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CKD. PATHOPHYSIOLOGY, PROGRESSION AND RISK FACTORS 1

FP330 **APABETALONE, A SELECTIVE BROMODOMAIN AND EXTRA-TERMINAL (BET) PROTEIN INHIBITOR, REDUCES SERUM FGF23 IN CARDIOVASCULAR DISEASE AND CHRONIC KIDNEY DISEASE PATIENTS**

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INTRODUCTION: Fibroblast growth factor-23 (FGF23) is an osteocytic phosphaturic hormone known to increase renal phosphorus excretion and reduce calcitriol synthesis via the alpha-klotho obligate co-receptor. FGF23 has been identified as an independent marker for cardiovascular (CV) risk in various patient populations, including chronic kidney disease (CKD). Research has linked elevated levels of FGF23 to mortality, left-ventricular dysfunction, cardiac hypertrophy, vascular and endothelial dysfunction, and progression of CKD. Apabetalone is a first-in-class orally active bromodomain and extra-terminal (BET) inhibitor associated with the reduction of major adverse cardiac events (MACE) in patients with cardiovascular disease (CVD) in phase II clinical trials, now undergoing confirmatory phase III testing (BETonMACE trial). Apabetalone has previously been shown to downregulate markers of atherosclerosis, vascular calcification, and vascular inflammation. Here we demonstrate the effects of apabetalone on FGF23 in high risk patient populations, especially CKD.

METHODS: In the phase II clinical studies, ASSERT & ASSURE, high risk CVD patients were treated with 100 mg b.i.d. apabetalone vs. placebo. In a phase I renal impairment study, CS-016, stage 4/5 CKD patients not on dialysis were matched with control subjects without renal impairment, both groups receiving a single 100 mg oral dose of apabetalone. Plasma samples were collected from patients for proteomic analysis using the SOMAScan^{TM} 1.3K platform to assess relative fluorescent units (RFUs) of 1,300 analytes. Changes in protein levels were measured following 12 weeks (ASSERT) and 26 weeks (ASSURE) of treatment, and at 12 hours post dose in CS-016.

RESULTS: In the ASSURE trial, patients treated with apabetalone (n=47) saw a greater reduction of serum FGF23 (median change and percent change relative to baseline) of -17.3 RFUs, -3.7% vs. placebo patients (n=47), -8.6 RFUs, -1.7% (ANCOVA p-values vs. placebo: change = 0.01; percent change = 0.02). In patients that had baseline FGF23 levels greater than the median value, those that were treated with apabetalone (n=23) demonstrated an even greater reduction of FGF23 vs. placebo (n=23): -82.5 RFUs and -12.5% vs. -15.5 RFUs and -3.0% (ANCOVA p-value vs. placebo: change = 0.05; percent change = 0.1). CKD patients from both ASSERT and ASSURE trials treated with apabetalone (n=5) showed a decrease in levels of FGF23 (-31.1 RFUs, -6.6%) vs. placebo (n=5), who saw an increase (+264.2 RFUs, +49.3%) (Mann-Whitney p-value vs. placebo = 0.06 for both change and percent change). In the renal impairment study CS-016, stage 4/5 CKD patients treated apabetalone (n=8) showed a significant reduction in median serum FGF23 at 12 hours (-151.7 RFUs, -18.4%) vs. matched controls treated with apabetalone (n=8) (-24.6 RFUs, -5.8%) (ANCOVA p-value CKD patients vs. matched controls: change = 0.08; percent change = 0.03).

CONCLUSIONS: In CVD and renally impaired CKD patients, BET inhibition and apabetalone demonstrates consistent reduction of circulating FGF23, a marker of CV risk and progression of CKD. This effect appears to be more pronounced in patients that are at higher risk, including those with elevated levels of FGF23 above the median baseline level, and patients with CKD. The potential impact of chronic treatment with apabetalone on biomarkers, renal function, and CVD outcomes is currently being evaluated in the phase III BETonMACE CVD outcomes trial.