BARDOXOLE METHYL

• BARDoxolone methyl (BARD) activates Nrf2 and suppresses NF-κB
  - NF-κB activation is reno-protective in kidney disease models1,2
  - BARD increases expression of antioxidants to reduce inflammation and pro-proliferative drive1,4
• BARD targets inflammatory pathways that contribute to GFR loss in chronic kidney diseases5-7

Diagnosis

Pre-Inflammatory Stimuli

- Diabetes, Hypertension, Excessive Tubular Protein Resorption, Mutated Type IV Collagen

Dynamic Processes

- Inflammation

Structural Processes

- Glomerular Endothelial Dysfunction
- Mesangial Cell Contraction
- Remodeling/Fibrosis

Reduced Glomerular Surface Area (K)

Total GFR Decline

GSM Thickening and Mesangial Expansion

Inflammation, fibrosis and mitochondrial dysfunction contribute to GFR loss and decreased kidney function in patients with Alport Syndrome5-9

CARDINAL STUDY DESIGN

CARDINAL STUDY (NCT03091185)

- Multicenter, multinational phase 2/3 study
- Patients 12 to 60 years of age with genetic or histologic confirmation of Alport syndrome
- Broad range of kidney function (eGFR between 30-90 ml/min/1.73 m²) and urine ACR ≤ 3500 mg/g
- Patients with history of cardiovascular disease or baseline risk for increased fluid retention (BNP > 200 pg/ml) will be excluded
- Dose-titration to goal BARD dose of 20 or 30 mg given orally, once daily

Phase 2 Cohort

- Open-label cohort enrolling a total of 30 patients: 15 with normo- or micro-albuminuria; 15 with macroalbuminuria
- Primary endpoint: change in eGFR at Week 12
- Following analysis at 12 weeks, patients will remain on treatment for 2 years

Phase 3 Cohort

- Enroll up to 180 patients for 2 years of treatment
- Placebo-controlled, double-blind, 1:1 randomization
- Primary endpoint - change in eGFR at Week 48
- Key secondary endpoint - change from baseline in eGFR at Week 52 following a 4-week drug withdrawal period

CARDINAL STUDY - SCHEMA AND DOSING SCHEDULE

Screen

Dose-Titration Period

Maintenance

W/D

Maintenance

F/U

W1

W2

W3

W7

W12

W16

W24

SRA

SrS8

D1

D2

D3

D4

D5

D6

D7

D8

T1

T2

T3

T4

T5

T6

T7

T8

Phase 2 primary efficacy analysis

Phase 3 primary efficacy analysis

Telephone Contact

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

CONCLUSION

CARDINAL is the first trial to test the hypothesis that BARD will improve kidney function in patients with Alport syndrome

REFERENCES

1. Saito K et al. Kidney Int. 2003; 64:1343-53
10. Pergola et al. NEJM. 2017; 376:775-86

DISCLOSURES

OM, MG, AO and Er are employees of Reata Pharmaceuticals.
DHR is an investor in Beata Pharmaceuticals.
PBET, GJ and EF are consultants to Reata Pharmaceuticals.