



REATA

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



Geoffrey A. Block¹, Pablo E. Pergola², Lesley A. Inker³, Peter A. McCullough⁴, Melanie Chin⁵, Colin J. Meyer⁵, Michelle N. Rheault⁶, Clifford E. Kashtan⁶, David G. Warnock⁷
¹Denver Nephrology, Denver, CO, ²Renal Associates PA, San Antonio, TX, ³Tufts Medical Center, Boston, MA, ⁴Baylor University Medical Center, Dallas, TX, ⁵Reata Pharmaceuticals, Irving, TX, ⁶University of Minnesota, Minneapolis, MN, ⁷University of Alabama at Birmingham, Birmingham, AL

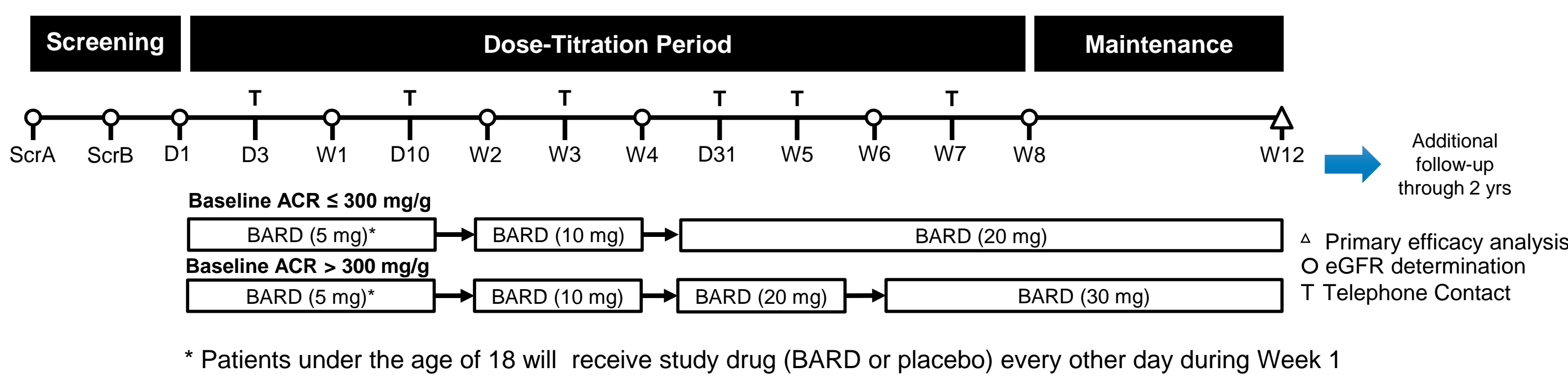
BACKGROUND AND RATIONALE

- Bardoxolone methyl (Bard) is an investigational drug that activates Nrf2 and suppresses inflammation¹, which contributes to GFR loss in chronic kidney diseases, including Alport syndrome²
- Mechanisms of eGFR increases with Bard in preclinical models³⁻⁵:
 - 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 disease⁶⁻¹¹:
 - 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 parameters¹²⁻¹⁴
- 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 m²
 - 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



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

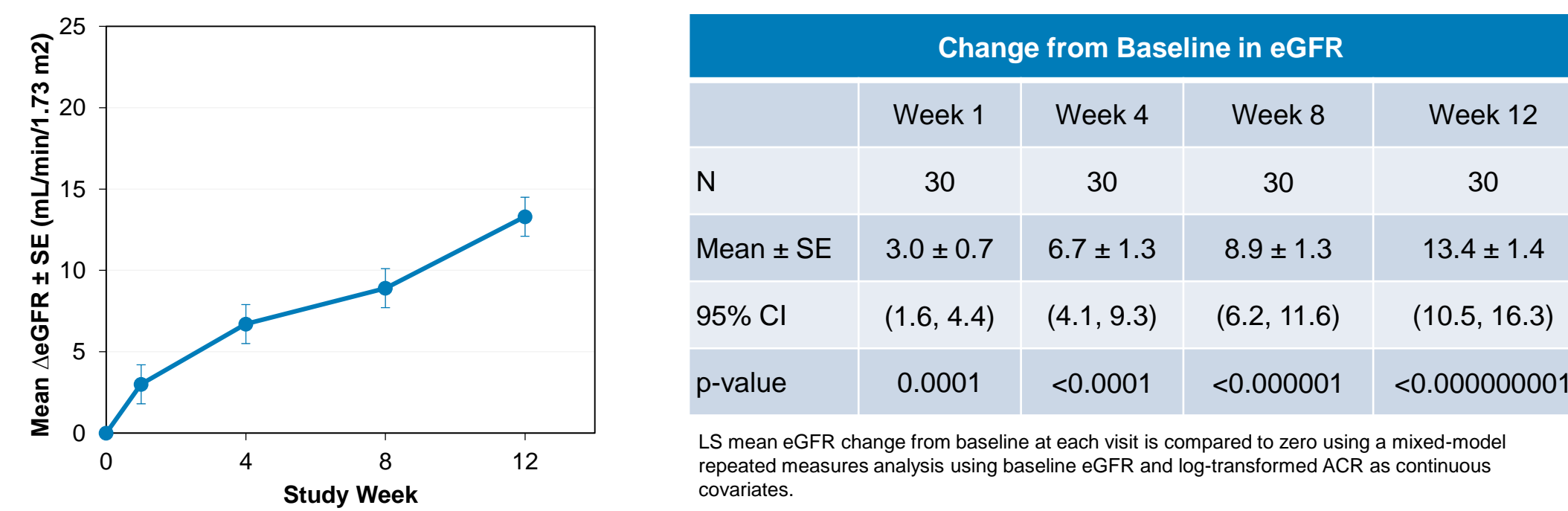
RESULTS – EFFICACY

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%)

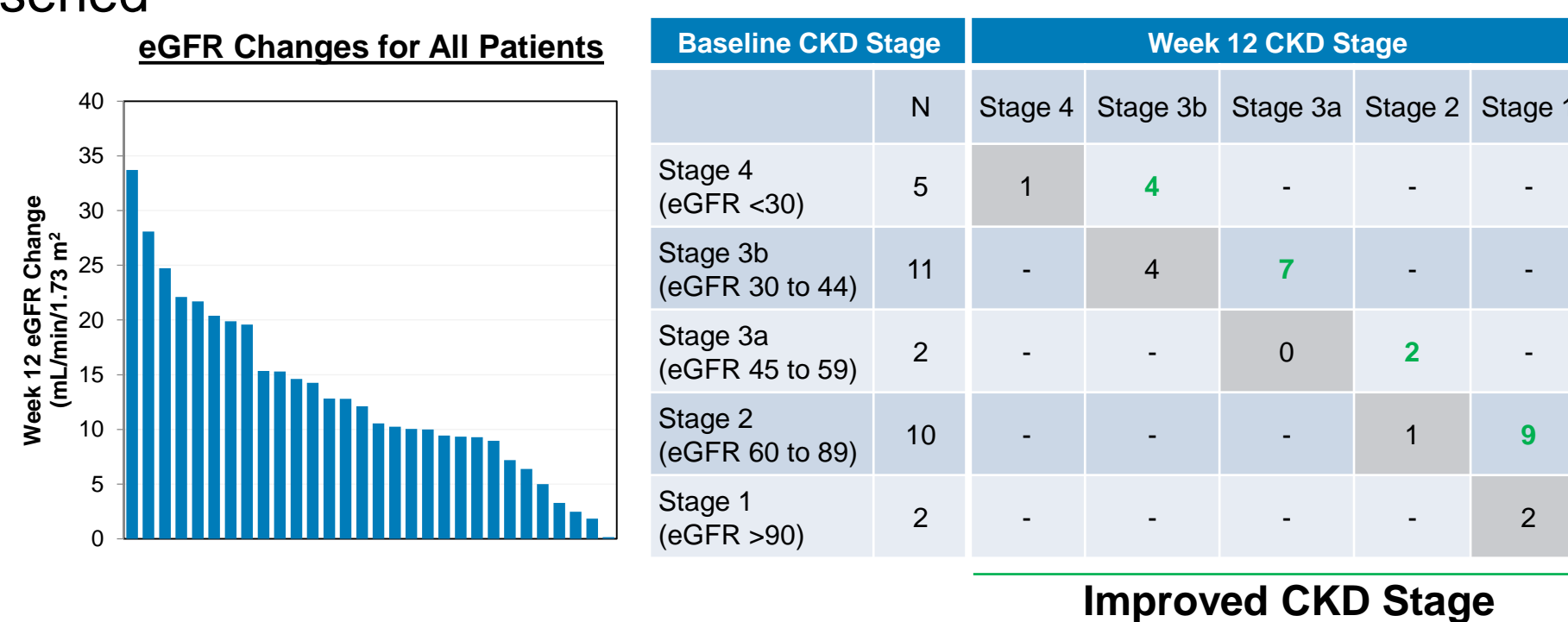
PRIMARY EFFICACY – Δ eGFR

- 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



DISTRIBUTION OF eGFR CHANGES

- All patients demonstrated eGFR increases from baseline
- 87% of patients demonstrated increases of at least 4 mL/min/1.73 m²
- 60% of patients demonstrated increases of at least 10 mL/min/1.73 m²
- 22/30 (73%) of patients had an improvement in CKD stage and none worsened



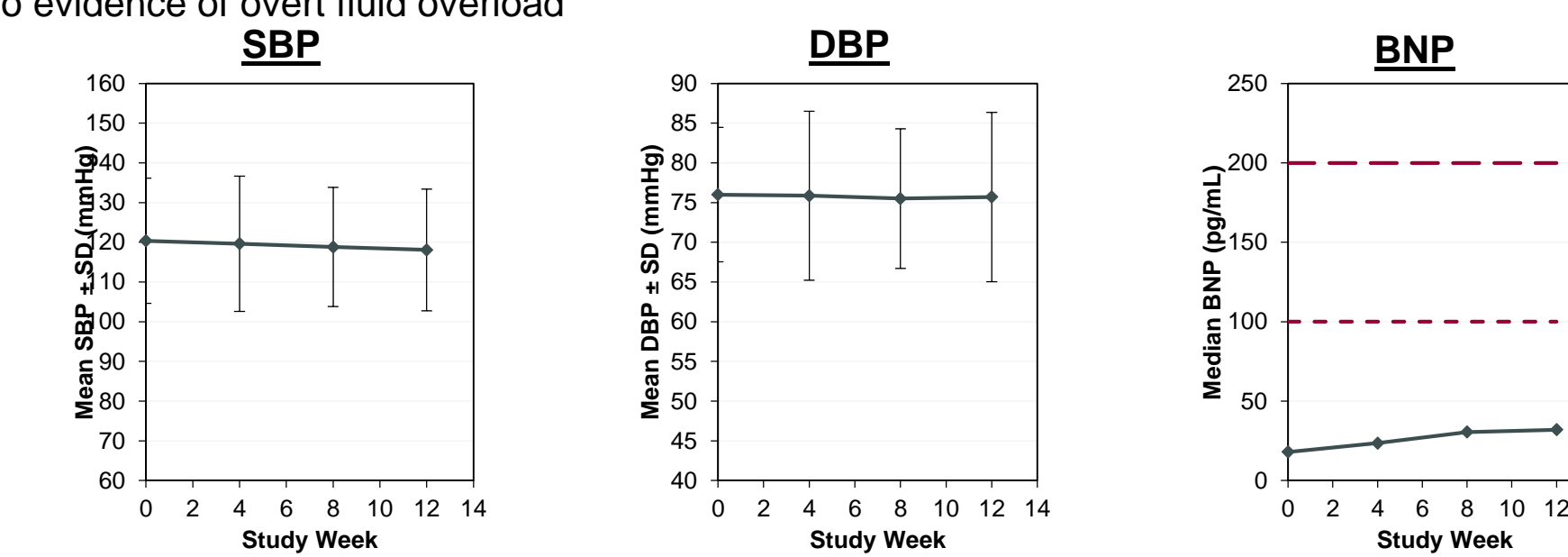
eGFR CHANGES BY SUBGROUP

- 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	19	48.4 ± 24.8	10.1 ± 9.5	20%

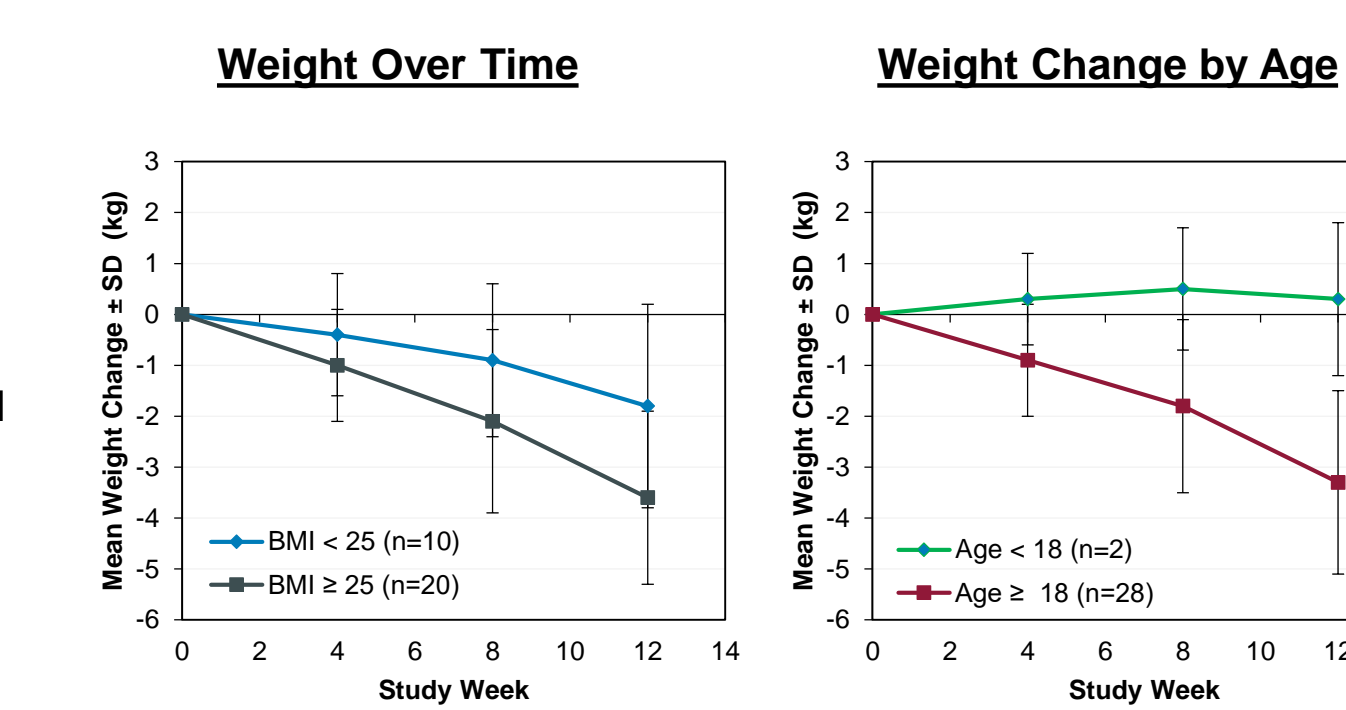
BLOOD PRESSURE AND BNP

- 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



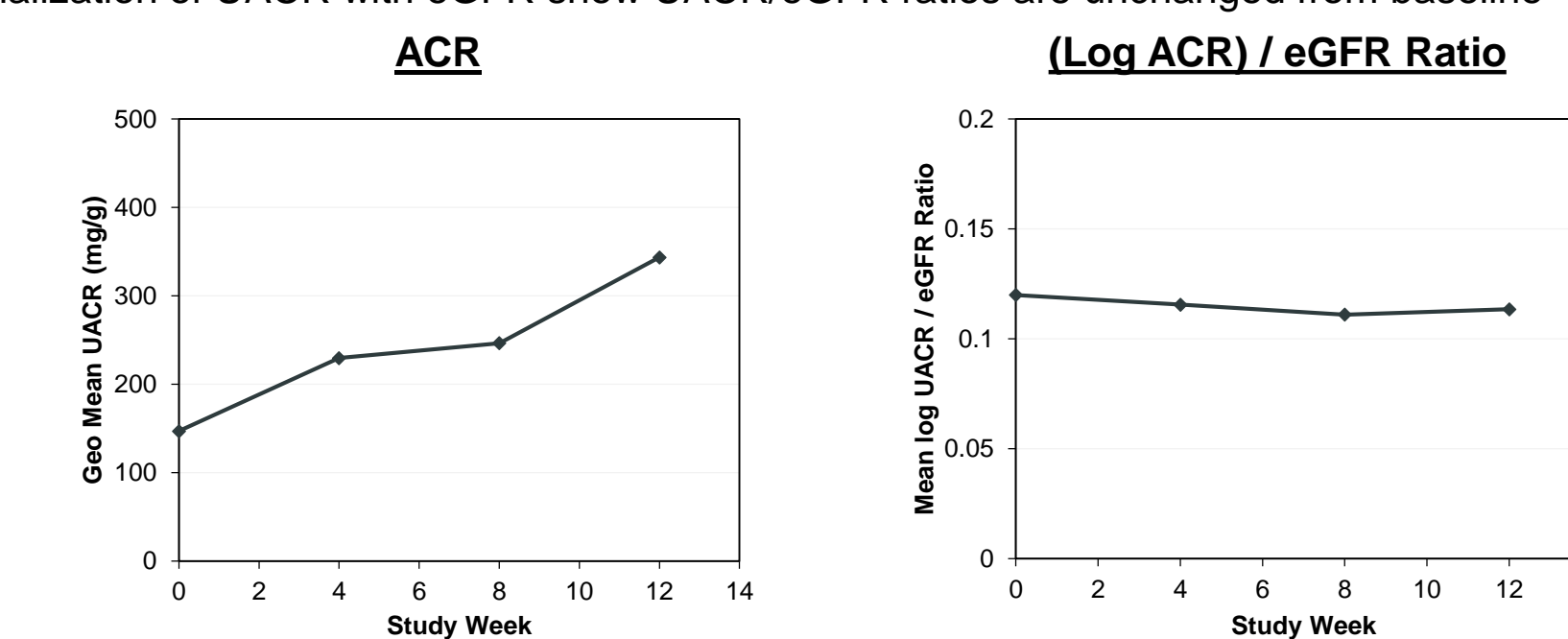
WEIGHT

- 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

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