

BARDOXOLONE, A NOVEL ORAL ANTI-INFLAMMATORY AGENT SHOWN TO IMPROVE RENAL FUNCTION

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Bardoxolone methyl (BARD) is a first-in-class Antioxidant Inflammation Modulator (AIM) in clinical trials for CKD. BARD potently induces Nrf2, a transcription factor that is a well-validated target for CKD. Nrf2 activates over 250 antioxidant and detoxification genes within the cell, thereby modulating ROS-mediated endothelial dysfunction and structural remodeling in the kidney.

BARD has demonstrated significant nephroprotective activity in animal models of kidney injury. In preclinical toxicology studies, reductions in serum creatinine (SC) have been observed across multiple species. These effects on SC are independent of tubular secretion and creatinine production and thus likely reflect an increase in GFR.

These observations have been replicated in two Phase 1 trials of oncology patients. Within 21 days, 82% (49/60) of BARD-treated patients experienced a mean decrease in SC of 19.3%, corresponding to a mean 20.9% increase in GFR. Baseline SC and GFR were 1.00 mg/dl and 79.9 ml/min/1.73m², respectively. GFR improvements were more pronounced in a subset (n=13) of patients with established CKD (GFR < 60 ml/min/1.73m² at baseline). In these patients, GFR increased a mean of 27.6%. Changes in GFR were unrelated to weight changes. Decreases in BUN were also observed in these patients. Importantly, these results were sustained throughout the study period (6+ months).

Based on this data, a Phase 2 study in diabetic patients with CKD was initiated in May of 2008. This trial is measuring a number of markers of CKD, endothelial dysfunction, and glycemic control. Enrollment of this trial was completed in November, 2008.