FP804

# Two-Year Durability of Improvements in eGFR with Bardoxolone Methyl in Patients with Pulmonary Arterial Hypertension: The LARIAT Study

Colin J. Meyer, MD; Murali M. Chakinala, MD, FCCP; Melanie P. Chin, PhD; Daniel W. Coyne, MD; Jeremy Feldman, MD; Angie Goldsberry, MS; Peter A. McCullough, MD, MPH; Megan O'Grady, PhD; Fernando Torres, MD; Ronald J. Oudiz, MD; Keith Ward, PhD; R. James White, MD, PhD

## BACKGROUND

**BARDOXOLONE METHYL**

- Bardoxolone methyl (BARD) is an oral, once-daily investigational therapy that activates Nrf2 and suppresses NF-κB; *in vitro,* BARD activates cellular metabolism[1]
- In prior clinical studies that enrolled over 2,000 patients, BARD increased eGFR[2,3]

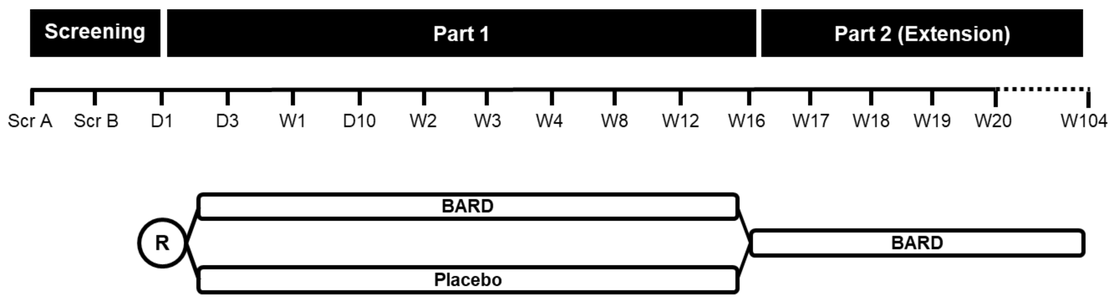
**KIDNEY FUNCTION IN PAH**

- Pulmonary arterial hypertension (PAH) is characterized by inflammation and vascular remodeling in the lung as well as impaired mitochondrial function in multiple organs[4-7]
- CKD complicates management of right heart failure in PAH[8]
- Kidney dysfunction is a powerful poor prognostic factor in PAH especially in those with scleroderma[8-10]

**LARIAT STUDY**

- Phase 2 trial assessing the safety and efficacy of BARD relative to placebo with various etiologies of pulmonary hypertension (PH)
  - Part 1: placebo-controlled study
    - Patients received BARD (2.5, 5, 10, or 20 mg; median 10 mg) or placebo
    - 16-week duration
  - Part 2: Open-label extension study
    - Patients received BARD (up to 20 mg)
- Primary efficacy results of change from baseline in 6-minute walk distance have been previously presented[11]

**This post-hoc analysis investigates the long-term safety and efficacy of BARD on eGFR in cohorts of patients with PAH over a 2-year time period**

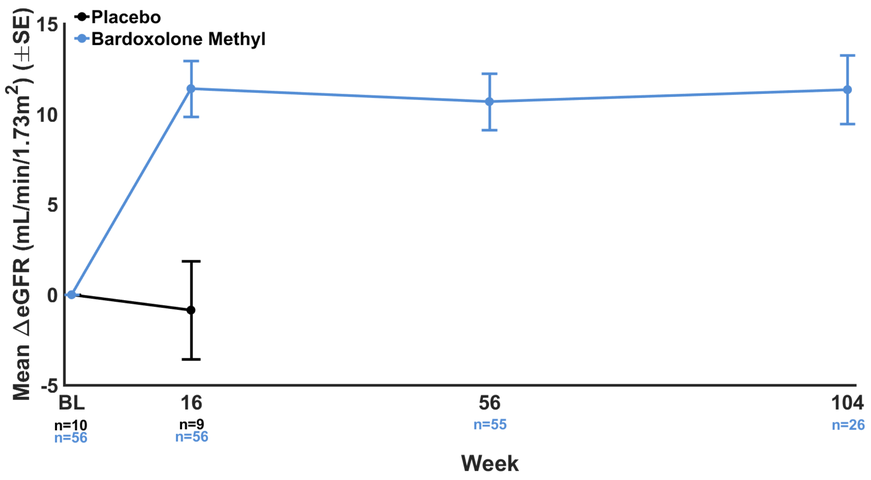



## METHODS

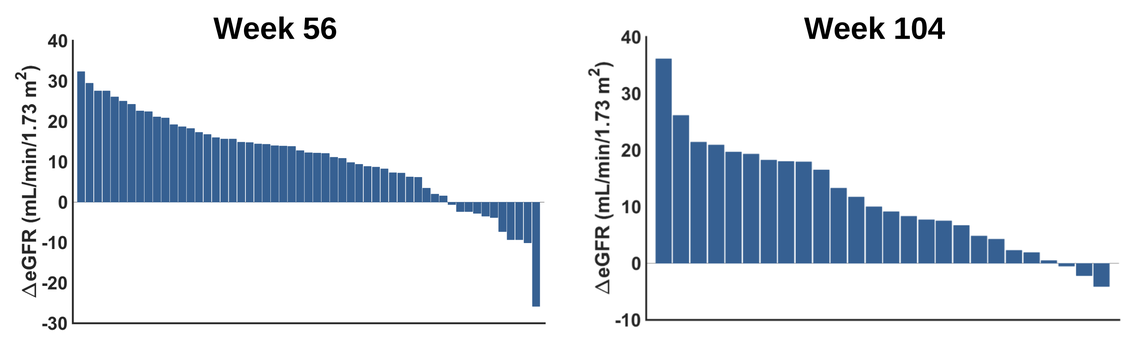
- Patients with a confirmed diagnosis of PAH were randomized to receive bardoxolone methyl for 16 weeks or placebo, followed-by an open-label extension
- Patients with BNP > 200 pg/mL or eGFR < 45 mL/min/1.73 $m^2$ at baseline were excluded
- Estimated GFR was calculated from serum creatinine data using the Modification of Diet in Renal Disease (MDRD) equation
- A paired t-test was used to assess change from baseline in eGFR after treatment with bardoxolone methyl for 16, 56, and 104 weeks

## RESULTS: CHANGE IN eGFR

- Part 1: BARD increased eGFR from baseline and relative to placebo after 16 weeks of treatment (p<0.001)
- Part 2: Increases in eGFR with BARD were durable for up to 2 years of treatment (p<0.001)




**Distribution of eGFR Changes**




## PATIENT DEMOGRAPHICS

| Parameter | Placebo (n=10) | Bardoxolone Methyl (n=46) | All (n=56) |
|---|---|---|---|
| Mean (± SD) Age (yrs) | 48.9 ± 10.5 | 52.2 ± 12.8 | 51.6 ± 12.4 |
| Female (n, %) | 8 (80%) | 37 (80%) | 45 (80%) |
| Mean (± SD) Weight (kg) | 75 ± 13.8 | 80.8 ± 19.1 | 79.7 ± 18.3 |
| Mean (± SD) BMI (kg/$m^2$) | 27.8 ± 5 | 30.2 ± 6.1 | 29.8 ± 5.9 |
| PAH Etiology (n, %) | | | |
| Idiopathic | 5 (50%) | 24 (52%) | 29 (52%) |
| CTD | 3 (30%) | 15 (33%) | 18 (32%) |
| Anorexigen associated | 2 (20%) | 4 (9%) | 6 (11%) |
| Heritable | 0 | 2 (4%) | 2 (4%) |
| Not specified | 0 | 1 (2%) | 1 (2%) |
| WHO/NYHA Function (n, %) | | | |
| Class II | 7 (70%) | 36 (78%) | 43 (77%) |
| Class III | 3 (30%) | 10 (22%) | 13 (23%) |
| Mean (± SD) Baseline 6MWD (m) | 424 ± 72 | 427 ± 90 | 426 ± 87 |
| Baseline eGFR, mean ± SD (mL/min/1.73 $m^2$) | 86.9 ± 17.4 | 71.7 ± 17.2 | 75.6 ± 21.1 |
| eGFR ≥ 90 mL/min/1.73 $m^2$, n (%) | 4 (40%) | 7 (15%) | 11 (20%) |
| Mean time (± SD) since PAH diagnosis (yrs) | 3.7 ± 2.2 | 4.6 ± 4.1 | 4.4 ± 3.8 |
| Mean PAH Background Therapies | 2.1 ± 0.6 | 1.8 ± 0.5 | 1.9 ± 0.5 |
| PDE5i (n, %) | 8 (80%) | 35 (76%) | 43 (77%) |
| ERA (n, %) | 9 (90%) | 37 (80%) | 46 (82%) |
| Both ERA and PDE5i (n, %) | 8 (80%) | 27 (59%) | 35 (63%) |

## SAFETY

- Most commonly reported AE was muscle spasms, which are associated with creatine kinase reductions
- No drug-related serious adverse events occurring in > 1 patient treated with BARD for up to 2 years

**ADVERSE EVENTS THROUGH 16 WEEKS OF TREATMENT**

| Preferred Term | Number (%) of Patients | |
|---|---|---|
| | Placebo (n=10) | Bardoxolone Methyl (n=46) |
| Muscle Spasms | 1 ( 10 %) | 10 ( 22 %) |
| Nausea | 2 ( 20 %) | 8 ( 17 %) |
| Upper Respiratory Tract Infection | 1 ( 10 %) | 8 ( 17 %) |
| Headache | 2 ( 20 %) | 7 ( 15 %) |
| Diarrhoea | 1 ( 10 %) | 7 ( 15 %) |
| Fatigue | 1 ( 10 %) | 6 ( 13 %) |
| Decreased Appetite | 1 ( 10 %) | 5 ( 11 %) |
| Gastrooesophageal Reflux Disease | 0 ( 0 %) | 5 ( 11 %) |
| Urinary Tract Infection | 0 ( 0 %) | 5 ( 11 %) |
| Pain In Extremity | 0 ( 0 %) | 5 ( 11 %) |

AEs occurring in ≥ 5 patients

## CONCLUSION

- **Consistent with previous studies of bardoxolone methyl in patients with chronic kidney disease, bardoxolone methyl significantly increased eGFR in patients with PAH**
- **The increase in eGFR with bardoxolone methyl was sustained through two years of treatment**

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## DISCLOSURES

CM, MC, AG, MO, and KW are employees of Reata Pharmaceuticals. RO and MC are consultants to Reata Pharmaceuticals and receive research support from Reata Pharmaceuticals. FT is a speaker for Reata Pharmaceuticals. PM and AW have no financial disclosures. RJW serves as a paid consultant to Reata Pharmaceuticals with full disclosure to the University of Rochester.

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