Bardoxolone Methyl Produces Durable Benefits in Participants with Pulmonary Arterial Hypertension: Data from an Open-Label Extension 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 PAH patients through 32 weeks of treatment (Part 2, open-label).
Initial, placebo-controlled results were presented after 16 weeks of treatment (Part 1).

Bardoxolone Methyl (BARD)

- BARD is an experimental therapy that activates Nrf2 and suppresses NF-κB
- BARD promotes mitochondrial respiration, while reducing ROS/ inflammation
- BARD improves energy production in skeletal muscle cells *in vitro*, in contrast to currently approved PAH therapies

Pulmonary Arterial Hypertension (PAH) – Insights from the Literature

- PAH involves multiple organs and is associated with inflammation
- NF-κB is activated in PAH patients, likely promoting inflammation, vascular remodeling and impaired mitochondrial function[1-4]
- PAH is associated with impaired mitochondrial metabolism in the heart, lungs, and other tissues.[5] This 'Warburg effect', a shift towards anaerobic glycolysis despite available oxygen for mitochondrial respiration, is also seen in cancer.

Potential Advantages for BARD as Treatment for PAH

- Activation of Nrf2-mediated transcription with potential for improvement in RV and skeletal muscle function in PAH patients
- Further improvement in exercise capacity on top of established PAH therapies without side effects typical for vasodilating therapies

Initial Results from Phase II LARIAT (Part 1): BARD in PAH through Week 16

- BARD increased 6MWD in patients (n=16) on up to 2 background therapies[6]
- BARD also reduced weight and creatine kinase in PAH patients (evidence for improvement in mitochondrial metabolism)
- CTD-PAH patient-subgroup (n=6) showed a numerically greater improvement in 6MWD relative to the overall group (+44 m placebo-corrected change from baseline)

Part 1 LARIAT Data - Mean Change in 6MWD in PAH patients

Treatment	N	Baseline 6MW (m)	Overall Δ6MWD (m)	
			Absolute Δ6MWD[a] (95% CI)	Placebo-corrected treatment effect (95% CI)
Bardoxolone methyl (all doses)	**16**	**377 ± 63**	**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	412 ± 20	30.3 (13.5, 47.0)	30.0 (6.0, 53.9)
Bardoxolone methyl 5 mg	6	373 ± 83	14.0 (-2.8, 30.9)	13.7 (-10.5, 37.9)
Bardoxolone methyl 10 mg	4	331 ± 55	19.7 (-0.8, 40.2)	19.4 (-7.2, 46.1)
Placebo	6	354 ± 49	0.2 (-16.8–17.1) (p = 0.983)[b]	-

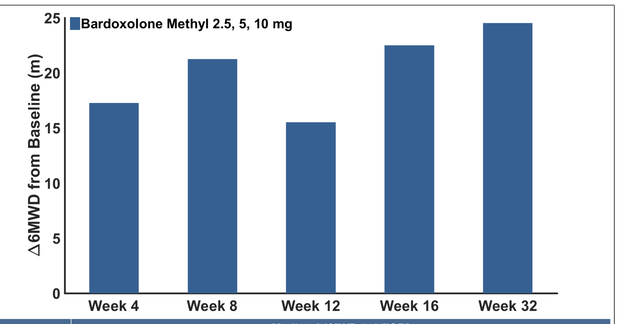
[a] Values are least-squared, time-averaged means from a longitudinal model with repeated measures at visits for each subject, adjusted for baseline, and use last-observation-carried-forward (LOCF) to impute missing data (imputations in 3/110 time points)
[b] Overall change from baseline across all visits compared to zero
[c] Overall change from baseline across all visits in bardoxolone methyl patients compared to placebo patients

Methods for Determining Sustained Efficacy with BARD

- Includes patients from interim LARIAT analysis with at least 32 weeks of treatment
- Summary statistics with no imputation for missing data

RESULTS - EFFICACY

6MWD Improvement (Primary Efficacy Analysis)

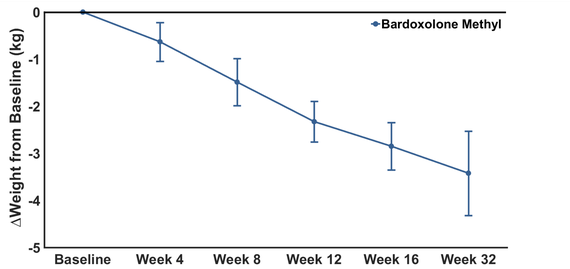


	Median Δ6MWD (m) [IQR]									
	N	Week 4	N	Week 8	N	Week 12	N	Week 16	N	Week 32
Bardoxolone Methyl	16	17.3 IQR [5.3, 21.8]	16	21.3 IQR [3.0, 31.3]	16	15.5 IQR [10.8, 34.8]	15	22.5 IQR [15.5, 49.0]	12	24.5 IQR [6.5,41.8]

- Median Δ6MWD at Week 32 is 24.5 m for bardoxolone methyl patients randomized to active in Part 1, at doses of 2.5, 5 and 10 mg
- >20 m Δ6MWD is sustained between Week 16 and Week 32 in patients treated with bardoxolone methyl

RESULTS - METABOLIC PHARMACODYNAMIC EFFECTS

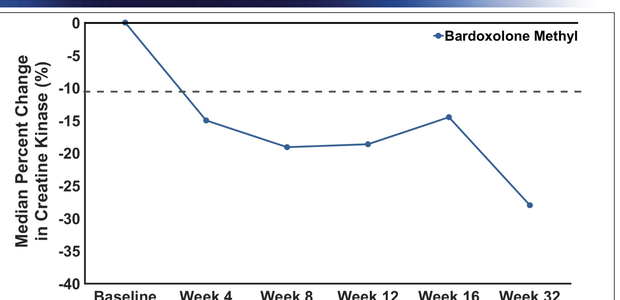
Decrease in Weight



	Mean Change from Baseline in Weight (kg) [±SD]									
	N	Week 4	N	Week 8	N	Week 12	N	Week 16	N	Week 32
BARD	16	-0.6 ± 1.6	16	-1.5 ± 2.0	16	-2.3 ± 1.7	15	-2.8 ± 2.0	13	-3.4 ± 3.6

- Patients randomized to bardoxolone methyl at Day 1 have an average decrease in weight from baseline of -3.4 kg at Week 32 in Part 2
  - Patients randomized to bardoxolone methyl at Day 1 have a baseline weight of 84.3 ± 13.3 kg

Decrease in Creatine Kinase



	Median % Change from Baseline in Creatine Kinase (%) [IQR]									
	N	Week 4	N	Week 8	N	Week 12	N	Week 16	N	Week 32
BARD	16	-15 IQR [-26.9, 2.9]	16	-19.1 IQR [-31.6, 2.3]	16	-18.7 IQR [-31.9, -2.4]	15	-14.5 IQR [-35.2, -9.6]	12	-28.0 IQR [-33.6, -12.9]

- Patients randomized to bardoxolone methyl at Day 1 have a median decline in CK of -28.0% at Week 32 in Part 2
  - Patients randomized to bardoxolone methyl at Day 1 have a mean baseline CK of 94 ± 57 U/L

RESULTS - SAFETY

Adverse Events Occurring in ≥10% of Patients

Adverse Events Which Occurred in ≥10% of Patients	Bardoxolone Methyl Part 1, up to Week 16 2.5, 5, 10, 20 mg (n = 35)	Bardoxolone Methyl Part 2, up to Week 32 2.5, 5, 10, 20 mg (n = 31)	Placebo Part 1, up to Week 16 (n = 11)
Headache	7 (20%)	2 (3%)	3 (27%)
Nausea	5 (14%)	2 (3%)	1 (9%)
Dyspnea	5 (14%)	0 (0%)	0 (0%)
Upper Respiratory Tract Infection	5 (14%)	2 (3%)	0 (0%)
Muscle Spasms	4 (11%)	2 (6%)	1 (9%)
Dizziness	4 (11%)	3 (10%)	0 (0%)
Epistaxis	4 (11%)	1 (3%)	0 (0%)
Somnolence	1 (9%)	0 (0%)	2 (20%)
Abdominal Distension	3 (9%)	2 (3%)	2 (18%)
Alopecia	3 (9%)	0 (0%)	2 (18%)
Back Pain	3 (9%)	0 (0%)	2 (18%)
Hypokalaemia	3 (9%)	3 (10%)	0 (0%)
Oropharyngeal Pain	0 (0%)	2 (6%)	2 (18%)
Nasopharyngitis	0 (0%)	0 (0%)	2 (18%)

- Adverse events in bardoxolone-treated patients occurred more often in Part 1
- 29 / 41 (71%) of LARIAT patients entered the extension study and reached Week 32 for this data cut
- 3 patients in the primary efficacy analysis (2.5 mg, 5 mg, 10 mg) and one additional 20 mg bardoxolone methyl patient completed their Week 16 visits but did not continue to Part 2 of the study

CONCLUSIONS

- **Interim data from this open-label extension suggest that the increase in 6MWD observed at 16 weeks in PAH patients treated with BARD at doses of 2.5-10 mg is sustained through Week 32 in the Phase II LARIAT study**
  - **Treatment with BARD yielded sustained improvements in 6MWD, even in combination with 1-2 approved PAH background therapies**
  - **Weight loss and reductions in creatine kinase were observed in BARD-treated patients, suggesting that BARD may produce metabolic improvements**
  - **BARD continues to be well tolerated in the PAH patients in this trial**
  - **Relatively few discontinuations were seen in this study through Week 32**
  - **The adverse events observed in this trial have been clinically manageable**
  - **LARIAT has been expanded to study cohorts of participants who also have interstitial lung disease with pulmonary hypertension (with and without CTD)**
- **A Phase III trial (CATALYST) has been initiated in WHO Group I CTD-PAH patients**
  - **Multi-national, double-blind, randomized, placebo-controlled trial**
  - **Patients can receive up to two PAH background therapies**
  - **Patients randomized 1:1 to BARD or placebo**
  - **Primary endpoint: Δ6MWD at Week 24**

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DISCLOSURES

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