SP104

DECREASES IN WEIGHT WITH BARDOXOLONE METHYL IN OBESE PATIENTS WITH CHRONIC KIDNEY DISEASE STAGE 4 AND TYPE 2 DIABETES - *POST-HOC* ANALYSES FROM BEACON

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BACKGROUND

- Bardoxolone methyl (BARD) is an investigational medicine that activates Nrf2 and suppresses NF-κB
- Nrf2 activation is reno-protective in kidney disease models[1,2]
- By activating Nrf2, BARD targets inflammatory pathways that contribute to GFR loss in chronic kidney diseases[3-5]
- BARD significantly increased eGFR and significantly reduced body weight in the BEACON clinical trial[6]
- While BEACON was terminated early due to imbalance in heart failure events, post-hoc analyses have identified BNP > 200 pg/ml and prior hospitalization for heart failure to be risk factors[7]

Post-hoc analyses were performed to further characterize body weight reduction due to BARD treatment

OBESITY AND CHRONIC KIDNEY DISEASE

- Obesity increases the risk of chronic kidney disease and its progression to end-stage renal disease[8]
- In animal models of obesity the anti-inflammatory effects of BARD and analogs shown to:
  - Decrease fatty-acid synthesis
  - Improve metabolism
  - Reduce fat accumulation[9]
  - Reduce high-fat diet-induced obesity, hypothalamic leptin resistance, and inflammation[10]

METHODS

BEACON (NCT01351675) was a Phase 3, randomized, double-blind, parallel-group, international, multicenter trial, in patients with Stage 4 CKD and Type 2 Diabetes

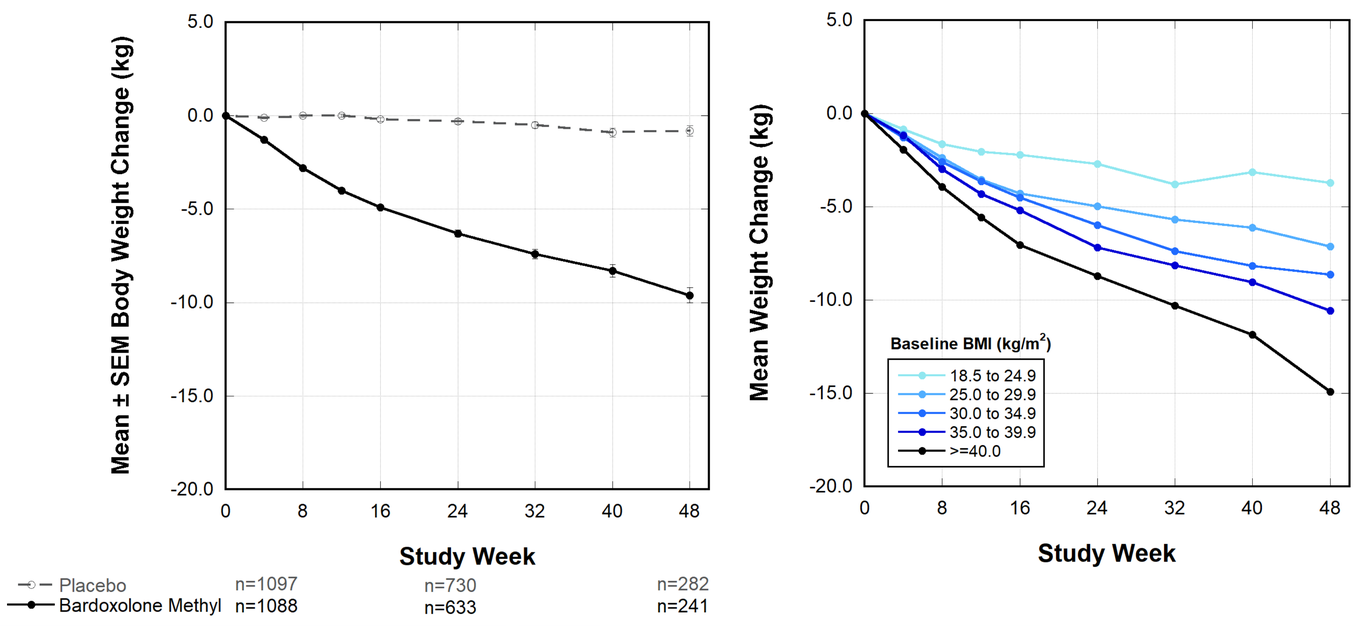
- **Primary efficacy outcome**: Time-to-first event in the composite outcome defined as end-stage renal disease (ESRD; need for maintenance dialysis, kidney transplantation, or death due to kidney failure) or death due to cardiovascular causes
- **Assessments:** Estimated GFR and vital signs (including body weight and Quételet's (body mass) index (BMI)) were assessed every 4 weeks through Week 12, followed by assessments every 8 weeks thereafter. Waist circumference and hemoglobin A1c (HbA1c) were assessed every 24 weeks. A subset of the patients (n=174, 8%) consented to additional 24-hour urine collections at baseline and Week 4

Relevant Baseline Characteristics

	Intent-to-treat Population		Patients with 24-hr Urine Collections	
	Placebo (n=1097)	Bardoxolone Methyl (n=1088)	Placebo (n=87)	Bardoxolone Methyl (n=87)
Weight, kg (mean ± SD)	95.3 ± 21.1	95.1 ± 22.0	95.9 ± 24.1	94.3 ± 20.5
BMI, kg/m^2 (mean ± SD)	33.9 ± 7.2	33.7 ± 7.1	34.3 ± 7.9	33.7 ± 6.4
HbA_{1c}, % (mean ± SD)	7.10 ± 1.17	7.15 ± 1.27	6.97 ± 0.97	7.36 ± 1.54
Serum creatinine, mg/dl (mean ± SD)	2.7 ± 0.6	2.7 ± 0.6	2.8 ± 0.6	2.7 ± 0.5
eGFR, ml/min/1.73 m^2 (mean ± SD)	22.5 ± 4.6	22.4 ± 4.3	21.8 ± 4.2	22.7 ± 4.3

eGFR AND BODY WEIGHT

- Patients randomized to BARD in BEACON experienced[6]:
  - Significant increases in eGFR (+6.4 ml/min/1.73 m^2 versus placebo, p<0.001)
  - Significant reductions in body weight (–5.7 kg versus placebo, p<0.001)
- Greater reductions in body weight occurred in patients with higher baseline BMI



URINARY CREATININE EXCRETION

- 24-hour urinary creatinine excretion was unchanged from baseline at Week 4 and relative to placebo
- Weight loss with BARD inconsistent with loss of muscle mass

Urinary Creatinine (mg/24hr)	Placebo n=65	Bardoxolone methyl n=61
Baseline	1159 ± 471	1191 ± 339
Week 4	1155 ± 457	1134 ± 394
Change from Baseline	–4 ± 327	–57 ± 280

Data are mean values ± SD and only include patients with baseline and Week 4 urinary creatinine values.

HEMOGLOBIN A_{1C}

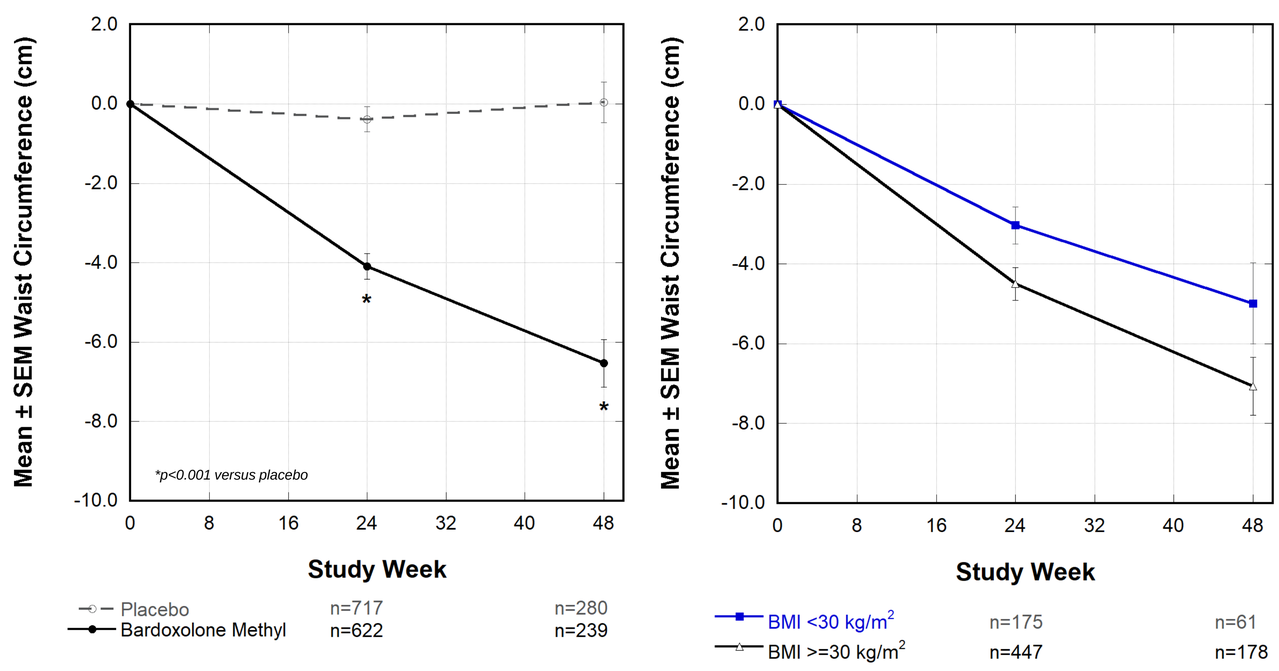
- BARD significantly decreased HbA_{1c} relative to baseline at Weeks 24 and 48
- Reductions in HbA1c induced by bardoxolone methyl were driven by results in patients with abnormal HbA1c (>7.0%) at baseline

	Observed HbA_{1c} (%)			Change from Baseline (%)	
	Baseline	Week 24	Week 48	Week 24	Week 48
All Patients					
Placebo[a]	7.10 ± 1.17 (n=1097)	7.11 ± 1.29 (n=721)	7.24 ± 1.44 (n=275)	0.00 ± 0.99 (p=0.92)	0.08 ± 1.12 (p=0.24)
Bardoxolone Methyl[a]	7.15 ± 1.27 (n=1088)	6.96 ± 1.30 (n=629)	6.90 ± 1.32 (n=236)	−0.12 ± 1.04 (p=0.0033)	−0.17 ± 1.13 (p=0.026)
Difference between Treatment Groups[b]				−0.13 ± 1.01 (p=0.023)	−0.25 ± 1.13 (p=0.014)
Baseline HbA_{1c} > 7.0%					
Placebo[a]	8.10 ± 0.91 (n=501)	7.90 ± 1.21 (n=338)	8.07 ± 1.41 (n=137)	−0.18 ± 1.14 (p=0.0043)	0.00 ± 1.39 (p=1.0)
Bardoxolone Methyl[a]	8.22 ± 0.98 (n=509)	7.76 ± 1.32 (n=283)	7.74 ± 1.44 (n=100)	−0.44 ± 1.29 (p<0.001)	−0.53 ± 1.47 (p<0.001)
Difference between Treatment Groups[b]				−0.26 ± 1.21 (p=0.0086)	−0.53 ± 1.42 (p=0.0051)
Baseline HbA_{1c} ≤ 7.0%					
Placebo[a]	6.25 ± 0.51 (n=596)	6.42 ± 0.90 (n=383)	6.41 ± 0.87 (n=138)	0.16 ± 0.80 (p<0.001)	0.16 ± 0.76 (p=0.015)
Bardoxolone Methyl[a]	6.21 ± 0.54 (n=579)	6.31 ± 0.83 (n=346)	6.28 ± 0.78 (n=136)	0.14 ± 0.69 (p<0.001)	0.10 ± 0.70 (p=0.084)
Difference between Treatment Groups[b]				0.03 ± 0.75 (p=0.60)	−0.05 ± 0.73 (p=0.53)

Data are mean values ± SD; [a] p-values comparing values at Week 24 or Week 48 to baseline values within each treatment group; [b] p-values comparing the difference in means between the bardoxolone ethyl and placebo groups.

WAIST CIRCUMFERENCE

- BARD significantly reduced waist circumference (Week 24: –4.1 ± 8.0 cm, Week 48: –6.5 ± 9.3 cm)
- More pronounced reductions in waist circumference in obese patients (BMI ≥ 30 kg/m^2)



CONCLUSIONS

- BARD treatment resulted in significant reductions in body weight in an obese, CKD patient population with type 2 diabetes
  - Magnitude and rate of weight loss was dependent on baseline BMI
  - Accompanied by a significant reduction in waist circumference, which was more pronounced in patients with higher baseline BMI
- 24-hr urinary creatinine excretion (a proxy for muscle mass) remained unchanged with BARD-treatment
- BARD treatment lead to improved glycemic control, particularly in patients with HbA_{1c} > 7.0%
- Data are consistent with the hypothesis that reductions in body weight with BARD are associated with loss of adipose tissue rather than muscle
- Although the mechanism of weight loss with BARD treatment in humans is not fully understood, it is hypothesized that BARD increases lipolysis of peripheral lipid stores and improvements in glycemic control as observed in preclinical studies

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DISCLOSURES

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MC, AG and CJM are employees of Reata Pharmaceuticals.

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