Design of the 1128-CL-0201 study, A Phase 2 Proof of Concept, Double-blind, Randomized, Placebo-controlled Study of ASP1128 in Patients at Risk for Acute Kidney Injury following Cardiac Surgery

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Introduction

AKI occurs in approximately 20-30% of all cardiac surgery patients, but can reach 70% in high risk or biomarker-defined populations[1,2]. 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 study. 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-surgery double-blind treatment period with a 90-day follow-up (Figure 1). To evaluate safety, tolerability and efficacy of study drug, patients with moderate/severe risk of AKI (based on urinary biomarkers [TIMP-2]*[IGFBP-7] measured with the NephroCheck device) at 2-6 hours post-surgery will be randomized to double blind treatment, while the biomarker negative patients will be followed-up as an observational standard-of-care cohort. Randomized patients will receive ASP1128 (n=110) or matching placebo (n=110) IV once daily for 3 days.

Eligible Population

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 AKIRisk Score® > 0.3 $[ng/mL]^2/1000$).

Sample Size

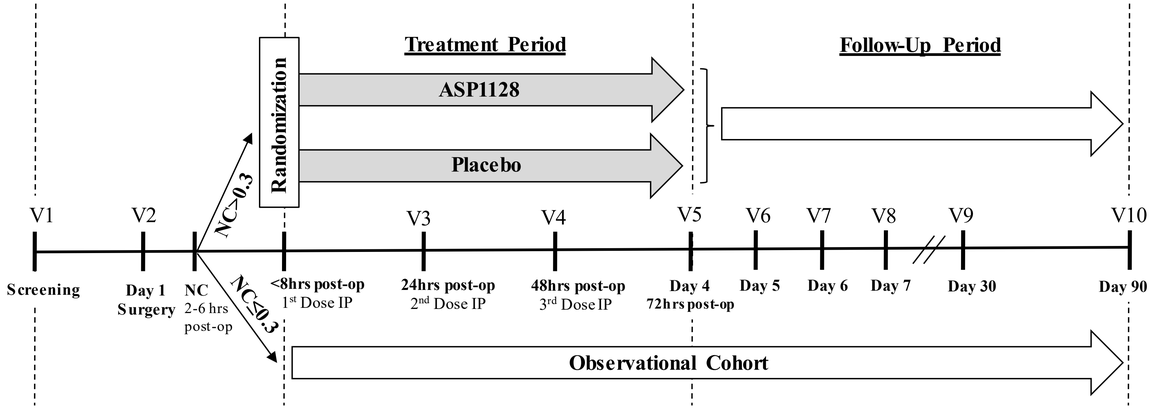
220 randomized subjects (110 subjects in the ASP1128 group and 110 subjects in the placebo group).

Objectives and Ethics

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.

Ethics: This study is approved by the relevant institutional review boards/independent ethics committees and conducted in accordance with the Declaration of Helsinki, guidelines of Good Clinical Practice, Code of Federal Regulations and all other applicable regulations. Trial registration: NCT03941483.

Figure 1. Flow Chart of the 1128-CL-0201 study



IP=investigational product; IV=intravenous; NC=NephroCheck

Endpoints

Primary Endpoint

- %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 (T0).

Secondary endpoints

- %patients developing AKI based on SCr criteria within 7 days
- %patients developing AKI based on both KDIGO Urinary Output and SCr criteria within 72 hours, and 7 days
- %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.

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.
- 220 patients at risk for AKI will be treated with placebo or ASP1128, a promising new drug that is hypothesized to improve mitochondrial dysfunction in patients flowing cardiac surgery.

Reference:

1. Billings FT, et al. JAMA. 2016; 315(9): 877–888. doi:10.1001/jama.2016.0548.
2. Hu J, et al., J Cardiovasc Vascul Anethes. 2016; 30 (1): 82–89. doi:10.1053/j.jvca.2015.06.017

INFORMATION: If you are interested in this study, would like to participate, and/or would like to refer patients to participating sites, please contact us at 1128-CL-0201_API_CMET@jp.astellas.com or olivier.vantill@astellas.com