AKI occurs in approximately 20-30% of all cardiac surgery patients, but can reach 70% in high risk or biomarker-defined populations. No treatments are approved to treat AKI. ASP1128 is a peripherally active selective modulator of PPARδ that improves metabolic and mitochondrial function. In AKI animal models, ASP1128 ameliorated renal function, histopathology, and injury biomarkers. It was shown to be safe in healthy human volunteers.

Design

This is a randomized, double-blind, placebo-controlled, proof-of-concept, phase IIa trial. Patients will be randomized at ~40 sites in North America. The study comprises three parts: 1) pre-surgery screening period, 2) CABG and/or valve surgery, and 3) post-operative period. Subjects undergoing CABG and/or valve surgery who have a moderate or high risk for developing AKI based on risk factors at screening (age, eGFR, congestive heart failure, diabetes mellitus, proteinuria) and post-operative urinary biomarkers (NephroCheck AKI Risk Score ≥ 0.3 [ng/mL]2/1000) will be followed-up as an observational cohort. Randomized patients will receive ASP1128 (n=110) or matching placebo (n=110) IV once daily for 48 hours. The primary objective of this study is to develop a short-term early intervention treatment for AKI to improve patient outcomes following cardiac surgery. The study will assess enhanced fatty acid oxidation as a means to restore mitochondrial function ameliorating kidney function in the early stage of AKI and its related clinical outcomes.

Objectives and Ethics

Primary Endpoint

1. % patients developing AKI based on KDIGO serum creatinine criteria within 72 hours post-surgery. Development of AKI will be judged based on Scr criteria from the kidney disease: improving global outcomes (KDIGO) guideline (i.e., increase in Scr ≥ 0.3 mg/dl/≥ 26.5 μmol/L) within any 48 hours, or increase in SCR to ≥ 1.5 times baseline) within 72 hours after end of surgery (TO).

Secondary endpoints

1. % patients developing AKI based on Scr criteria within 7 days
2. % patients developing AKI based on both KDIGO Urinary Output and Scr criteria within 72 hours, and 7 days
3. % patients with major adverse kidney events (MAKE) defined as all-cause mortality, renal replacement therapy (RRT) and/or ≥ 25% sustained reduction in eGFR within 30 and 90 days after day of surgery.

Endpoints

Summary and References

The 1128-CL-0201 study is the first study to use a biomarker to identify patients at risk for AKI in conjunction with an investigational agent, thereby selecting those that potentially may or may not benefit from a novel drug which has a new mechanism of action in AKI management. ASP1128 is a promising new drug that is hypothesized to improve mitochondrial dysfunction in patients flowing cardiac surgery.

References: