

SYNOPSIS

Study Title:

A Phase 2 Proof of Concept, Double-blind, Randomized, Placebo-controlled Study to Evaluate the Efficacy of ASP1128 (MA-0217) in Subjects at Risk for Acute Kidney Injury following Coronary Artery Bypass Graft (CABG) and/or Valve Surgery

ISN/Protocol:

1128-CL-0201

Study Phase:

2

Study Investigational Product:

ASP1128

Indication:

Acute Kidney Injury

Sponsor:

Astellas Pharma Inc.
2-5-1, Nihonbashi-Honcho, Chuo-ku,
Tokyo 103-8411 Japan

Date and Version of This Report:

09 Jun 2022 version 1.0

Number of Study Centers and Countries:

This study was conducted at 32 centers that enrolled subjects in 1 country (United States).

Publications Based on the Study:

No publications based on the results of this study were available at the time this report was approved.

Study Period:

Study Initiation Date (date of first evaluation): 01 Nov 2019

End of Study Date (date of last evaluation): 20 Oct 2021

Rationale:

A dose of 100 mg once daily was selected for this proof-of-concept study. This dose was considered safe and well-tolerated in the phase 1 study 1128-CL-0101 with up to 7 days multiple dosing in healthy nonelderly and elderly subjects.

Methodology:

The study was a double-blind, placebo-controlled, randomized study with 1 ASP1128 treatment arm and 1 placebo treatment arm. Randomization occurred in a 1:1 manner. There was a cap on the proportion of

subjects randomized with an estimated glomerular filtration rate (eGFR) < 45 mL/min per 1.73 m^2 (assessed at visit 1 as per the Chronic Kidney Disease Epidemiology Collaboration equation) of 20% of the total randomized. Randomization was stratified for eGFR at visit 1 < 45 mL/min per 1.73 m^2 . The eGFR was calculated using the GFR estimation equation. The subject's age at visit 1 was used for calculation in this study.

Subjects were eligible for screening if they were scheduled for nonemergent (i.e., non-acute or directly life threatening) CABG and/or valve surgery within 4 weeks after screening. Subjects could not be rescreened once screening had failed.

Study visits included safety and efficacy assessments: chemistry, hematology and urinalysis laboratory assessments, urinary output, pregnancy test, physical examination, vital signs, blood pressure and assessment of adverse events (AEs). In addition, blood and urine were sampled for pharmacokinetics (PK), pharmacodynamics (PD), pharmacogenomics (PGx), metabolomics and biomarker assessments.

Subjects who met the presurgery selection criteria were enrolled in the study. Subjects who meet the postsurgery criterion of having a NephroCheck® (NC) AKIRisk® score > 0.3 (ng/mL) ^{2} /1000 between 2 and 22 hours after surgery were enrolled in the randomization cohort; randomized either to the placebo or the ASP1128 treatment group. The subjects that had an AKIRisk score of ≤ 0.3 (ng/mL) ^{2} /1000 at the postsurgery assessment were enrolled in the observational cohort. The rationale for following the subjects in the observational cohort is to further evaluate the AKIRisk score, as well as other risk factors (including clinical characteristics and biomarkers) for acute kidney injury (AKI) and major adverse kidney events (MAKE). Detailed study design including study visits, follow-up and the observational cohort are described in the protocol. The flow chart and schedule of assessments are also provided in the protocol.

Number of Participants (planned and analyzed):

The number of subjects planned to be randomized was 220.

The Data Monitoring Committee (DMC) reviewed the interim analysis results from 133 subjects and determined the results met the futility stop criteria (conditional power to detect the relative difference between ASP1128 and placebo on the primary endpoint of AKI proportion is less than 10%). The DMC recommended the study discontinuation and the 1128-CL-0201 was stopped on 30 July 2021. Randomized subjects or subjects in the observational cohort completed 90-day follow-up visits in accordance with the protocol schedule of assessments. The study did not enroll the preplanned sample size of 220 subjects (110/arm) due to the early termination.

Diagnosis and Main Criteria for Inclusion and Exclusion:

Subjects in this study were at least 35 years of age at the time of screening (visit 1), undergoing CABG and/or valve surgery within 4 weeks of screening and had a moderate or high risk for developing acute kidney injury based on serum creatinine KDIGO criteria (AKI-SCr) postsurgery.

Subjects were excluded from this study if they had chronic kidney disease (CKD) stage 4 or 5 or stage 3 (i.e., eGFR 30-59 mL/min per 1.73 m^2) with a known history of eGFR < 30 mL/min per 1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) or Modification of Diet in Renal Disease (MDRD) equation within 6 months prior to screening, had surgery scheduled to be performed without CPB (i.e., "Off-Pump" surgery), used left ventricular assist device, intra-aortic balloon pump or other cardiac devices, or

catecholamines within 7 days prior to screening or had any of the following abnormal liver or kidney function parameters as assessed at screening:

- alanine aminotransferase, aspartate aminotransferase to > 2 times the upper limit of normal (ULN) or bilirubin increased to > 1.5 times the ULN (not due to previously diagnosed Gilbert's syndrome).
- eGFR < 30 mL/min per 1.73 m^2 as per CKD-EPI equation.

Detailed inclusion and exclusion criteria are provided in the protocol.

Study Interventions, Dose and Mode of Administration:

Randomized subjects received 100mg ASP1128 or matching placebo once daily for 3 days, which were administered intravenously through a peripheral/central catheter. Detailed study treatment is described in the protocol.

Objectives, Endpoints and Statistical Methods

Study Objectives

Primary Objective

- To evaluate the efficacy of postsurgery treatment with ASP1128 in subjects at risk for acute kidney injury (AKI) following CABG and/or valve surgery

Secondary Objectives

- To investigate the safety and tolerability of postsurgery treatment with ASP1128 in subjects at risk for AKI following CABG and/or valve surgery
- To investigate the PK characteristics of ASP1128 in subjects at risk for AKI following CABG and/or valve surgery

Exploratory Objectives

- To investigate the pharmacodynamic characteristics of ASP1128 in subjects at risk for AKI following CABG and/or valve surgery
- To evaluate subject characteristics and biomarkers (including the NephroCheck® [NC] device) for identifying subjects at risk for AKI following CABG and/or valve surgery

Study Endpoints

Primary Endpoint

Proportion of subjects developing AKI (any stage) based on SCr criteria from the KDIGO guideline (i.e., increase in SCr ≥ 0.3 mg/dL [$\geq 26.5\text{ }\mu\text{mol/L}$] within any 48 hours, or increase in SCr to ≥ 1.5 times baseline) within 72 hours after T0 (AKI-SCr72h).

Secondary Endpoints

- Proportion of subjects developing AKI (any stage) based on SCr criteria from the KDIGO guideline within 7 days after T0 (AKI-SCr7d)
- Proportion of subjects developing AKI based on all captured criteria from the KDIGO guideline (i.e., AKI-SCr stage 1 to 3: increase in SCr ≥ 0.3 mg/dl [$\geq 26.5\text{ }\mu\text{mol/L}$] within any 48 hours, increase in SCr to ≥ 1.5 times baseline, and/or AKI-UO stage 2 and 3: urine volume < 0.5 ml/kg per hour for 12 consecutive hours) within 72 hours after T0 (AKI-KDIGO72h)

- Proportion of subjects developing AKI based on all criteria from the KDIGO guideline within 7 days after T0 (AKI-KDIGO7d)
- Proportion of subjects with MAKE defined as all-cause mortality, renal replacement therapy (RRT) and/or $\geq 25\%$ sustained reduction in eGFR based on SCr within 30 days after day of surgery (MAKE30). Sustained loss of renal function is defined as a reduction of kidney function (i.e., a reduction of eGFR of 25% or more compared to the baseline presurgery sample at visit 2) at the time of assessment (i.e., at day 30)
- Proportion of subjects with MAKE defined as all-cause mortality, RRT and/or $\geq 25\%$ sustained reduction in eGFR based on SCr within 90 days after day of surgery (MAKE90)
- Nature, frequency and severity of AEs
- Vital signs
- Safety laboratory tests: biochemistry, hematology and urinalysis
- ASP1128 plasma concentrations

Exploratory Endpoints

- Target gene expression
- Additional exploratory endpoints are detailed in the protocol.

Statistical Methods

Primary Analysis

The primary analysis was conducted on the full analysis set (FAS), Analysis group: Randomization Arm.

- The primary efficacy endpoint of AKI (AKI-SCr72h) proportion was planned to be analyzed using the Cochran-Mantel-Haenszel (CMH) test with strata to control for baseline eGFR based on SCr (< 45 mL/min per 1.73 m², ≥ 45 mL/min per 1.73 m²) on the FAS. The hypothesis testing on the primary analysis was planned to be performed at 2-sided 0.10 significance level to test the null hypothesis that the AKI-SCr72h proportion was equal between the 2 treatment arms versus the alternative hypothesis that AKI-SCr72h proportion was different between the ASP1128 treatment arm versus the placebo treatment arm.
- The Mantel-Haenszel (MH) estimate of the adjusted common risk ratio and 2-sided 90% confidence interval were calculated.

As described in the SAP, since the proportion of subjects with baseline eGFR based on SCr < 45 mL/min per 1.73 m² for FAS was less than 10%, the above stratified analyses of CMH test and MH estimate of adjusted common risk ratio were replaced with unstratified analyses of chi-square test and unadjusted risk ratio. These unstratified analyses also applied to the sensitivity analyses 2, 3 and 4 listed in the SAP.

Secondary Analysis

The analysis of secondary endpoints was conducted on the FAS, Analysis group: Randomization Arm.

- The secondary efficacy endpoints proportions (AKI-SCr7d, AKI-KDIGO72h, AKI-KDIGO7d, MAKE30 and MAKE90) were to be analyzed using the stratified CMH test with strata to control for baseline eGFR based on SCr (< 45 mL/min per 1.73 m², ≥ 45 mL/min per 1.73 m²). The hypothesis testing was to be

performed at 2-sided 0.10 significance level. The MH estimate of the adjusted common risk ratio and 2-sided 90% confidence intervals were calculated.

Further details on sensitivity and subgroup analysis and analysis of exploratory endpoints are detailed in the SAP.

Safety

Summaries and listings of serious adverse events (SAEs) and Serious treatment-emergent adverse events (TEAEs) included SAEs upgraded by the sponsor based on review of the Sponsor's list of Always Serious terms if any upgrade was done. The coding dictionary MedDRA was used to summarize AEs by system organ class (SOC) and preferred term (PT).

The number and percentage of subjects with TEAEs, as classified by SOC and PT were summarized for each treatment group.

The number of TEAEs and the number and percentage of subjects with TEAEs, as classified by SOC and PT were also summarized by severity using National Cancer Institute-Common Terminology Criteria for Adverse Events grades.

The number and percentage of subjects with TEAEs, as classified by SOC and PT were also summarized for each treatment group by time interval and by subgroups defined in the SAP.

Pharmacokinetic and Pharmacodynamic

For PK, descriptive statistics were presented for plasma concentration. Individual and mean concentrations of ASP1128 versus time were plotted. Plasma concentration and sample times data were listed.

For PD, the natural logarithm of gene expression data and its change from baseline were summarized using descriptive statistics. The natural logarithm of gene expression data using mean (SD) plot were presented graphically by treatment group. Additionally, the gene expression data and its fold change from baseline were summarized using descriptive statistics, and the fold change from baseline of gene expression data using box plot at each visit was presented graphically by treatment group.

Interim Analysis

The various interim analyses are detailed in the interim analysis plans.

Summary of Results:

Disposition of Participants:

Overall, 428 subjects signed informed consent for this study. Of those, 365 subjects entered the surgery period, 351 subjects were registered, 151 subjects were randomized and 200 subjects were enrolled in the observational cohort.

Of the 151 subjects enrolled in the randomization cohort, 81 subjects were randomized to the placebo treatment arm and 70 subjects were randomized to the ASP1128 treatment arm. One subject in the ASP1128 treatment arm did not receive the study drug (due to the study being terminated by the sponsor). The FAS and safety analysis set (SAF) were comprised of 150 subjects (69 in the ASP1128 treatment arm and 81 in the placebo treatment arm) who received at least 1 dose of study treatment. A total of 200 subjects were enrolled in the observational cohort.

Demographic and Other Baseline Characteristics:

In general, treatment groups were similar with respect to baseline characteristics, including age, baseline AKIRisk Score, baseline eGFR, surgery parameters, AKI risk factors (except for female gender and CKD) and baseline values of efficacy variables.

The majority of subjects were male (127 [84.7%] subjects overall) and white (144 [96.0%] subjects overall). The percentage of female patients was higher in ASP1128 treatment arm (23.2%) compared to placebo treatment arm (8.6%). Baseline CKD was more observed in the placebo treatment arm (25.9 %) than in the ASP1128 treatment arm (8.7%).

The age of all randomized subjects ranged from 42 to 89, with a mean age of 68 years.

Exposure:

Of the 150 subjects who received study drug, the majority (145 [96.7%] subjects) received all 3 doses of placebo or ASP1128.

Efficacy Results:

No effect of ASP1128 was observed on any AKI parameter (including AKI-SCr 72/7d), MAKE parameter (on day 30 or 90), and kidney injury biomarkers (SCr, serum Cystatin-C, KIM-1). This study did not demonstrate a treatment effect by ASP1128 for cardiac associated AKI.

The absence of effect on AKI could be attributed to an overall good renal reserve of the study population at baseline (e.g., high eGFR) which negatively impacted the sensitivity of serum creatine as a defining parameter of AKI, and it could hinder the evaluation of a robust effect of the compound on kidney injury outcomes.

Safety Results:

In general, the frequency of TEAEs (overall, drug-related, serious, and discontinuations) and severity of AEs were similar between treatment arms.

Overall, 75.4% in the ASP1128 treatment arm and 72.8% in the placebo treatment arm reported at least one TEAEs. The percentage of subjects who reported serious TEAEs were 49.3% for the ASP1128 treatment arm and 51.9% for the placebo treatment arm.

Pharmacokinetic Results:

- Blood samples for PK were collected as follows:
 - First administration: predose, at end of the first infusion, and twice after study drug administration at 2 to 4 hours postdose and 4 to 12 hours postdose.
 - Second administration: at the end of infusion
 - Third administration: predose and at end of infusion
- ASP1128 plasma concentrations at end of infusion for the first, second and third administrations were similar.
- ASP1128 plasma concentrations decreased rapidly from end of infusion to 4 to 12 hours postdose.

Pharmacodynamic Results:

- Of the 7 peroxisome proliferator activated receptor δ (PPAR δ) target genes measured, the ASP1128 treated arm genes demonstrating increases in gene expression from baseline were acetyl-coenzyme A

acyltransferase 2, solute carrier family 25 member 20, acyl-CoA dehydrogenase very long chain, carnitine palmitoyltransferase 1A, and pyruvate dehydrogenase lipoamide kinase isozyme 4. No clear fold change in gene expression in the placebo treatment arm throughout the study was observed.

- Blood samples for gene expression measurements were collected at predose and 2 to 4 hours postdose of first and third administrations.
- Consistent increase of fold changes for the 5 genes (ACAA2, SLC25A20, ACADVL, CPT1a and PDK4) suggests that there was consistent treatment-dependent up-regulation following ASP1128 dosing. In comparison, there were no treatment-related trends for ABCA1 and CAT.
- The gene up-regulation appeared to persist from 2 to 4 hours postdose of first administration through 2 to 4 hours postdose of third administration.

Conclusions:

Overall, ASP1128 is considered safe but lacked efficacy in cardiac surgery associated AKI. Proof of concept for ASP1128 in subjects at risk for AKI following CABG and/or valve surgery was not met, as analysis of all efficacy endpoints in this study did not support sufficient efficacy in this population. The overall safety profile was tolerable. Adequate PK and PD were collected in this study.

Efficacy

- ASP1128 did not show a positive treatment effect for the primary efficacy endpoint of AKI-SCr72h compared to placebo.
- The secondary efficacy endpoints of AKI-SCr7d, AKI-KDIGO72h, AKI-KDIGO7d, MAKE30 and MAKE90 also did not demonstrate statistically significant treatment differences.

Safety

- Treatment with ASP1128 was generally safe and well-tolerated in subjects at risk for AKI following CABG and/or valve surgery.
- The ASP1128 and placebo treatment arms had comparable safety profiles. There were no new significant safety findings in the ASP1128 treatment arm.

Pharmacokinetics

- ASP1128 plasma concentrations at end of infusion were similar throughout the treatment period.
- ASP1128 plasma concentrations decreased rapidly after end of infusion.

Pharmacodynamics

- ASP1128 appeared to have a treatment-related up-regulation on 5 PPAR δ target genes. The gene up-regulation appeared to persist from 2 to 4 hours postdose of first administration through 2 to 4 hours postdose of third administration.