Interim Analysis of the Efficacy and Safety of Bardoxolone Methyl in Patients with Pulmonary Arterial Hypertension Associated with Connective Tissue Disease (CTD) (The LARIAT Study)

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BACKGROUND AND METHODS

This presentation reports additional interim results from the ongoing Phase II LARIAT study of the experimental therapy, bardoxolone methyl, in the subset of CTD-PAH patients

Bardoxolone Methyl (BARD)

- Once-daily, oral experimental therapy that activates Nrf2 and suppresses NF-κB
- Nrf2 activation restores ATP reserves by promoting mitochondrial respiration, increases expression of antioxidant genes and reduces ROS/ inflammation[1]
- No direct vasodilator activity, in contrast to currently approved PAH therapies

Pulmonary Arterial Hypertension (PAH) – Insights from Preclinical Studies

- PAH: now recognized as a systemic illness associated with inflammation
- NF-κB is activated in PAH patients, likely promoting inflammation, vascular remodeling and impaired mitochondrial function[2-5]
- PAH is associated with impaired mitochondrial metabolism in the heart, lungs, and other tissues[5]

Potential Advantages for BARD as Treatment for PAH

- Improvements in mitochondrial metabolism might facilitate better skeletal muscle and right ventricular function
- Different mechanism of action might add to established PAH therapies without side effects typical for vasodilating therapies

Rationale for Current Analysis

- **The traditionally less-responsive CTD-PAH patient subset in phase II reported at CHEST 2016 improved their 6MWD at Week 16 by a placebo-corrected 44m[7]**
- **The present interim analysis includes an additional cohort of CTD-PAH patients who have completed treatment with up to 10 mg of BARD (N=22)**
- **Further analysis excluding patients with moderate to severe anemia (N=19) informed patient selection for Phase 3 CATALYST in CTD-PAH**

Methods Longitudinal analysis was used to assess time-averaged change from baseline in 6MWD and change from baseline at Week 4, Week 8, Week 12, and Week 16 (end of treatment). Mean difference between active drug and placebo groups was compared using mixed-model repeated measures (MMRM). Missing 6MWD data were imputed using last-observation-carried-forward. Because treatment of anemia with IV iron during the blinded study period might have influenced 6MWD, an additional analysis excluding patients with moderate to severe anemia at screening (defined as hemoglobin < 10.5 g/dL). Three patients were excluded on that basis for the 'CATALYST eligible subgroup'.

REFERENCES

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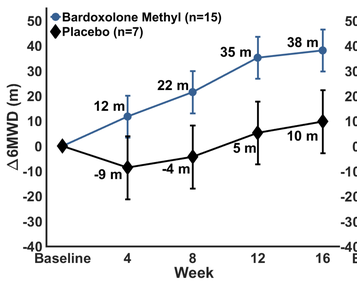
INTERIM RESULTS - EFFICACY

BASELINE CHARACTERISTICS: 22 CTD-PAH PATIENTS

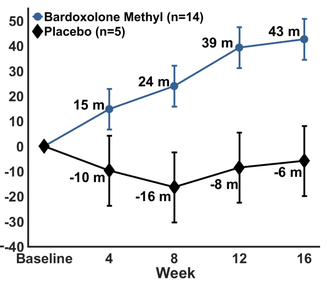
	Bardoxolone Methyl (N = 15)	Placebo (N = 7)
Female N (%)	12 (80%)	7 (100%)
BMI kg/m^2 (Mean ± SD)	27.5 ± 3.8	26.3 ± 5.7
Age (Mean ± SD)	56 ± 12	52 ± 12
Years since diagnosis (Mean ± SD)	2.9 ± 3.0	3.0 ± 2.5
WHO/ NYHA Class II	9 (60%)	4 (57%)
WHO/ NYHA Class III	6 (40%)	3 (43%)
CTD Etiology		
Limited scleroderma	4 (27%)	2 (29%)
Lupus erythematosus	3 (20%)	2 (29%)
Mixed CTD	1 (7%)	1 (14%)
Systemic sclerosis scleroderma	7 (47%)	2 (29%)
PAH background medications (average)	1.5 ± 0.5	2.1 ± 0.7
PAH background medication class		
Endothelin-receptor antagonists	12 (80%)	7 (100%)
PDE5 inhibitors	9 (60%)	6 (86%)
Riociguat	1 (7%)	0
Prostacyclins	1 (7%)	2 (29%)
Baseline 6MWD (m)	381 ± 59	396 ± 83

6MWD IMPROVEMENT IN CTD-PAH

All CTD-PAH Subjects (N=22)



Only CATALYST-eligible (N=19):
Excluding Subjects with Moderate to Severe Anemia at baseline



Summary of time-averaged 6MWD Changes in CTD-PAH Patients

Treatment	N	All Patients[a] Change from baseline[b]	All Patients[a] Placebo-corrected[c]	N	CATALYST-Eligible Patients[a] Change from baseline[b]	CATALYST-Eligible Patients[a] Placebo-corrected[c]
Placebo	7	0.6 (p =0.96)	-	5	-10.1 (p =0.39)	-
BARD	15	26.7 (p < 0.001)	26.1 (p = 0.06)	14	30.2 (p < 0.001)	40.3 (p =0.009)

[a] Values are least-squared means from a longitudinal model with repeated measures at visits for each subject, adjusted for Day 1 hemoglobin, and use last-observation-carried-forward (LOCF) to impute missing data (only 3/88 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

INTERIM RESULTS - SAFETY

ADVERSE EVENTS OCCURRING IN >1 CTD-PAH Patient

	Bardoxolone Methyl (N = 15)	Placebo (N= 7)
Headache	2 (13.3%)	4 (57.1%)
Nausea	1 (6.7%)	3 (42.9%)
Upper Respiratory Tract Infection	4 (26.7%)	0 (0%)
Tooth Abscess	0 (0%)	2 (28.6%)
Syncope	0 (0%)	2 (28.6%)
Neck Pain	0 (0%)	2 (28.6%)
Diarrhoea	3 (20%)	0 (0%)
Vomiting	2 (13.3%)	0 (0%)
Fatigue	2 (13.3%)	1 (14.3%)
Non-cardiac Chest Pain	2 (13.3%)	1 (14.3%)
Nasopharyngitis	2 (13.3%)	1 (14.3%)
Cough	2 (13.3%)	1 (14.3%)
Anemia	2 (13.3%)	0 (0%)
Tachycardia	2 (13.3%)	0 (0%)
Abdominal Distension	2 (13.3%)	0 (0%)
Muscle Spasms	2 (13.3%)	0 (0%)
Dizziness	2 (13.3%)	0 (0%)
Alopecia	2 (13.3%)	0 (0%)

- One of 7 patients in the placebo arm discontinued prematurely
- No discontinuations occurred in the BARD arm

CONCLUSIONS

- **In this expanded cohort of CTD-PAH patients, BARD improved 6MWD and continues to be well-tolerated**
- **Treatment of anemia during the study period appeared to influence 6MWD results**
- **Phase 3 (CATALYST) study in CTD-PAH patients excludes patients with moderate to severe anemia**

LIMITATIONS

- **These results are from an interim analysis of the CTD-PAH subset of LARIAT, and thus the number of patients analyzed is small. The findings remain to be confirmed in the Phase 3 (CATALYST) study, currently underway.**

DISCLOSURES

RO is a consultant to and receives research support from Reata Pharmaceuticals. CM, MC, AG and MO are employees of Reata Pharmaceuticals. JM is a consultant to Reata, Actelion, Gilead, United therapeutics, Bayer Pharmaceuticals, Eiger Pharmaceuticals, Genentech. VT is a consultant to Actelion, Bayer, Gilead, Reata Pharmaceuticals and United Therapeutics and receives research support from Actelion, Arena, Bayer, Reata Pharmaceuticals and United Therapeutics and speaker fees from Actelion and Bayer. FT receives grants from Gilead, GeNO LLC, Arena Pharmaceuticals, Eiger Pharmaceuticals, United Therapeutics and Medtronic. He is also a speaker for Actelion, Bayer, Boehringer Ingelheim, Reata Pharmaceuticals and SteadyMed. RJW serves as a consultant to Reata Pharmaceuticals with full disclosure to the University of Rochester. PM and AW have no financial disclosures.

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