

Bardoxolone Methyl Evaluation in Patients with Pulmonary Arterial Hypertension (PAH)

Initial Data Report from LARIAT: A Phase 2 Study of Bardoxolone Methyl in PAH Patients on Stable Background Therapy

Ronald J. Oudiz¹; Colin J. Meyer²; Melanie Chin², Jeremy Feldman³, Angie Goldsberry², John McConnell⁴, Peter A. McCullough⁵, Megan O'Grady², Victor F. Tapon⁶, Fernando Torres⁷, Aaron B. Waxman⁸, R. James White⁹

Presenter: Ronald J. Oudiz¹

¹ Los Angeles Biomedical Research Institute, Harbor-UCLA Medical Center, Torrance, CA, USA;

² Reata Pharmaceuticals, Irving, TX, USA;

³ Arizona Pulmonary Specialists LTD, Phoenix, AZ, USA;

⁴ University of Kentucky, Lexington, KY, USA;

⁵ Baylor University Medical Center, Baylor Heart and Vascular Institute, Baylor Jack and Jane Hamilton Heart and Vascular Hospital, Dallas, TX, USA;

⁶ Cedars-Sinai Medical Center, Division of Pulmonary and Critical Care Medicine, Los Angeles, CA, USA;

⁷ UT Southwestern Medical Center, Dallas, TX, USA;

⁸ Division of Pulmonary and Critical Care Medicine, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA;

⁹ University of Rochester Medical Center, Rochester, NY, USA



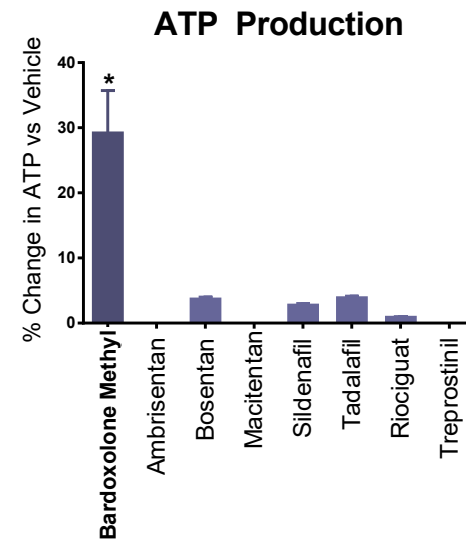
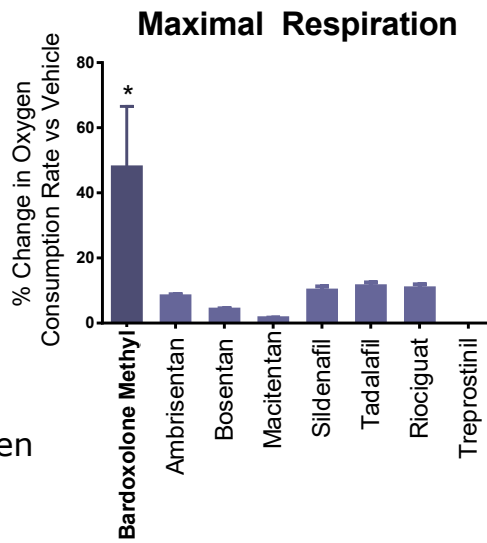
Disclosures

- Colin Meyer, Melanie Chin, Angie Goldsberry, and Megan O'Grady are employed by and have a financial interest in Reata
- Ronald Oudiz, Peter McCullough, Victor Tapson, and R. James White are consultants to Reata
- Ronald Oudiz, Jeremy Feldman, John McConnell, Fernando Torres, Aaron Waxman, and R. James White are investigators involved in the LARIAT study



Background: Bardoxolone Methyl

- An oral, once-daily Nrf2 activator and NF-κB suppressor
- Promotes mitochondrial respiration and reduces ROS and inflammation
- Genetic activation of Nrf2 in a preclinical model of PAH reduces arterial and RV remodeling without affecting systemic hemodynamics¹
- Unlike other PAH therapies, bardoxolone methyl:
 - Directly improves mitochondrial function and energy production in skeletal muscle cells
 - Does not influence systemic hemodynamics



ROS: reactive oxygen species

¹ Eba et al.; AJRCMB (2013)

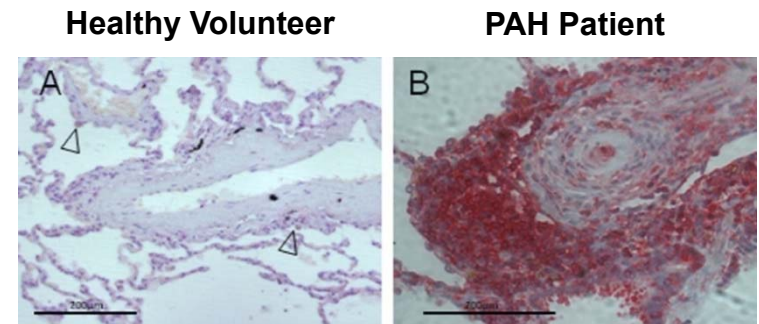
Data plotted as mean ± SD; (*) denotes statistically significant increases, $p < 0.05$; Data from Reata Study #RTA400-R-1505



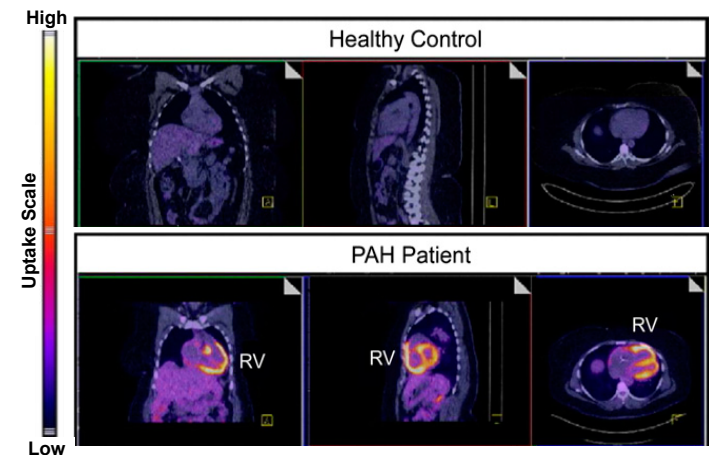
Background and Study Rationale

NF- κ B (Red Staining) is Activated in PAH Patients

- PAH involves multiple organs and is associated with inflammation
- NF- κ B is activated in PAH patients, which promotes inflammation, remodeling, and impaired mitochondrial function^{1, 2, 3, 4}
- Increased cardiac glycolytic metabolism in PAH⁵
- Improvements in mitochondrial function with bardoxolone methyl could:
 - Improve RV and skeletal muscle function in PAH patients
 - Further improve exercise capacity on top of established PAH therapies



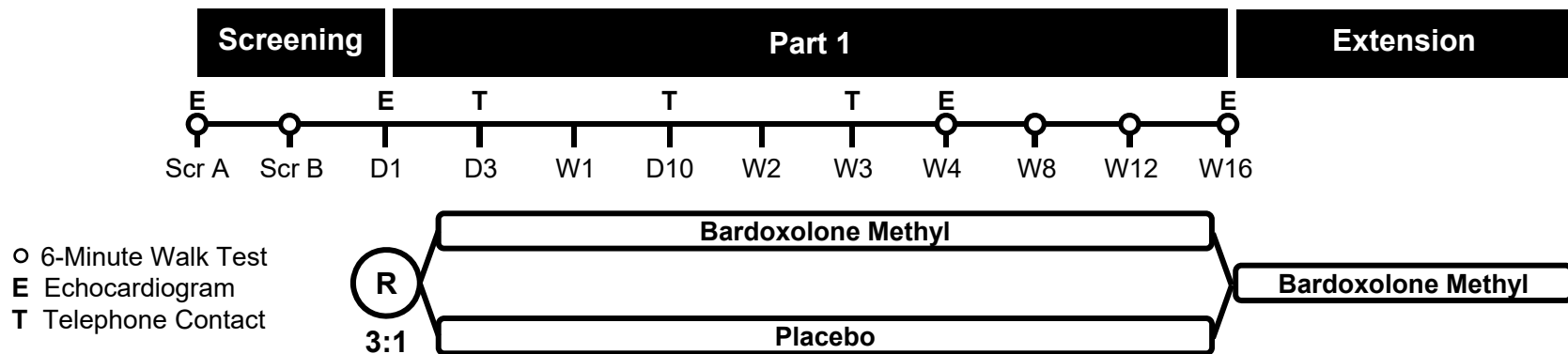
FDG-PET Scans Show Increased Glycolysis in PAH Patients



¹ Sutendra and Michelakis, *Cell Metabolism* (2014); ² de Man et al., *Eur Resp J* (2009); ³ Batt et al., *Am J Resp Cell Mol Biol* (2014); ⁴ Price et al., *PLoS One* (2013); ⁵ Lundgrin et al., *Ann AM Thorac Soc* (2013)

LARIAT : Schema, Design and Objectives

- Study Design
 - US-only, phase 2, double-blind, randomized, placebo-controlled study
 - WHO Group I patients required to be on 1-2 background therapies
 - Part 1: dose ranging study with 2.5, 5, 10, 20 mg (n=8 per dose group) given orally once-daily
 - Primary Efficacy Analysis: 2.5 mg, 5 mg, 10 mg dose groups with baseline 6MWD \leq 450 m
 - Safety Analysis: also includes 5 and 20 mg dose group with baseline 6MWD $>$ 450 m
 - Part 2: open-label extension study
- Primary Objectives
 - Change in 6MWD from baseline through 16 weeks
 - Safety and tolerability through 16 weeks
 - Determine the recommended dose range for further study of bardoxolone methyl



LARIAT: Baseline Characteristics

Parameter	Placebo	Bardoxolone Methyl		
		2.5 mg	5 mg	10 mg
N	6	6	6	6
Mean Age (\pm SD, yrs)	50.4 (8.8)	52.5 (7.1)	61.3 (9.7)	60.5 (12.5)
Female (n, %)	4 (67)	4 (67)	5 (83)	5 (83)
Mean Weight (\pm SD, kg)	75 (17.9)	81.8 (11.1)	86.1 (14.0)	80.9(19.9)
Mean BMI (\pm SD, kg/m ²)	28.2 (5.6)	30.6 (5.7)	31.4 (7.1)	29.5 (5.4)
PAH Etiology (n, %)				
Idiopathic	4 (67)	3 (50)	3 (50)	3 (50)
CTD	2 (33)	2 (33)	3 (50)	1 (17)
Anorexigen associated	0	1 (17)	0	2 (33)
WHO/NYHA Function (n, %)				
Class II	2 (33)	3 (50)	5 (83)	4 (67)
Class III	4 (67)	3 (50)	1 (17)	2 (33)
Mean Baseline 6MWD (\pm SD, m)	354 (49)	412 (20)*	373 (83)	364 (71)
Mean time since diagnosis (\pm SD, yrs)	4.6 (4.6)	3.5 (3.0)	6.8 (5.0)	4.5 (4.2)
Mean PAH Background Therapies	1.7	1.8	2	1.4
PDE5i (n, %)	4 (67)	6 (100)	4 (67)	4 (67)
ERA (n, %)	5 (83)	4 (67)	5 (83)	4 (67)

* $P < 0.05$ vs. Placebo



RESULTS: Mean Change in 6MWD

- Bardoxolone methyl increased 6MWD on top of background PAH therapies versus placebo
 - 6MWD increases seen at lowest dose
 - No dose-response overall

Treatment	N	Overall Δ 6MWD (m)	
		Absolute Δ 6MWD ^a (95% Confidence Interval)	Placebo-corrected treatment effect (95% Confidence Interval)
Bardoxolone Methyl 2.5 mg, 5 mg, 10 mg	16	21.6 (11.3, 31.8) (p = <0.001) ^b	21.4 (1.4, 41.4) (p = 0.037) ^c
Bardoxolone Methyl 2.5 mg	6	30.3 (13.5, 47.0)	30.0 (6.0, 53.9)
Bardoxolone Methyl 5 mg	6	14.0 (-2.8, 30.9)	13.7 (-10.5, 37.9)
Bardoxolone Methyl 10 mg	4	19.7 (-0.8, 40.2)	19.4 (-7.2, 46.1)
Placebo	6	0.2 (-16.8 – 17.1) (p = 0.983) ^b	-

^a Values are least-squared means from a longitudinal model with repeated measures at visits for each subject, adjusted for baseline, and use last-observation-carried-forward (LOCF) to impute missing data (only 3/110 time points)

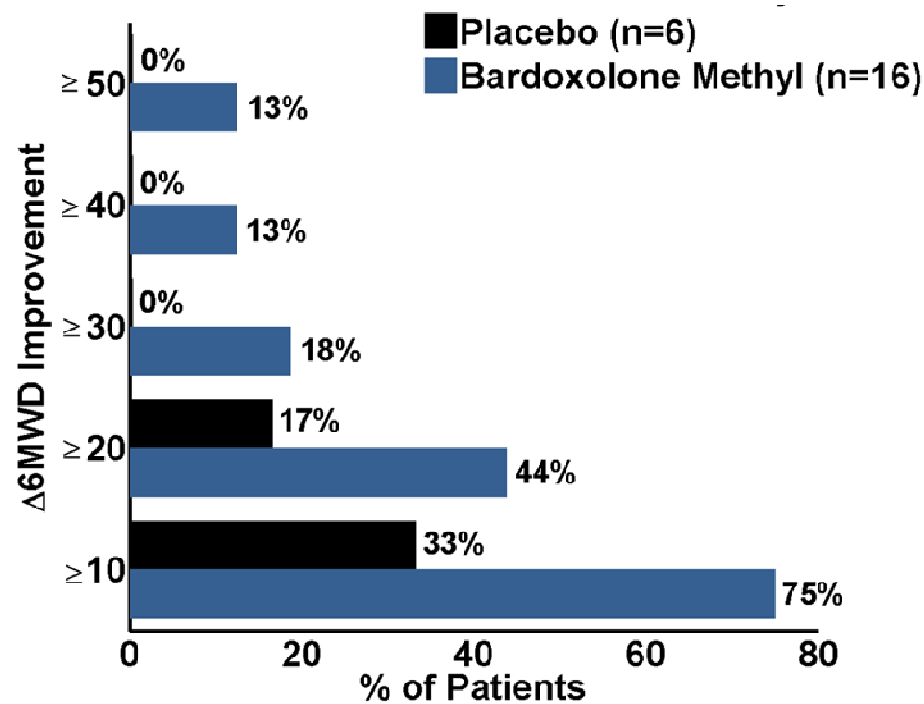
^b Overall change from baseline across all visits compared to zero

^c Overall change from baseline across all visits in bardoxolone methyl patients compared to placebo patients



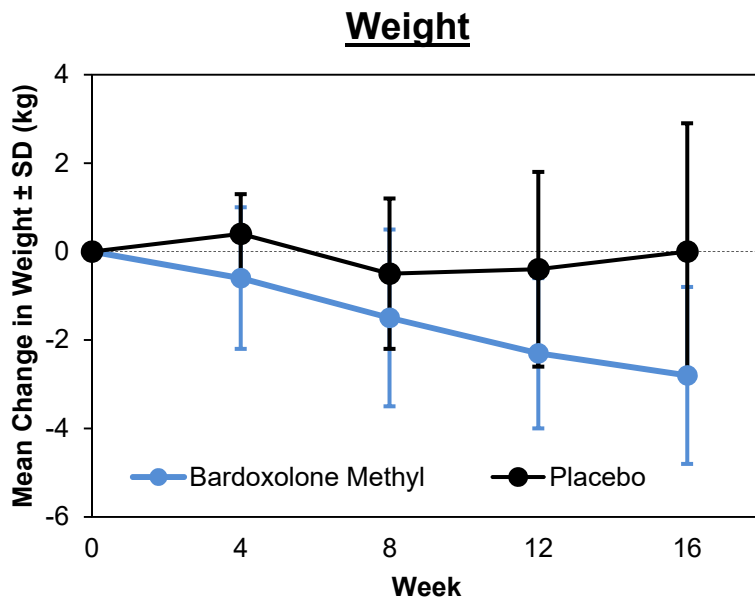
High Response Rate in Bardoxolone Methyl Group

- Shift in distribution of 6MWD change for bardoxolone methyl vs placebo

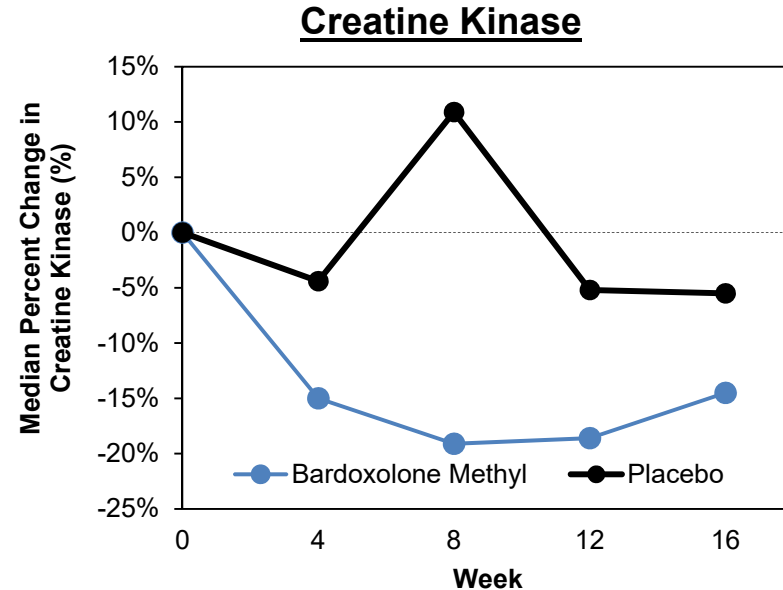


Metabolic Effects of Bardoxolone Methyl

- In preclinical studies, Nrf2 induction increases beta oxidation of lipids, reduces weight, and increases muscle function and regeneration^{1,2,3}
- As seen in prior studies, bardoxolone methyl reduces weight and CK in PAH patients^{4,5}
 - Weight reduced by approximately 3 kg versus placebo at Week 16



Placebo	n=6	n=6	n=5	n=5
Bardoxolone methyl	n=16	n=16	n=16	n=15



Placebo	n=6	n=6	n=5	n=5
Bardoxolone Methyl	n=16	n=16	n=16	n=15

¹ Uruno et al., MCB (2013); ² Ludtmann et al., Biochem J (2014); ³ Al-Sawaf et al., J Path (2014); ⁴ Pergola et al., NEJM (2011); ⁵ Saha et al., JBC (2010)



Additional Parameters of Interest

- No meaningful or dose-related changes in:
 - Ambulatory blood pressure monitoring or heart rate
 - BNP
 - Echocardiographic parameters of interest, including TAPSE*
- Bardoxolone methyl-treated CTD patients (n=6) showed a numerical 6MWD increase relative to the overall group
 - +30 m increase from baseline and +44 m placebo-corrected change
- 6MWD increase in bardoxolone methyl-treated patients was similar regardless of baseline 6MWD (≤ 450 m or > 450 m)
- Patients did not appear to have a ceiling effect, which has been described in prior studies of PAH therapies¹

**Tricuspid Annular Plane Systolic Excursion*

¹ Frost AE et al., *Vascular Pharmacology* (2005); 43;pp.36-39.



Bardoxolone Methyl: Safety and Tolerability

- Bardoxolone methyl well-tolerated with few discontinuations
- No treatment-related SAEs
- Unlike advanced CKD patients, no signs or symptoms of fluid retention
- Only dose-related AE: nausea increased at 20 mg (36% of 20 mg patients vs 9% of placebo patients)

Discontinuations

Treatment	Total Enrolled	Discontinuations	
		Total	Due to AE
Placebo	11	3 (27)	2 (18)
BARD All Doses	35	5 (15)	2 (6)
BARD 2.5 mg	6	1 (17)	0
BARD 5 mg	12	1 (8)	0
BARD 10 mg	6	2 (33)	1 (17)
BARD 20 mg	11	1 (9)	1 (9)

Adverse Events

Adverse Event*	BARD 2.5, 5, 10, 20 mg (n = 35)	Placebo (n = 11)
Headache	7 (20%)	3 (27%)
Nausea	5 (14%)	1 (9%)
Dyspnea	5 (14%)	0 (0%)
Upper Respiratory Tract Infection	5 (14%)	0 (0%)
Muscle Spasm	4 (11%)	1 (9%)
Dizziness	4 (11%)	0 (0%)
Epistaxis	4 (11%)	0 (0%)
Somnolence	1 (9%)	2 (20%)
Abdominal Distension	3 (9%)	2 (18%)
Alopecia	3 (9%)	2 (18%)
Back Pain	3 (9%)	2 (18%)
Nasopharyngitis	0 (0%)	2 (18%)
Oropharyngeal Pain	0 (0%)	2 (18%)

*Listed are any adverse events that occurred in $\geq 10\%$ of placebo or BARD patients



Summary and Conclusions

- Bardoxolone methyl improves mitochondrial function by reducing oxidative stress and inflammation
- Bardoxolone methyl was well-tolerated
 - Relatively few discontinuations in bardoxolone methyl-treated patients
 - Manageable adverse event profile
- Efficacy analyses suggest that bardoxolone methyl increases 6MWD in PAH patients across doses of 2.5 to 10 mg
 - 6MWD improvements were:
 - On top of background therapies, with no apparent ceiling effect
 - Seen in CTD-PAH patients as well as non-CTD patients
 - Associated with improvements in metabolic parameters
- LARIAT is expanding to study interstitial lung disease patients with PH
- Phase 3 study in CTD-PAH planned for 2016
 - FDA concurred with plan based on review of LARIAT efficacy and safety data
 - Additional phase 3 studies under consideration



LARIAT Investigators

Roblee Allen	University of California Davis Medical Center
David Badesch	University of Colorado Denver
Sonja Bartolome	University of Texas Southwestern Medical Center
Murali Chakinala	Washington University School of Medicine
Ira Dauber	South Denver Cardiology Associates
Teresa DeMarco	University of California San Francisco
Shilpa DeSouza	Winthrop University Hospital
Jean Elwing	University of Cincinnati
Peter Engel	The Lindner Clinical Trial Center
Harrison Farber	Boston University School of Medicine Pulmonary Center
Jeremy Feldman	Arizona Pulmonary Specialists
Adaani Frost	Houston Methodist Hospital
Hernando Garcia	BreatheAmerica
Mardi Gombert-Maitland	University of Chicago
Tony Hage	Cedars-Sinai Medical Center
Nicholas Hill	Tufts Medical Center
Evelyn Horn	Weill Cornell Medical Center
John McConnell	Kentuckiana Pulmonary Associates
Ronald Oudiz	Harbor UCLA Medical Center
Bela Patel	The University of Texas Health Science Center
Franck Rahaghi	Cleveland Clinic of Florida
Justin Roberts	Lancaster General Hospital
Zeenat Safdar	Baylor College of Medicine
Shelley Shapiro	VA Healthcare System of Greater Los Angeles
Namita Sood	The Ohio State University Wexner Medical Center
Aaron Waxman	Brigham and Women's Hospital
Jim White	University of Rochester
Joel Wirth	Maine Medical Center
Roham Zamanian	Stanford University School of Medicine
Dianne Zwicke	Aurora St. Luke's Medical Center



Presentation available at:
www.reatapharma.com

