FP152

Effect of Bardoxolone Methyl on Urinary Albumin in Patients with Type 2 Diabetes and Chronic Kidney Disease: *Post-hoc* Analyses from BEAM and BEACON

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BACKGROUND AND RATIONALE

Bardoxolone methyl (BARD) increases eGFR and albuminuria

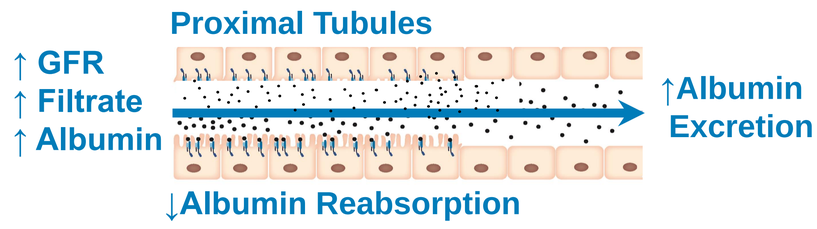
- In the BEAM and BEACON trials, BARD treatment increased eGFR compared to placebo[1,2]
- Increases in urinary albumin to creatinine ratio (UACR) were observed in both trials

BARD improves kidney function with no evidence of histological kidney damage in preclinical models

- BARD is an investigational medicine that activates Nrf2 and suppresses NF-κB
- Through Nrf2 induction, BARD targets pro-inflammatory and fibrotic pathways that contribute to GFR loss in CKD[3]
- A BARD analog attenuates interstitial inflammation and fibrosis in protein overload-induced secondary nephropathy[4]
- In a non-human primate study, treatment with BARD was associated with durable improvements in kidney function and kidney tissues showed normal histological features, despite presence of albuminuria[5]

What can affect urinary albumin excretion?

- Rate of filtrate delivery *to* tubule (↑ by eGFR increase) and residence time of filtrate *in* tubule (↓ by eGFR increase)[6]
- Reabsorptive capacity of tubule (megalin expression, important for protein transport, decreased with BARD treatment in preclinical studies)[5,6]



***Post-hoc* analyses, aimed to determine the effect of BARD on albuminuria accounting for increases in eGFR, are presented**

METHODS

BEAM was a Phase 2, randomized, double-blind, placebo-controlled trial, in patients with Stage 3b or Stage 4 CKD and Type 2 Diabetes, that tested 25 mg, 75 mg and 150 mg of a crystalline formulation of BARD

- **Primary efficacy outcome:** Change from baseline in eGFR at 24 weeks
- **Patients:** Baseline eGFR (± SD) was 32.7 ± 7.0 ml/min/1.73m^2 in patients randomized to BARD (N=170) and 31.2 ± 6.3 ml/min/1.73m^2 in patients randomized to placebo (N=57). Baseline UACR was 82 mg/g in BARD and 62 mg/g placebo patients respectively. 98% of BARD and 100% of placebo patients were on ACEi and ARB background therapy
- **Assessments:** UACR and eGFR (by MDRD) were assessed during screening and every 4 weeks by a central laboratory

BEACON was a Phase 3, randomized, double-blind, parallel-group, international, multicenter trial, in patients with Stage 4 CKD and Type 2 Diabetes, that tested 20 mg of an amorphous formulation of BARD

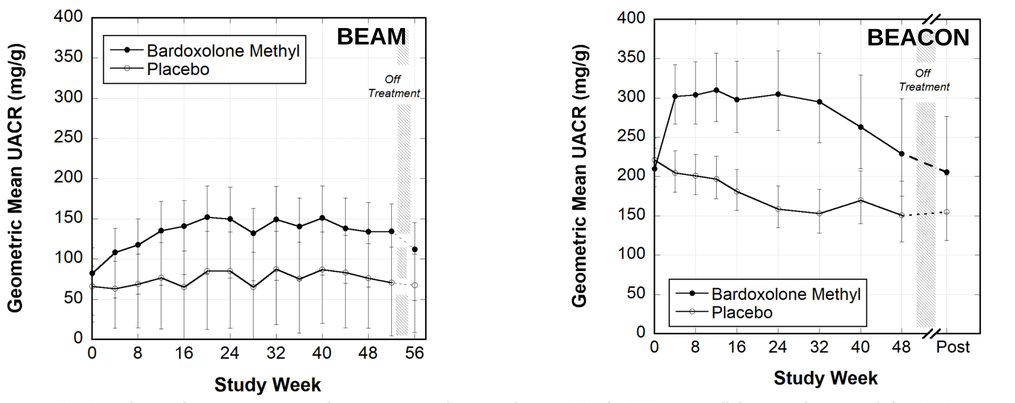
- **Primary efficacy outcome**: Time-to-first event in the composite outcome defined as end-stage renal disease (ESRD; need for maintenance dialysis, kidney transplantation, or death due to kidney failure) or death due to cardiovascular causes
- **Patients:** Baseline eGFR (± SD) was 22.4 ± 4.3 ml/min/1.73m^2 in patients randomized to BARD (N=1088) and 22.5 ± 4.6 ml/min/1.73m^2 in patients randomized to placebo (N=1097). Baseline UACR was 210 mg/g and 221 mg/g in BARD and placebo-treated patients respectively. 89% of BARD and 91% of placebo patients were on ACEi and ARB background therapy
- **Assessments:** UACR and eGFR (by MDRD) were assessed every 4 weeks through week 12, followed by assessment every 8 weeks thereafter, and 4 weeks after the last dose of BARD was administered

Post-hoc Statistical Analyses

- Prior to analysis, UACR values were log-transformed (log (UACR)) to adjust for the measure's highly skewed distribution
- Longitudinal analysis using mixed effects regression with treatment, time, treatment-by-time interaction, and baseline log-UACR/eGFR as covariates compared mean changes in log(UACR)/eGFR between BARD and placebo groups in BEAM and BEACON
- Multivariable regression analyses using longitudinal mixed effects models with log(UACR) in BEACON as the dependent variable were used to identify which of the following factors were associated with the degree of urinary albumin excretion across all visits:
  - Baseline log(UACR), treatment (BARD or placebo), time (in weeks), treatment by time interactions, baseline eGFR, eGFR at corresponding time points
  - Best-fit model whose combination of factors yielded the lowest Akaike's Information Criterion (AIC) was selected

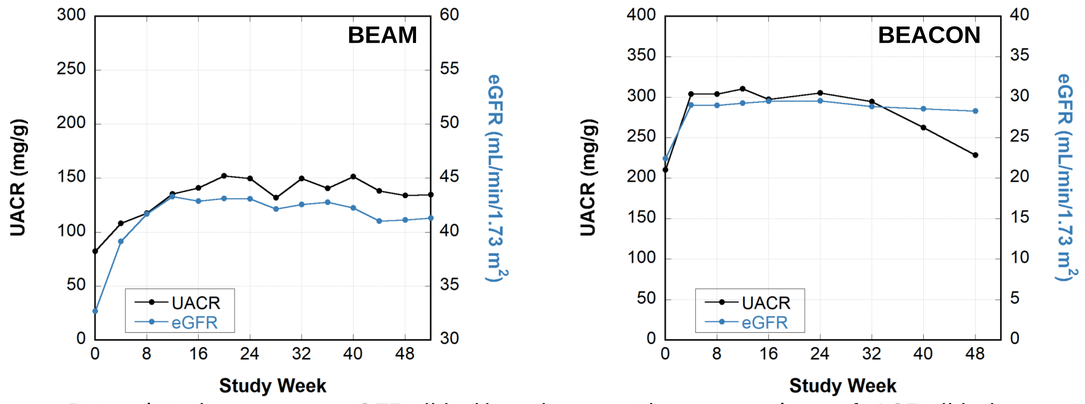
UACR PROFILE in BEAM and BEACON

Figure 1: UACR over Time for BARD versus Placebo



Data plotted are geometric mean values of UACR (±95% confidence intervals). Data at Week 56 in BEAM and post-treatment in BEACON are UACR values measured 4 weeks after the last dose of study drug.

Figure 2: eGFR and UACR over Time with BARD

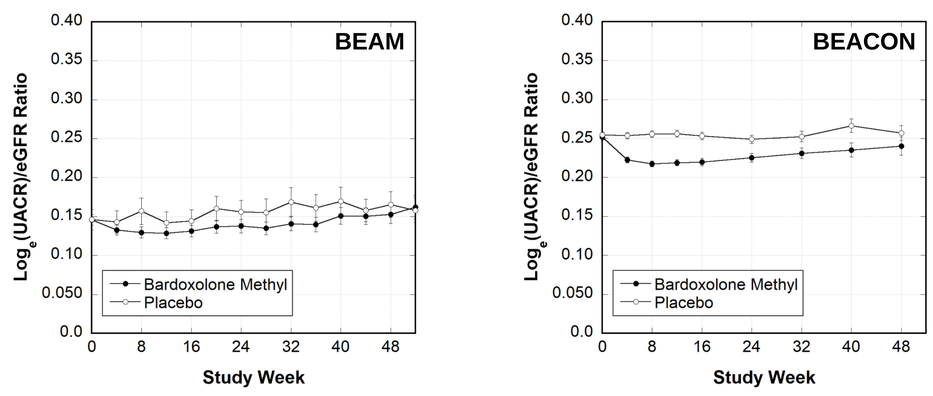


Data plotted are mean eGFR (*black)* and geometric mean values of ACR (*blue*). Analyses include all available eGFR and UACR data for patients randomized to receive BARD (BEAM n= 170 ; BEACON n=1088).

- UACR in both BEAM and BEACON increased significantly in the BARD group and correlated with increases in eGFR
- Increases in UACR were attenuated after 5-6 months and trended towards baseline after withdrawal of BARD

POST-HOC ANALYSES OF UACR IN BEAM AND BEACON

Figure 3: UACR/eGFR over Time for BARD versus Placebo



Log-transformed UACR/eGFR ratios over time for patients randomized to bardoxolone methyl or placebo in BEAM (BARD: n=170, placebo: n=57) and BEACON (BARD: n=1088, placebo: n=1097). Data plotted are mean values of the ratios (± SEM).

Table 1: Multivariate Model of log(UACR) over Time in BEACON

Effect	B Coefficient (95% CI) [a]	p-value
Treatment (BARD vs placebo)	0.33 (0.30, 0.36)	p<0.001
Time (week)	0.0068 (0.0058, 0.0078)	p<0.001
Baseline log-UACR [b]	0.96 (0.95, 0.96)	p<0.001
Baseline eGFR [c]	-0.013 (-0.017, -0.0099)	p<0.001
ΔeGFR [c]	0.010 (0.0088, 0.012)	p<0.001

[a] For a positive β coefficient, increase the covariate corresponds to an increase in UACR while negative β coefficients describe a decrease in UACR with increases in the covariate; [b] per unit increase; [c] per mL/min/1.73m^2 increase

- Changes in log(UACR)/eGFR ratios with BARD were lower than placebo (least-squared means: -0.017 and -0.035 versus placebo in BEAM and BEACON, respectively)
- When adjusted for eGFR changes, bardoxolone methyl may reduce albumin excretion relative to placebo

CONCLUSIONS

- Increase in albuminuria significantly correlated with increase in eGFR, supporting the hypothesis that increased albuminuria may be, in part, due to increased flow rate
- Increases in albuminuria were attenuated after 5-6 months of BARD treatment and trended towards baseline after drug withdrawal
- Increased eGFR and decreased megalin expression with BARD treatment may decrease reabsorption of filtered albumin and may explain the increase in albuminuria
- Inflammation and fibrosis generally triggered by protein reabsorption may be reduced by BARD treatment
- The profile of albuminuria increase by BARD is distinct from those associated with glomerular injury or disease progression in CKD

DISCLOSURES

GAB, GMC, PAM, DGW and PEP are consultants to Reata Pharmaceuticals; DP and SMS receive grants from Reata Pharmaceuticals; DGW is an investor in Reata Pharmaceuticals; MC, AG and CM are employees of Reata Pharmaceuticals.

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