al., AJP Renal Physiol (2011)

Clinical Studies

Study	N	Study Population	Dosage	Treatment Duration
Phase 2a dose-ranging	60	Stage 3/4 CKD and T2DM	25/75/150 mg (crystalline)	4 weeks
Phase 2a dose-titration	20	Stage 3/4 CKD and T2DM	25/75 mg (crystalline)	8 weeks
BEAM	227	Stage 3b/4 CKD and T2DM	PBO/25/75/150 mg (crystalline)	52 weeks
Cross-over PK study	19	Healthy Subjects	150 mg (crystalline)/ 20 mg (amorphous SDD)	Single dose
Phase 2 dose-ranging	131	Stage 3b/4 CKD and T2DM	2.5/5/15/30 mg (amorphous SDD)	12 weeks

BEACON was Terminated Due to an Increase in Heart Failure and Other SAEs

- At termination, the data monitoring committee and other reviewers did not know:
  - Final distribution of adjudicated events, since many events were in the process of being adjudicated
  - Clinical presentation, onset, and etiology of heart failure (HF)
  - If HF would worsen, possibly increasing the mortality imbalance
  - Relationship to other events in composite safety endpoint
  - BNP levels, which were collected at baseline and every 6 months
  - If exclusion criteria could be applied to identify at-risk patients
  - If BARD was producing any clinical benefit

	Final DSMB Meeting	
	PBO (n = 1097)	BARD (n = 1088)
SAEs		
Cardiac disorders	61 (6%)	105 (10%)
Events		
Adjudicated HF	27 (8%)	47 (11%)
Adjudicated HF/MI/CVA	39 (4%)	61 (6%)
All-Cause Mortality	23 (2%)	34 (3%)

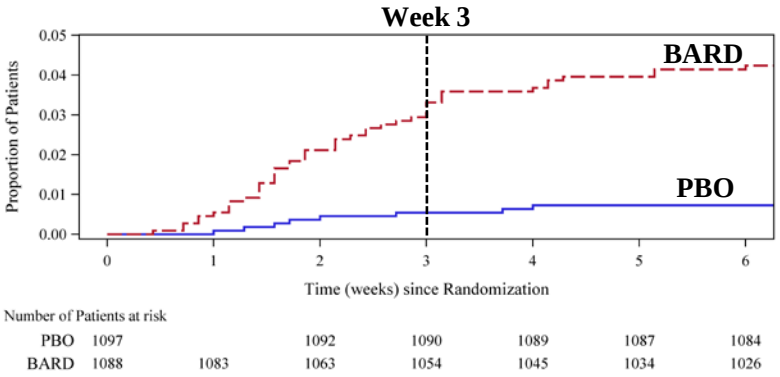
Adjudicated Data as of Final Data Monitoring Committee Meeting (8 Oct 2012)

What Did the Final Data Tell Us about the SAE Imbalances?

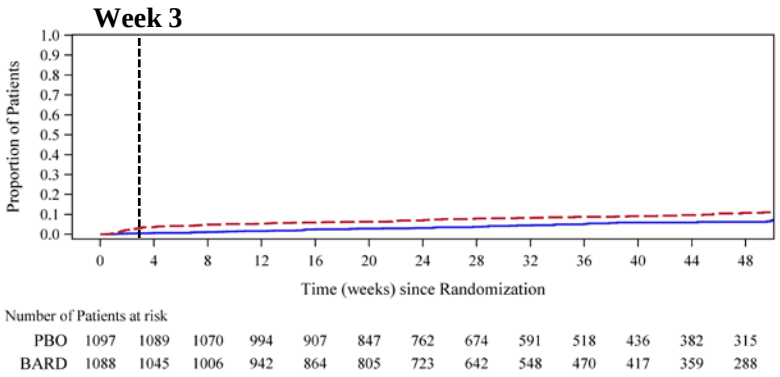
- Adjudicated data show primary imbalance was HF hospitalizations
- Clinical phenotype of HF suggests acute fluid retention
  - Rapid weight gain, dyspnea, central edema, and increased BP
  - Renal function unchanged relative to baseline
- Increase in HF risk only during first three weeks
- Effect was unlikely due to generalized cardiotoxicity
  - Preserved LVEF on ECHO at time of hospitalization
  - Events did not worsen over time
  - Thorough QT Study: no increase in BP or QT interval at 80 mg

	Final Data	
	PBO (n = 1097)	BARD (n = 1088)
SAEs		
Cardiac disorders	84 (8%)	124 (11%)
Adjudicated Events		
HF	55 (5%)	96 (9%)
Hospitalization	55 (5%)	93 (9%)
Death	0	3 (<1%)
HF/MI/CVA/CV Death	86 (8%)	139 (13%)
All-Cause Mortality	31 (3%)	44 (4%)

Heart Failure Through Week 6



Heart Failure Through Week 48

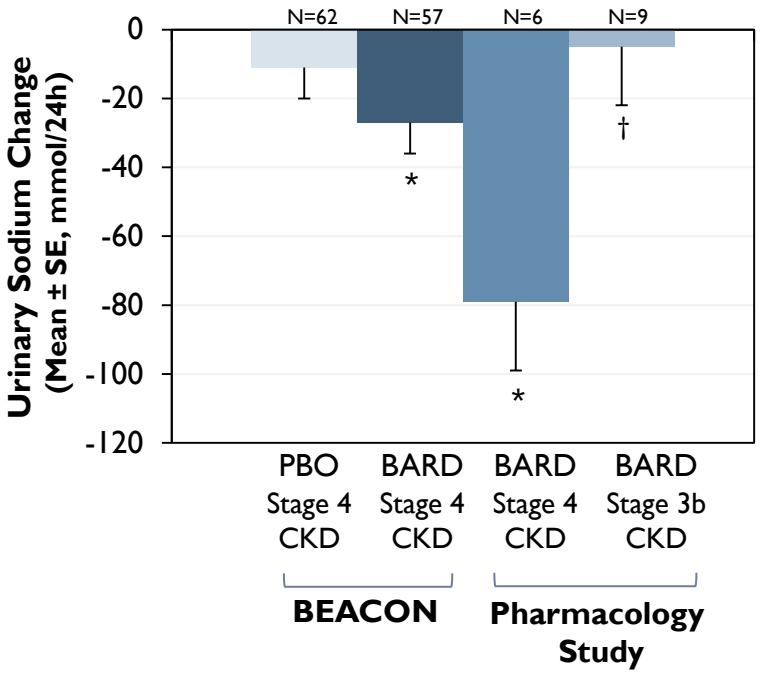


de Zeeuw et al., NEJM (2014)

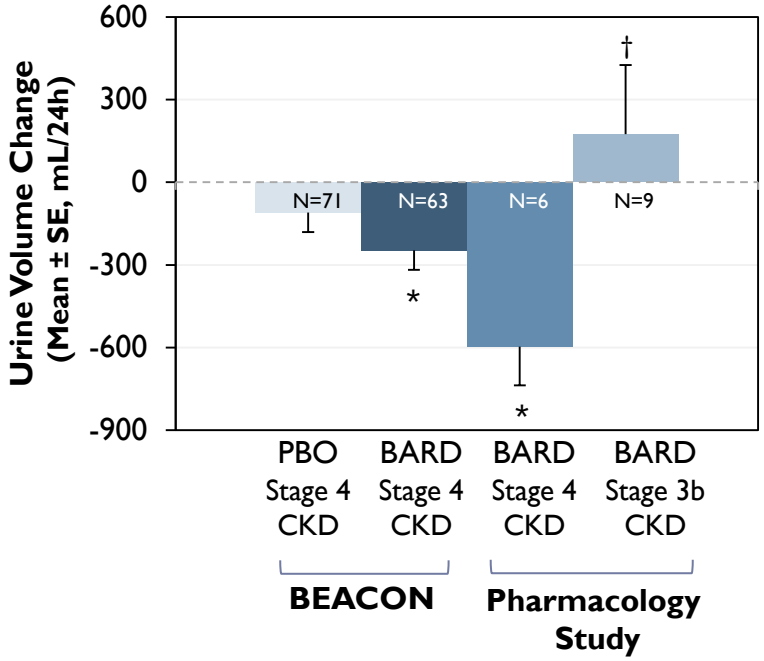
What Happened to Other Measures of Volume Status?

- BARD acutely increased Na^+ and volume retention in Stage 4 CKD patients
  - Reductions not observed in PBO group in BEACON
  - Reductions not observed in Stage 3b CKD patients in phase 2 study
- BARD increased BNP in BEACON

24 Hour Sodium Excretion



24 Hour Urine Output



* $p < 0.05$ for Week 4 or Week 8 versus baseline values
† $p < 0.05$ for Week 8 changes in stage 3b versus stage 4 CKD patients in the pharmacology study

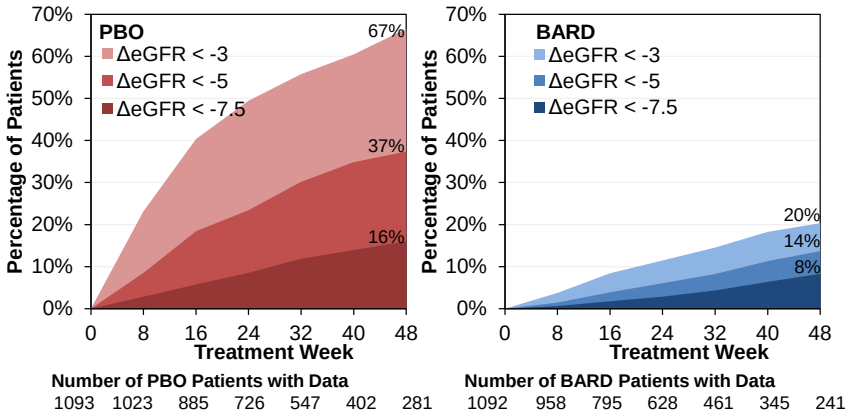
Chin et al., AJN (in press); de Zeeuw et al., NEJM (2014)

Did Renal Toxicity Cause Fluid Retention?

- Renal SAEs reduced
- ESRD events non-significantly reduced
- eGFR increased and not associated with HF
- Clinically-significant eGFR losses reduced
- No evidence of tubular toxicity
  - Urinary Mg^{++} excretion unchanged or reduced
  - Uric acid significantly reduced
  - Serum Na^{+}, K^{+}, Cl^{-} unchanged
  - No acid-base disturbances
- No clinical evidence of renal toxicity in BEACON

	PBO (n = 1097)	BARD (n = 1088)
Renal SAEs	71 (6)	52 (5)
Adjudicated ESRD events	51 (5)	43 (4)

Proportions of Patients with eGFR Losses of 3, 5, or 7.5 ml/min/1.73m^2



de Zeeuw et al., NEJM (2014); Chin et al., AJN (in press)

Did Other Renal Mechanisms Cause Fluid Retention?

- Investigated pattern of fluid retention to determine if it matched any known etiologies
  - BARD promoted Na^+ retention while increasing eGFR
  - BARD did not affect K^+ excretion,
  - BARD promotes, not depletes, endothelial NO
  - Other etiologies had divergent profiles from BARD
  - Pattern is similar to that observed with non-selective antagonism of endothelin pathway

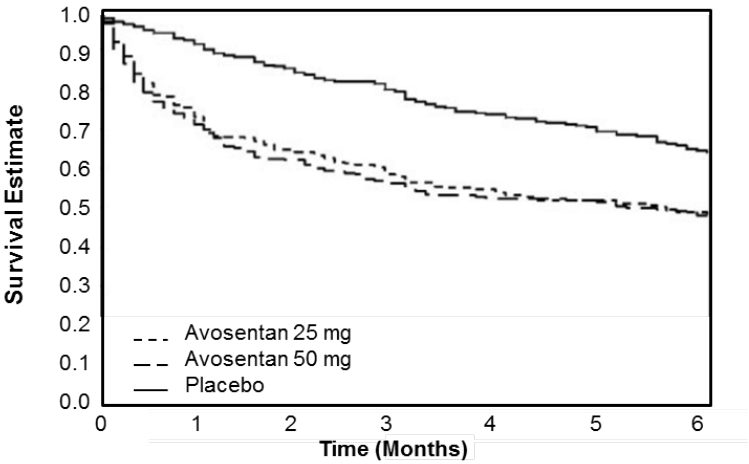
	Na^+ Retention	**K^+ Retention**	**Effect on GFR**
Bardoxolone Methyl Pattern	↑	**None**	↑
RAAS	↑	↓	↑
Antidiuretic Hormone (ADH)	↑	↑	↓ at high levels
Transtubular ion gradients	↑ with ↑ GFR	↑	-
Peritubular factors	↑ with ↑ GFR	↑ with ↑ GFR	None
Pressure natriuresis	↓	↓	Slight ↑
Prostaglandins (PGE_2, PGI_2)	↓	Slight ↓	↑
Natriuretic peptides	↓	Slight ↓	↑
Endothelial Nitric Oxide	↓	None	↓
Endothelins (ET-1)	↓	**None**	↓

Brenner and Rector's The Kidney, 9th Edition; Dhuan et al., Am J Physiol Renal Physiol (2009)

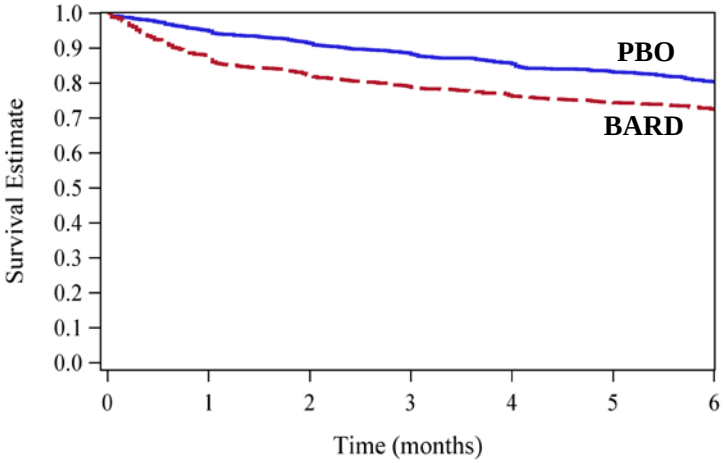
Was Phenotype Similar to Fluid Overload with Non-selective Endothelin Antagonism?

- Fluid overload timing and pattern in BEACON similar to ASCEND*
- ASCEND study tested "high doses" of avosentan in advanced CKD patients
- ASCEND DSMB recommended termination:
  - After median follow-up of 4 months
  - Due to "an excess of cardiovascular events with avosentan, mainly congestive heart failure (CHF) and fluid overload"

ASCEND Fluid Overload Adverse Events



BEACON Fluid Overload Adverse Events

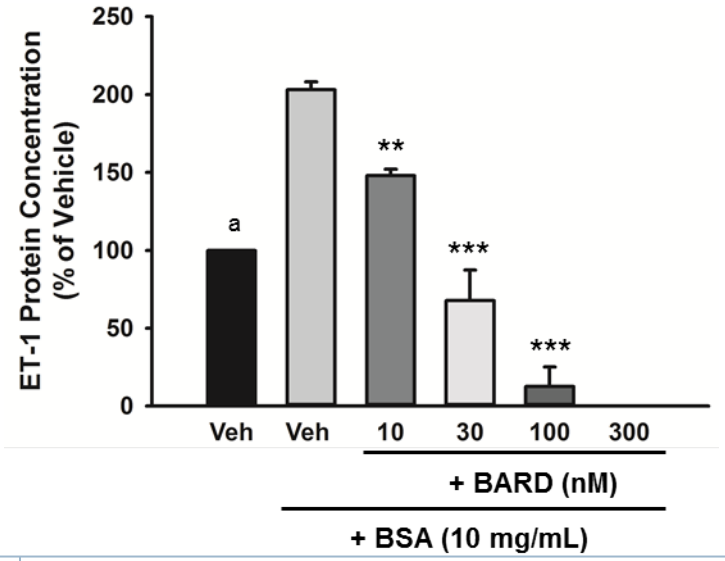


*ASCEND: A Randomised, Double Blind, Placebo Controlled, Parallel Group Study to Assess the Effect of the Endothelin Receptor Antagonist Avosentan on Time to Doubling of Serum Creatinine, End Stage Renal Disease or Death in Patients With Type 2 Diabetes Mellitus and Diabetic Nephropathy - Mann et al., JASN (2010); Chin et al., AJN (in press)

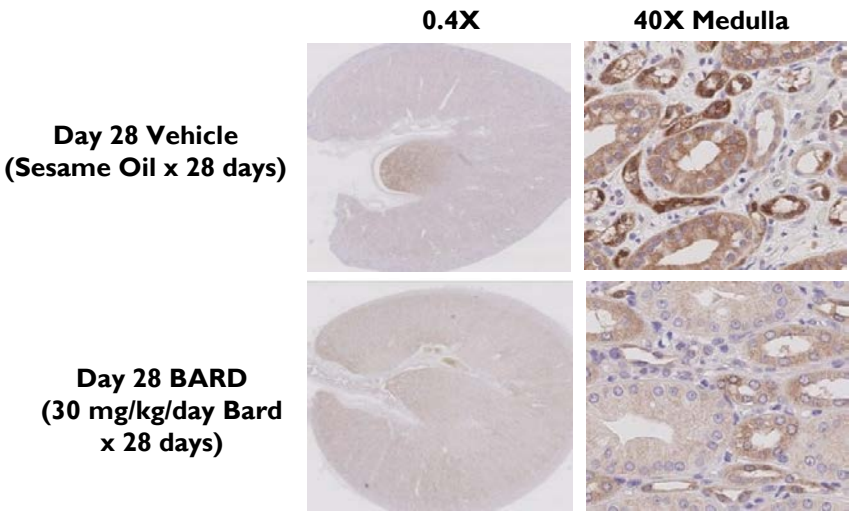
Does BARD Affect the Endothelin Pathway?

- Endothelin (ET)-1 is vasoconstrictive and can bind to the ET_A or ET_B receptor
  - Induced by protein challenge and NF-κB activation in proximal tubules
  - Acute suppression can reduce tubular sodium and water excretion
- BARD dose-dependently suppresses ET-1 secretion in proximal tubule cells after 24 hours
- BARD decreases vasoconstrictive ET_A receptor protein levels in monkey kidneys
  - ET_A receptor expression reduced within 28 days with no effect on ET_B receptor
  - Modulation is not associated with histological injury
- BARD reduces both ET_A receptor as well as ET-1 secretion, unlike ERAs

BARD Suppresses Inducible ET-1



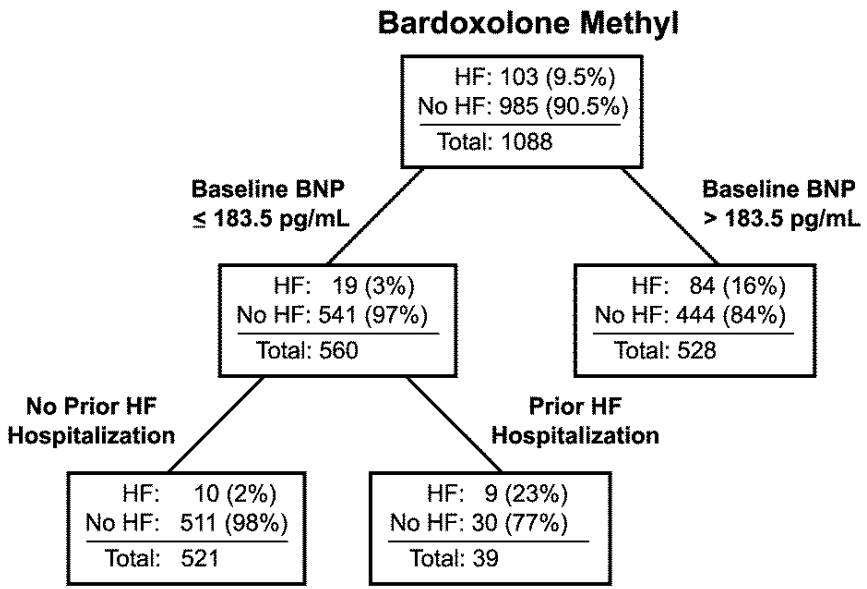
BARD Suppresses ET_A Receptor

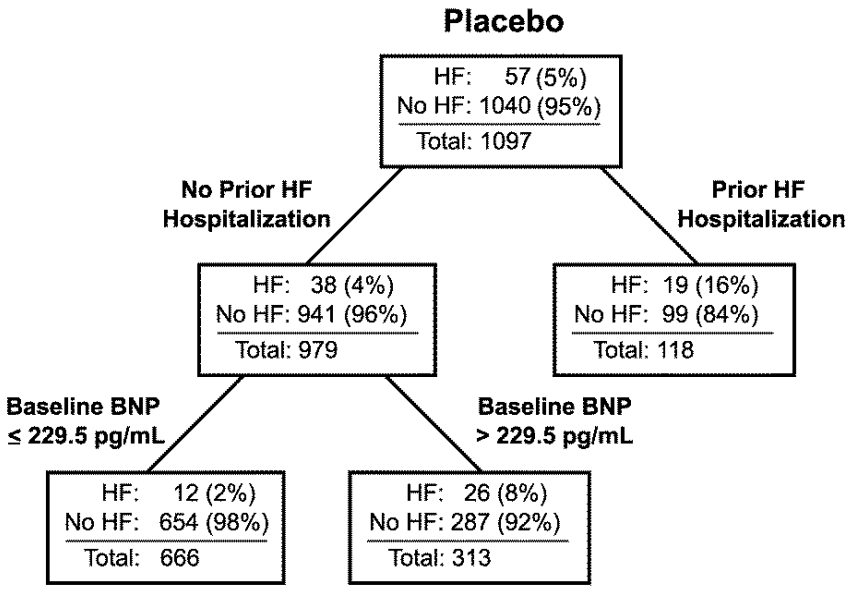


Chin et al., AJN (in press)

Were there Pre-disposing Factors to Development of Heart Failure in BEACON?

- Classification and regression tree (CART) analysis used to identify HF risk
  - Allows for determination of clinically-relevant risk thresholds
  - Assessed treatment, age, baseline ACR, eGFR, BNP, ACEi or ARB use, prior hx for HF hospitalizations
- Identified two risk factors
  - 1) Baseline BNP > 183.5 pg/mL
  - 2) Prior history of HF
- Risk of HF similar (2%) among BARD and PBO patients without these factors



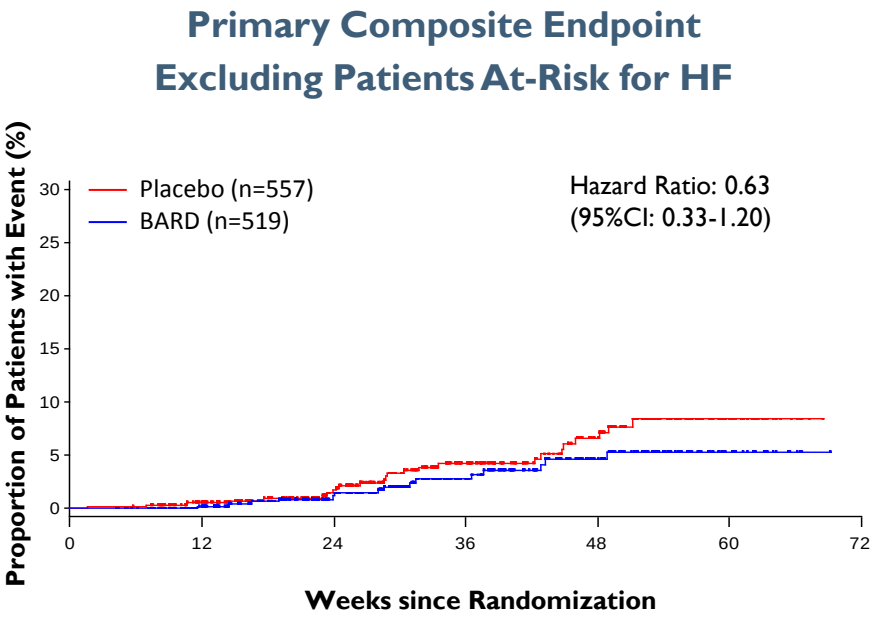


Chin et al., manuscript submitted

Would Excluding At-Risk Patients for HF Improve Other BEACON Outcomes?

- Post-hoc analysis of primary and secondary outcomes excluding at-risk BEACON patients (BNP > 200 pg/mL and prior HF history):
  - Greatly reduces HF imbalance to non-significant difference
  - Improves distribution of ESRD, primary composite events, and SAEs
  - Reduces number of patients by ~50%

	All Patients		BNP ≤ 200, No Prior HF	
Treatment	PBO (n = 1097)	BARD (n = 1088)	PBO (n = 557)	BARD (n = 519)
Primary Composite	69 (6%)	69 (6%)	25 (5%)	15 (3%)
ESRD	51 (5%)	43 (4%)	20 (4%)	8 (2%)
CV Death	19 (2%)	27 (2%)	6 (1%)	7 (1%)
Secondary Endpoints				
Heart Failure	55 (5%)	96 (9%)	10 (2%)	12 (2%)
MI	16 (1%)	19 (2%)	6 (1%)	6 (1%)
Stroke	11 (1%)	14 (1%)	5 (1%)	2 (<1%)
All-Cause Death	31 (3%)	44 (4%)	8 (1%)	11 (2%)

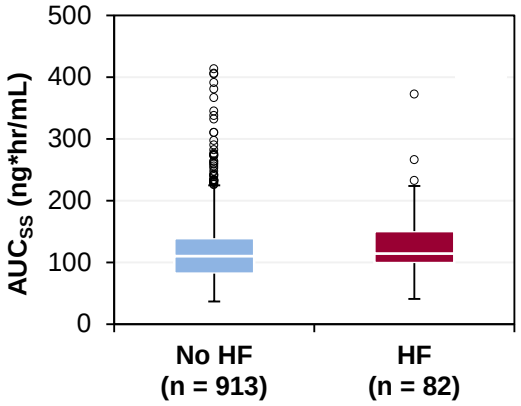


Chin et al., manuscript submitted

Were there Other Notable Findings in the ITT Data?

Finding	Clinical Data
Safety	▸ No difference in hepatobiliary SAEs (8 PBO vs 4 BARD) ▸ No Hy's Law cases observed ▸ No difference in neoplasm SAEs (10 PBO vs 11 BARD)
Renal	▸ BARD reduced renal SAEs and of proportion of patients with eGFR loss ▸ BARD increased eGFR and improved other markers of renal function (↓BUN, ↓uric acid)
PK	▸ No difference in BARD exposure (AUC or Cmax) in patients who had HF vs those who did not ▸ No drug-drug interactions at clinically-relevant doses per in vitro and clinical studies (non-BEACON studies)

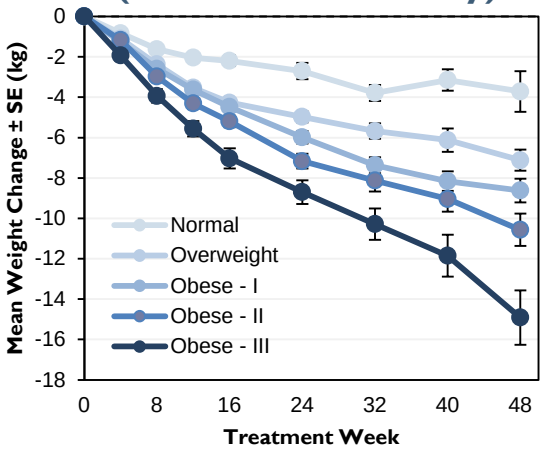
BARD Plasma Levels in Patients with or Without HF



Were there Other Notable Findings in the ITT Data?

Finding	Clinical Data
Weight	▸ Large weight loss that was inversely correlated with baseline BMI ▸ Significant reduction in waist circumference
Muscle	▸ No change in urinary excretion of creatinine (no muscle wasting) ▸ Significant reduction in creatine phosphokinase (CK)
Glycemic Control	▸ Decreased HbA1c in patients with abnormal values at baseline (>7.0%) ▸ No change in patients with normal values at baseline (≤7%)

BEACON Weight Data (BARD Patients Only)

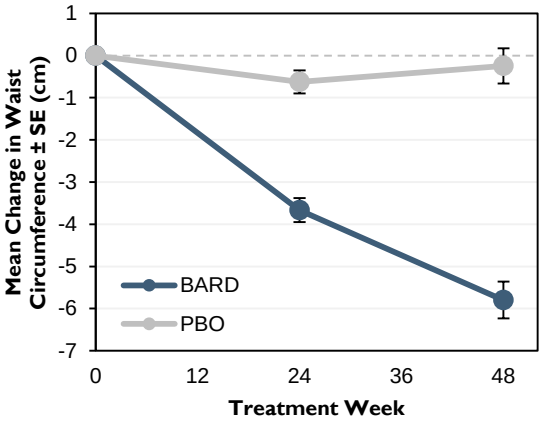


BEACON HbA1c Data

	BARD		PBO	
	BL A1c ≤7%	BL A1c >7%	BL A1c ≤7%	BL A1c >7%
Mean Baseline ± SD	6.21 ± 0.54 (n=579)	8.22 ± 0.98 (n=509)	6.25 ± 0.51 (n=596)	8.10 ± 0.91 (n=501)
Mean Week 48 Change ± SD	0.06 ± 0.79 (n=381)	**-0.59 ± 1.40*** **(n=283)**	0.14 ± 0.76* (n=361)	**-0.16 ±1.35*** **(n= 347)**

*** p < 0.05 vs baseline**

BEACON Waist Circumference Data



BEACON Conclusions

- Primary adverse safety finding was hospitalization for "HF"
  - No significant difference in mortality
  - Risk window was first three weeks
  - Placebo-adjusted excess was 3.8 per 100 patients
  - No evidence of overt or generalized renal or cardiac toxicity
  - Related to acute Na+ and fluid retention
  - Consistent with acute, non-selective modulation of endothelin pathway
- Baseline BNP >200 pg/mL and prior history of HF are risk factors for fluid overload in patients with Stage 4 CKD and type 2 diabetes treated with BARD
  - Risk of HF similar (2%) among BARD and PBO patients without identified risk factors
  - Risk factors limit the use of bardoxolone methyl in some populations
- Multiple findings suggest potential clinical benefit where risk of fluid retention is limited
  - Improvement in multiple renal function parameters and renal SAEs
  - Reduction of weight and waist circumference
  - Reduction of markers of muscle injury
  - Improved metabolic parameters, including HbA1c

Lessons Learned and Moving Forward

Lessons learned from studying BARD in patients with Stage 4 CKD and T2D

- Exclude patients at risk for developing fluid retention
- Closely monitor patients within first month of treatment
- In appropriate patient populations, BARD may have a favorable risk-benefit profile

Moving forward

- Insights are allowing study of BARD in appropriate patient populations
- In the US, BARD is currently being studied in a phase 2 pulmonary arterial hypertension trial (NCT02036970)
  - Strong pharmacological rationale
  - Excluding patients with risk factors for fluid retention
  - Closely monitoring patients during first month
- In Japan, Kyowa Hakko Kirin Co., Ltd. is considering a new development program of BARD in patients with CKD and T2D

Colin Meyer

Presentation Title:

INVESTIGATION OF SERIOUS ADVERSE EVENTS IN BARDOXOLONE METHYL PATIENTS IN BEACON

Session Number:

S 18

Thanks to all investigators, site personnel, steering committee members, national leaders, adjudication committee members, data monitoring committee members and patients who participated in the design, conduct, and analysis of BEACON

Use the e-materials module in the Congress App to capture this code automatically via the camera or enter it manually

E-Materials Order Code

X9943X

X9943X
X9943X
X9943X