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Initial Data Report from "CARDINAL": A Phase 2/3 Study of Bardoxolone Methyl in Patients with Alport Syndrome

Geoffrey A. Block[1], Pablo E. Pergola[2], Lesley A. Inker[3], Peter A. McCullough[4], Melanie Chin[5], Colin J. Meyer[5], Michelle N. Rheault[6], Clifford E. Kashtan[6], David G. Warnock[7]

[1]Denver Nephrology, Denver, CO, [2]Renal Associates PA, San Antonio, TX, [3]Tufts Medical Center, Boston, MA, [4]Baylor University Medical Center, Dallas, TX, [5]Reata Pharmaceuticals, Irving, TX, [6]University of Minnesota, Minneapolis, MN, [7]University of Alabama at Birmingham, Birmingham, AL

BACKGROUND AND RATIONALE

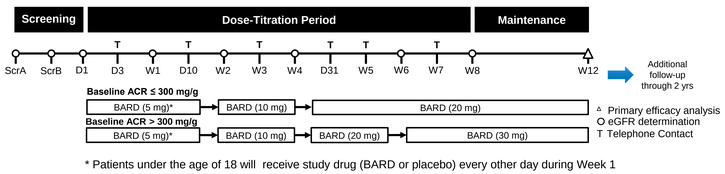
- Bardoxolone methyl (Bard) is an investigational drug that activates Nrf2 and suppresses inflammation[1], which contributes to GFR loss in chronic kidney diseases, including Alport syndrome[2]
- Mechanisms of eGFR increases with Bard in preclinical models[3-5]:
  - Dynamic increases in glomerular surface area for filtration (↑ Kf)
  - Chronic suppression of remodeling and fibrosis
- Bard and analogs have been shown to improve renal function and have protective effects in multiple preclinical models of renal disease[6-11]:
  - 5/6 nephrectomy model of hyperfiltration
  - Protein overload-induced secondary nephropathy
  - Diabetic nephropathy
  - Hypertensive CKD
  - Lupus nephritis
- Previous clinical studies that enrolled over 2,600 patients with type 2 diabetes and CKD demonstrate that Bard significantly increases eGFR, inulin clearance, creatinine clearance, and other renal function parameters[12-14]
- Post-hoc analyses of the BEACON study identified a specific subset of at-risk patients for fluid overload, who can be excluded from future trials[15,16]
- CARDINAL study conducted to evaluate safety and efficacy of Bard in patients with Alport Syndrome, who have progressive loss of kidney function and no approved therapies

CARDINAL PHASE 2 OPEN-LABEL STUDY DESIGN

- Enrolled 30 patients with genetic or histologic confirmation of Alport syndrome
- Dose-titration scheme used to reach goal dose of 20 or 30 mg given orally, once daily
- Primary efficacy endpoint: change from baseline in eGFR at Week 12
- Key eligibility criteria:

Inclusion
- Age: 12 to 60 years old
- eGFR: 30 to 90 mL/min/1.73 m^2
- Stable dosage of RAAS blockade for 6 weeks, unless medically contraindicated

Exclusion
- BNP > 200 pg/mL
- Serum albumin < 3 g/dL
- ACR > 3500 mg/g



* Patients under the age of 18 will receive study drug (BARD or placebo) every other day during Week 1

- Data presented in this presentation include all efficacy and safety data through the primary endpoint, Week 12

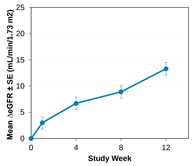
RESULTS – EFFICACY

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristic	Total (N=30)
Age, years	
Mean ± SD	44 ± 13
Median (range)	49 (14, 59)
Age < 18 years (n,%)	2 (7%)
Female (n,%)	18 (60%)
White/Caucasian (n,%)	26 (87%)
Baseline eGFR, mL/min/1.73 m^2	
Mean ± SD	54 ± 24
Median (range)	42 (28, 94)
Baseline ACR, mg/g (geometric mean)	148
ACR ≤ 300 mg/g (n,%)	18 (60%)
ACR > 300 to ≤ 1000 mg/g (n,%)	7 (23%)
ACR > 1000 to ≤ 3500 mg/g (n,%)	5 (17%)
Histologic Confirmation	2 (7%)
Genetic Confirmation	28 (93%)
X-linked (n,%)	22 (73%)
Autosomal (n,%)	5 (17%)
Unknown (n,%)	1 (3%)
Receiving ACEi or ARB (n,%)	25 (83%)

PRIMARY EFFICACY – Δ eGFR

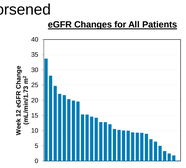
CHANGE FROM BASELINE IN eGFR
- All patients completed treatment through Week 12
- eGFR data show time-dependent increases through Week 12
- Changes consistent with Bard treatment in prior diabetic CKD studies



Change from Baseline in eGFR				
	Week 1	Week 4	Week 8	Week 12
N	30	30	30	30
Mean ± SE	3.0 ± 0.7	6.7 ± 1.3	8.9 ± 1.3	13.4 ± 1.4
95% CI	(1.6, 4.4)	(4.1, 9.3)	(6.2, 11.6)	(10.5, 16.3)
p-value	0.0001	<0.0001	<0.000001	<0.000000001

LS mean eGFR change from baseline at each visit is compared to zero using a mixed-model repeated measures analysis using baseline eGFR and log-transformed ACR as continuous covariates.

DISTRIBUTION OF eGFR CHANGES
- All patients demonstrated eGFR increases from baseline
- 87% of patients demonstrated increases of at least 4 ml/min/1.73 m^2
- 60% of patients demonstrated increases of at least 10 ml/min/1.73 m^2
- 22/30 (73%) of patients had an improvement in CKD stage and none worsened



Baseline CKD Stage		Week 12 CKD Stage				
	N	Stage 4	Stage 3b	Stage 3a	Stage 2	Stage 1
Stage 4 (eGFR <30)	5	1	4	-	-	-
Stage 3b (eGFR 30 to 44)	11	-	4	7	-	-
Stage 3a (eGFR 45 to 59)	2	-	-	0	2	-
Stage 2 (eGFR 60 to 89)	10	-	-	-	1	9
Stage 1 (eGFR >90)	2	-	-	-	-	2

Improved CKD Stage

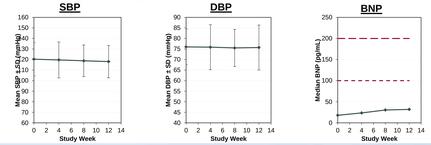
eGFR CHANGES BY SUBGROUP

- Clinically meaningful increases in eGFR across multiple subgroups
- Activity in earlier and later stages of disease

Baseline Characteristic	Subgroup	N	Baseline	Week 12 Mean ΔeGFR	
				Change ± SD	% Change
eGFR	≥ 60	12	81.3 ± 7.5	18.4 ± 7.7	23%
	< 60	18	36.1 ± 9.3	10.0 ± 6.6	30%
UACR	Non-macro	18	62.5 ± 22.2	16.0 ± 8.6	29%
	Macro	12	41.7 ± 22.0	9.4 ± 5.5	24%
Gender	Male	12	50.5 ± 25.1	14.0 ± 8.3	30%
	Female	18	56.6 ± 23.8	12.9 ± 8.1	25%
Age	< 18	2	86.1 ± 9.1	26.1 ± 10.8	31%
	≤ 45	11	48.4 ± 24.8	10.1 ± 9.5	20%
	> 45	19	57.5 ± 23.7	15.3 ± 6.7	31%

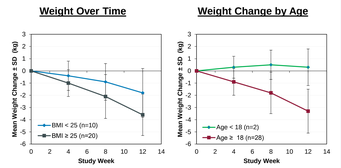
BLOOD PRESSURE AND BNP

- Patients with poorly controlled hypertension or BNP > 200 pg/mL were ineligible
- Blood Pressure and volume under control upon study entry and maintained post-initiation of treatment
- Average BNP upon entry was 1/10th allowable limit and 1/5th ULN
  - Median BNP levels maintained well below ULN threshold
  - No evidence of overt fluid overload



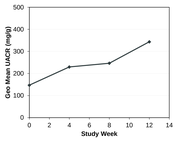
WEIGHT

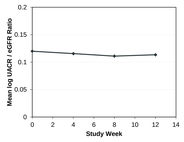
- Weight decreases with Bard, possibly due to improved mitochondrial function and metabolism as shown in preclinical models
- Mean decrease in weight (~1 kg / month) consistent with prior clinical trials with Bard
  - Patients with higher baseline BMI demonstrated larger weight loss
  - Mean decreases in weight not observed in patients < 18 years of age



URINE ALBUMIN TO CREATININE RATIO

- Increases in UACR with Bard consistent with increases in filtration (↑ GFR)
- Normalization of UACR with eGFR show UACR/eGFR ratios are unchanged from baseline



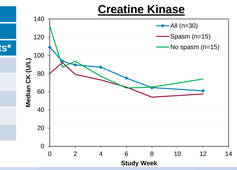


RESULTS – SAFETY

- No discontinuations
- No serious adverse events
- AEs to date have generally been mild to moderate in intensity
- No reports of fluid overload
- No consistent AEs yet, except muscle spasms
  - Also observed in prior diabetic CKD trials
  - Present as muscle contraction, usually in the lower extremity, and similar to exercise-induced cramps
  - Usually transient; occur in first month and resolve a few weeks after titration is completed
  - Not associated with evidence of muscle toxicity as assessed by CK

Number of Patients Reporting AEs	27 (90%)
Number of AEs	87
Preferred Term	Number (%) of Patients*
Muscle spasms	15 (50%)
Nausea	4 (13%)
Fatigue	4 (13%)
Headache	4 (13%)
Hyperkalemia	3 (10%)

*AEs reported in >2 patients



CONCLUSIONS

- Phase 2 CARDINAL study demonstrates bardoxolone methyl significantly increases eGFR in patients with Alport syndrome after 12 weeks of treatment
  - eGFR increases in CARDINAL were observed over full range of baseline eGFR values (range: 28 to 94 mL/min/1.73 m2) and across multiple subgroups
  - Most patients demonstrated improvements in CKD stage
  - Increases are similar in magnitude to those previously observed in patients with type 2 diabetes and Stage 3b-4 CKD
- Bard was well tolerated in patients with Alport syndrome
  - No discontinuations from study
  - No serious adverse events
  - No effect on blood pressure
  - When normalized by change in eGFR, urinary protein was unchanged from baseline
  - AEs to date have been mild to moderate in intensity
  - Muscle spasms were most commonly reported AE and not associated with evidence of muscle toxicity
- Phase 3 portion of CARDINAL study is actively enrolling. For more information, go to: https://www.cardinalclinicaltrial.com/
- Phase 2 PHOENIX trial studying Bard in ADPKD, type 1 diabetic CKD, IgA nephropathy, and FSGS is underway

REFERENCES

1. Sporn MB et al., J Nat Prod 2011; 74:537-45
2. Kruegel J et al., Nat Rev Nephrol 2013; 9:170-8
3. Ding Y et al., Kidney Int 2013; 83: 845-54
4. Aminzadeh MA et al., Redox Biol 2013; 1:527-31
5. Ferguson DA et al., ASN Poster 2010
6. Aminzadeh MA et al., Xenobiotica 2014; 44(6):570-8
7. Ma et al., NKF Presentation 2010
8. Ding Y et al., Kidney Int 2013; 83:845-54
9. Tan SM et al., Diabetes 2014; 63(9):3091-103
10. Wu T et al., Arthritis Rheumatol 2014; 66(11):3129-39
11. Hisamichi M et al., Hypertens Res 2017; Epub ahead of print
12. Pergola PE et al., Am J Nephrol 2011; 33(5):469-76
13. Pergola PE et al., N Engl J Med 2011; 365(4):327-36
14. De Zeeuw D et al., N Engl J Med 2013; 369(26):2492-503
15. Chin M et al., Am J Nephrol 2014; 39(6):499-508
16. Chin M et al., J Card Fail 2014; 12:953-958

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