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

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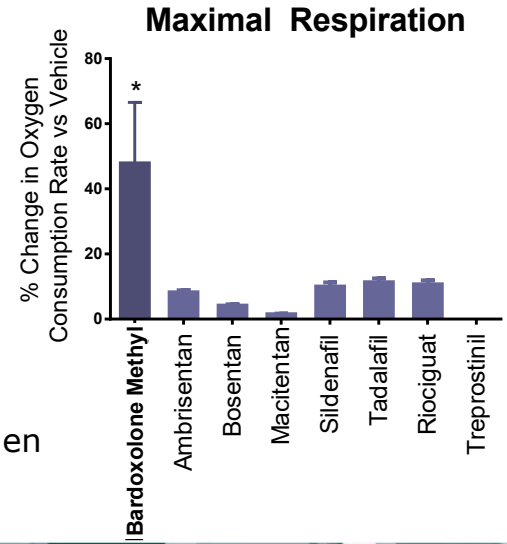
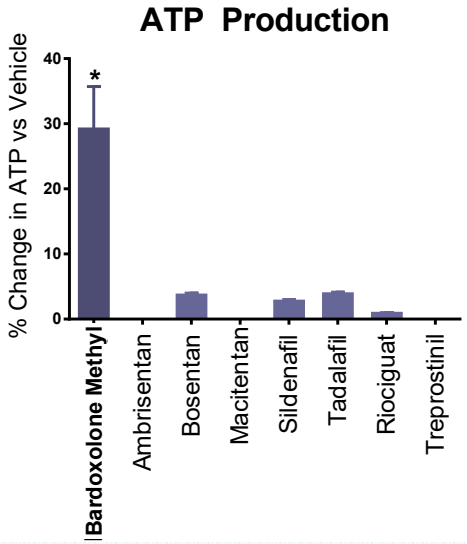
Disclosures

- 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 hemodynamics[1]
- 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

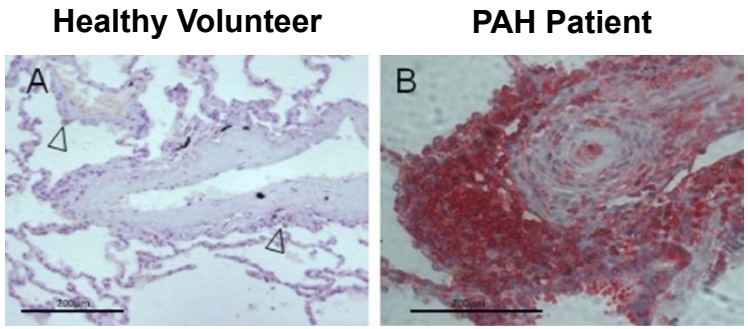
[1] *Eba et al.; AJRCMB (2013)*

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

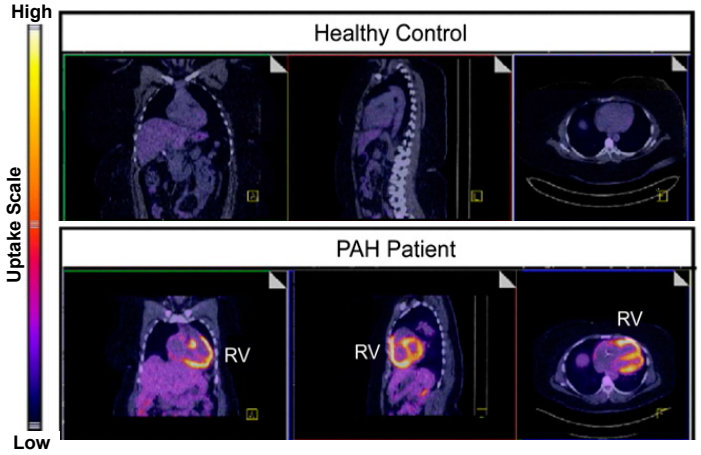
Background and Study Rationale

- PAH involves multiple organs and is associated with inflammation
- NF-κB is activated in PAH patients, which promotes inflammation, remodeling, and impaired mitochondrial function[1, 2, 3, 4]
- Increased cardiac glycolytic metabolism in PAH[5]
- 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

NF-κB (Red Staining) is Activated in PAH Patients



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)*

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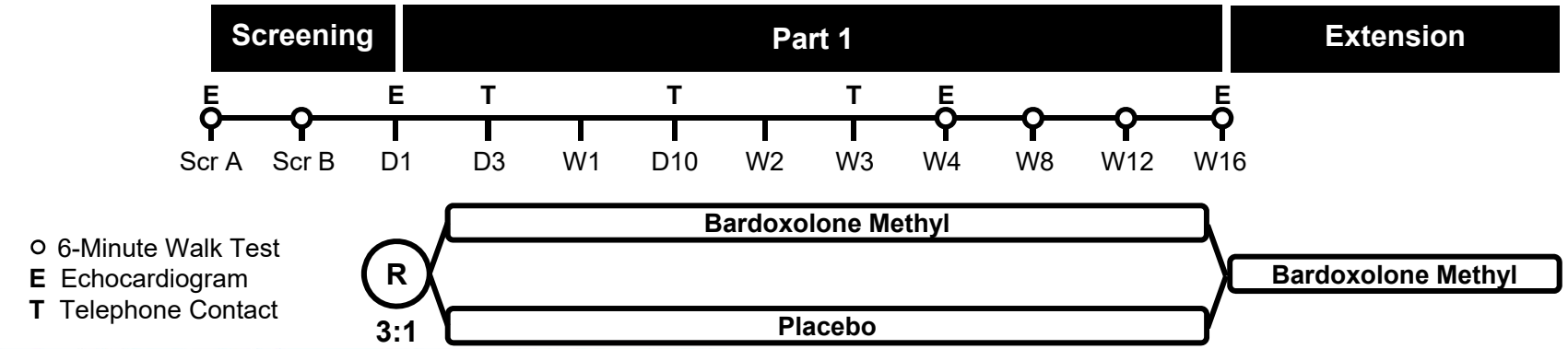
LARIAT : Schema, Design and Objectives

- 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 ≤ 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 (± 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 (± SD, kg)	75 (17.9)	81.8 (11.1)	86.1 (14.0)	80.9(19.9)
Mean BMI (± 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 (± SD, m)	354 (49)	412 (20)*	373 (83)	364 (71)
Mean time since diagnosis (± 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

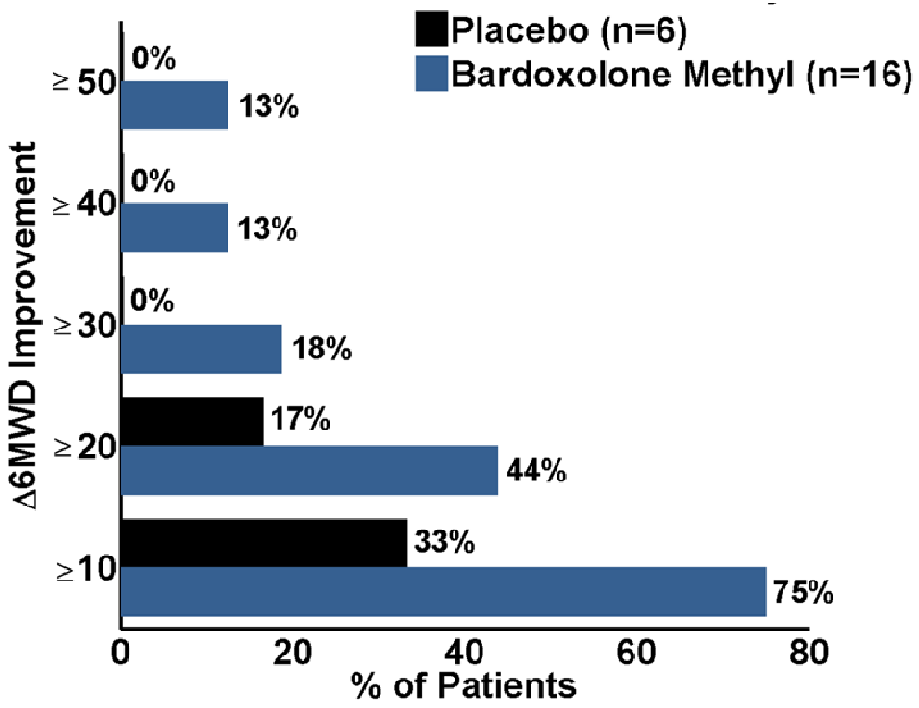
- Bardoxolone methyl increased 6MWD on top of background PAH therapies versus placebo
  - 6MWD increases seen at lowest dose
  - No dose-response overall

Treatment	N	Overall Δ6MWD (m)	
		Absolute Δ6MWD[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

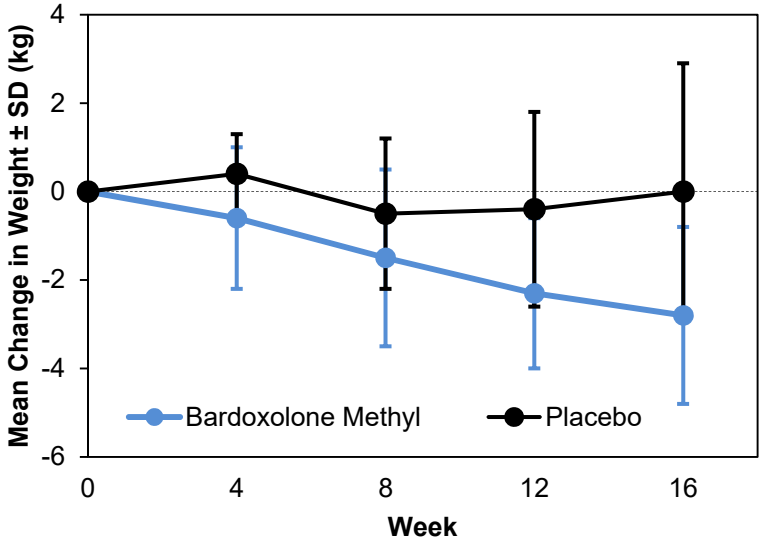
- Shift in distribution of 6MWD change for bardoxolone methyl vs placebo



Metabolic Effects of Bardoxolone Methyl

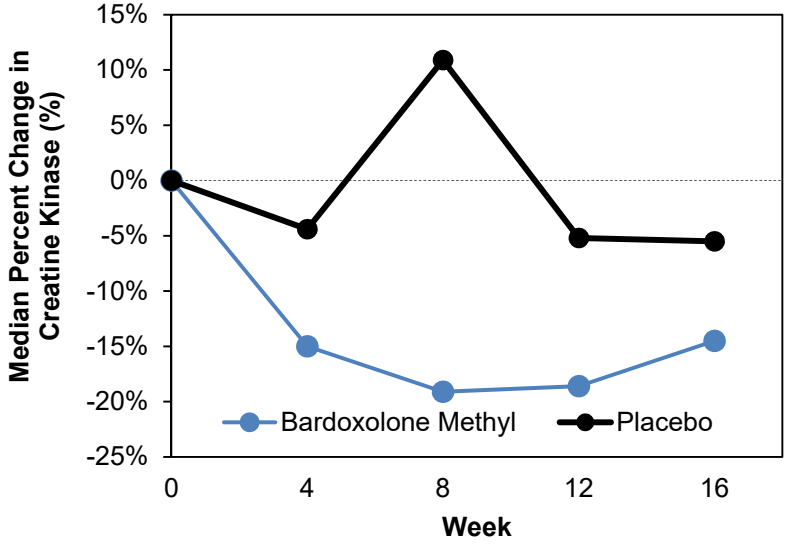
- In preclinical studies, Nrf2 induction increases beta oxidation of lipids, reduces weight, and increases muscle function and regeneration[1,2,3]
- As seen in prior studies, bardoxolone methyl reduces weight and CK in PAH patients[4,5]
  - Weight reduced by approximately 3 kg versus placebo at Week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

Weight



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

Creatine Kinase



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 therapies[1]

**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 ≥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

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