Bardoxolone Methyl Prevents eGFR Decline in Patients with Chronic Kidney Disease Stage 4 and Type 2 Diabetes — Post-hoc Analyses from BEACON

Christoph Wanner, MD; George Bakris, MD; Geoffrey A. Block, MD; Melanie Chin, PhD; Angie Goldsberry, MS; Lesley A. Inker, MD; Colin J. Meyer, MD; Megan O'Grady, PhD; Pablo E. Pergola, MD, PhD; David G. Warnock, MD; Glenn M. Chertow, MD, MPH

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Disclosures

• Geoffrey A. Block, Pablo E. Pergola, David G. Warnock and Glenn M. Chertow are consultants to Reata Pharmaceuticals

• Lesley A. Inker receives research funding from Reata Pharmaceuticals

• David G. Warnock is an investor in Reata Pharmaceuticals

• Colin Meyer, Melanie Chin, Angie Goldsberry, and Megan O’Grady are employed by and have a financial interest in Reata Pharmaceuticals
Background

• Bardoxolone methyl (BARD) activates Nrf2 and suppresses inflammation, which contributes to GFR loss in CKD\(^1\)

• BARD shown to improve kidney function and have protective effects in multiple models of kidney disease and diabetes\(^2\)-\(^6\)

• Mechanisms of eGFR increases with BARD in preclinical models\(^7,8\):
  – Dynamic increases in glomerular surface area for filtration
  – Chronic suppression of remodeling and fibrosis

• Phase 2 clinical trials showed BARD lowered serum creatinine concentration and improved other markers of kidney function\(^9,10\)

• On the basis of these data, Phase 3 study (BEACON) was designed and initiated

\(^1\)Imig, Compr Physiol (2013); \(^2\)Aminzadeh, Xenobiotica (2013); \(^3\)Huang, J Med Chem (2017); \(^4\)Hisamichi, Hypertens Res (2017), \(^5\)Zoja, Poster ASN (2010); \(^6\)Wu, Arthritis Rheumatol (2010); \(^7\)Aminzadeh, Redox Biol (2013); \(^8\)Ding, Kidney Int (2013); \(^9\)Pergola, AJN (2011); \(^10\)Pergola NEJM (2011)
Overview of BEACON

Study characteristics:
- Phase 3, randomized, double-blind, parallel group, multi-national outcomes study
- Enrolled 2185 patients with type 2 diabetes and stage 4 CKD (eGFR 15 to 29 mL/min/1.73 m²)
- Patients randomized 1:1 to receive BARD (20 mg) or placebo
- Primary outcome: ESRD or cardiovascular death

Summary of results:
- BEACON terminated early due to increased risk of hospitalizations due to fluid overload-related heart failure (8.8% in BARD vs 5% in placebo), which occurred during first 4 weeks of study¹
  - Post-hoc analysis identified risk factors for fluid overload: BNP > 200 pg/mL and prior HF history²
  - Risk of fluid overload same (2%) for BARD and placebo patients without these factors²
- Primary endpoint showed no difference¹
  - Numerically fewer ESRD events with BARD (43/1088 [4.0%]) versus placebo (51/1097 [4.6%])
  - Due to early termination, too few events occurred to reliably determine BARD’s effect on delaying progression to kidney failure

Additional post-hoc analyses from BEACON performed to further characterize efficacy profile of BARD

¹ de Zeeuw et al., NEJM (2013); ² Chin, J Card Fail (2014)
Statistical Methods

• 30% decline from baseline in eGFR and eGFR < 15 mL/min/1.73 m² shown to be validated surrogate for progression to kidney failure in CKD trials¹,²

• Time-to-event analyses using:
  – Confirmed ≥ 30% eGFR decline
  – Confirmed ≥ 30% eGFR decline, eGFR <15 mL/min/1.73 m², adjudicated ESRD events

• Confirmation of event: eGFR decline occurring at two or more visits

• Hazard ratios and 95% confidence intervals computed using Cox proportional-hazards regression models

• Censoring of patients who did not experience events:
  – Patients who died from any cause prior to the end of the study censored at the date of death
  – Patients who discontinued the study prematurely, withdrew consent, or were lost to follow-up censored at last date of contact
  – Patients who were alive and still being followed were censored on the study termination date (October 12, 2012)

¹ Inker et al., Am J Kidney Dis (2014); ²Levey et al., Am J Kidney Dis (2014)
## BEACON Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intent-to-treat Population(^1)</th>
<th>Patients on study through Week 48</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=1097)</td>
<td>Bardoxolone Methyl (n=1088)</td>
</tr>
<tr>
<td>Age, yr (mean ± SD)</td>
<td>68.2 ± 9.4</td>
<td>68.9 ± 9.7</td>
</tr>
<tr>
<td>Female (n, %)</td>
<td>472 (43)</td>
<td>462 (42)</td>
</tr>
<tr>
<td>Race (n, %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>848 (77)</td>
<td>846 (78)</td>
</tr>
<tr>
<td>Black</td>
<td>176 (16)</td>
<td>185 (17)</td>
</tr>
<tr>
<td>Other</td>
<td>73 (7)</td>
<td>57 (5)</td>
</tr>
<tr>
<td>Weight, kg (mean ± SD)</td>
<td>95.3 ± 21.1</td>
<td>95.1 ± 22.0</td>
</tr>
<tr>
<td>HbA1c, % (mean ± SD)</td>
<td>7.1 ± 1.2</td>
<td>7.2 ± 1.3</td>
</tr>
<tr>
<td>Serum creatinine, mg/dl (mean ± SD)</td>
<td>2.7 ± 0.6</td>
<td>2.7 ± 0.6</td>
</tr>
<tr>
<td>eGFR, ml/min/1.73 m(^2) (mean ± SD)</td>
<td>22.5 ± 4.6</td>
<td>22.4 ± 4.3</td>
</tr>
<tr>
<td>UACR, mg/g (geometric mean)</td>
<td>221</td>
<td>210</td>
</tr>
<tr>
<td>CV History (n, %)</td>
<td>619 (56)</td>
<td>609 (56)</td>
</tr>
<tr>
<td>HF hospitalization (n, %)</td>
<td>118 (11)</td>
<td>120 (11)</td>
</tr>
<tr>
<td>ACE inhibitor and/or ARB (n, %)</td>
<td>994 (91)</td>
<td>964 (89)</td>
</tr>
<tr>
<td>Insulin (n, %)</td>
<td>677 (62)</td>
<td>667 (61)</td>
</tr>
</tbody>
</table>

\(^1\) de Zeeuw et al., NEJM (2013)
Change from Baseline in eGFR

- Consistent with prior studies, BARD significantly increased eGFR ($p<0.001$)\(^1\)
- Increases were durable through Week 56
- Over 75% of patients had increase from baseline in eGFR at Week 48\(^2\)

\(^1\) de Zeeuw et al., NEJM (2013); \(^2\) Chin et al., AJN (2018)
Kidney Function Improvement Partially Retained After Withdrawal of BARD

- Treatment with BARD for at least 48 weeks resulted in significant eGFR increase 4 weeks after withdrawal\(^1\)
  - Four week withdrawal corresponds to three weeks after loss of pharmacologic activity
  - Data suggest BARD may affect kidney remodeling and fibrosis in humans as observed in CKD animal models

- Acute eGFR increases (Week 12) with BARD positively correlate with durable increase through one year and retained eGFR increase post-withdrawal\(^1\)

### Withdrawal Analysis

<table>
<thead>
<tr>
<th>Mean eGFR Change from Baseline ± SEM</th>
<th>N</th>
<th>End of Treatment</th>
<th>4 Weeks Post-Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>273</td>
<td>-1.2 ± 0.3</td>
<td>-0.8 ± 0.3</td>
</tr>
<tr>
<td>Bardoxolone methyl</td>
<td>225</td>
<td>5.7 ± 0.6(^*)</td>
<td>1.0 ± 0.5(^*)</td>
</tr>
</tbody>
</table>

\(^*p<0.001\) vs Placebo

\(^1\)Chin et al., AJN (2018)
Kidney Failure Outcomes

• BARD significantly reduced likelihood of kidney failure outcomes
  – ≥ 30% eGFR decline: HR=0.44 (95% CI: 0.27, 0.73), p=0.001
  – Composite of adjudicated ESRD, 30% decline, or eGFR < 15: HR=0.48
    (95% CI: 0.36, 0.65), p<0.001

1Chin et al., AJN (2018)
Conclusions and Next Steps

- BARD significantly increased eGFR from baseline and relative to placebo in BEACON
  - eGFR increases with BARD sustained through 48 weeks and retained after drug withdrawal
  - Profile is distinct from eGFR increase due to pressure-mediated hyperfiltration
- Improvements in eGFR with BARD treatment in BEACON translated to significant reduction in risk of kidney failure outcomes
- Subsequent studies with BARD exclude at-risk patients and have not shown increased risk for fluid overload to date
- BARD may offer the potential to prevent or delay kidney function decline and progression to ESRD in CKD
- Limitations include post-hoc nature of analyses and insufficient follow-up to assess additional endpoints such as 40% eGFR decline or doubling of serum creatinine
- Additional studies needed to further evaluate risk-benefit profile for BARD
- KHK is conducting a study with BARD in patients with diabetic CKD using 30% eGFR decline or ESRD as primary efficacy endpoint
Acknowledgements

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