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 inflammatory 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?

- Reabsorptive delivery to tubule (↑ by eGFR increase) and residence time of filtrate in tubule (↑ by eGFR increase)
- Reabsorptive capacity of tubule (megalin expression, important for protein transport, decreased with BARD treatment in preclinical studies).6,7

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 ± 7.5 ml/min/1.73m² in patients randomized to BARD (N=70) and 31.2 ± 6.2 ml/min/1.73m² in patients randomized to placebo (N=45). Baseline UACR was 62 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.
- Assessment: 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) or death due to kidney failure or death due to cardiovascular causes.
- Patients: Baseline eGFR (SD) was 22.1 ± 4.3 ml/min/1.73m² in patients randomized to BARD (N=1088) and 22.5 ± 4.8 ml/min/1.73m² in patients randomized to placebo (N=1087). Baseline UACR was 710 mg/g in BARD and placebo patients respectively. 99% of BARD and 90% of placebo patients were on ACEi and ARB background therapy.
- Assessment: UACR and eGFR (by MDRD) were assessed every 4 weeks through week 72. Followed by assessment every 3 months thereafter and 4 weeks after the last dose of BARD was administered.

Post-hoc Statistical Analyses

- In this analysis, UACR values were log-transformed (log(UACR)) to adjust for the measure’s highly skewed distribution.
- Longitudinal analyses using mixed effects representation with treatment, time, treatment-by-time interaction, and baseline log(UACR) as covariates compared mean changes in log(UACR)/eGFR between BARD and placebo groups in BEAM and BEACON.
- Multivariable regression analyses using longitudinal mixed models with log(UACR) in BEACON as the dependent variable were used to identify when 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 at corresponding time points
  - Beck R model whose combination of factors yielded the lowest Akaike’s Information Criterion (AIC) was selected

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

REFERENCES


DISCLOSURES

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

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