

Hepatocyte Growth Factor Mimetic ANG-3777 for Cardiac Surgery–Associated Acute Kidney Injury



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Introduction: Nearly one-third of patients undergoing cardiac surgery involving cardiopulmonary bypass (CPB) experience cardiac surgery–associated (CSA) acute kidney injury (AKI); 5% require renal replacement therapy. ANG-3777 is a hepatocyte growth factor mimetic. *In vitro*, ANG-3777 reduces apoptosis and increases cell proliferation, migration, morphogenesis, and angiogenesis in injured kidneys. In animal models, ANG-3777 mitigates the effects of renal damage secondary to ischemia reperfusion injury and nephrotoxic chemicals. Phase 2 data in AKI of renal transplantation have shown improved renal function and comparable safety relative to placebo. The Guard Against Renal Damage (GUARD) study is a phase 2 proof of concept trial of ANG-3777 in CSA-AKI.

Methods: GUARD is a 240-patient, multicenter, double-blind, randomized placebo-controlled trial to assess the efficacy and safety of ANG-3777 in patients at elevated pre-surgery risk for AKI undergoing coronary artery bypass graft (CABG) or heart valve repair/replacement requiring CPB. Subjects are randomized 1:1 to receive ANG-3777 (2 mg/kg) or placebo. Study drug is dosed via 4 daily intravenous 30-minute infusions. The first dose is administered less than 4 hours after completing CPB, second at 24 ± 2 hours post-CPB, with two subsequent doses at 24 ± 2 hours after the previous dose.

Results: The primary efficacy endpoint is percent change from baseline serum creatinine to mean area under the curve from days 2 through 6. Secondary endpoints include change in estimated glomerular filtration rate from baseline to day 30, the proportion of patients diagnosed with AKI by stage through day 5, and the length of CSA-AKI hospitalization. Safety will include adverse events and laboratory measures.

Conclusion: This phase 2 study of ANG-3777 provides data to develop a phase 3 registrational study in this medically complex condition.

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KEYWORDS: acute kidney injury; cardiac surgery; cardiopulmonary bypass; ANG-3777; hepatocyte growth factor; clinical trial

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A KI is an abrupt decrease in renal function resulting from a variety of types of injury. The 2012 Kidney Disease: Improving Global Outcomes guidelines established the Acute Kidney Injury Network classification as the standard for diagnosing AKI in the following manner: A ≥ 0.3 mg/dl (≥ 26.5 μ mol/l) increase in serum creatinine (SCr) within 48 hours, or an increase in SCr ≥ 1.5 times over baseline levels occurring within 7 days, or urine volume < 0.5 ml/kg per hour for 6 hours.¹ AKI has numerous causes including

urinary tract obstruction, exposure to nephrotoxic drugs and chemicals, acute infection, inflammation, or thromboembolic events.^{2–8} Another common cause of AKI is ischemia reperfusion injury associated with vascular surgeries, especially those involving CPB, known as CSA-AKI.

Approximately one-third of patients undergoing cardiac procedures involving CPB, such as CABG and heart valve replacement/repair, experience CSA-AKI.^{3,4} Approximately 5% of patients with CSA-AKI require renal replacement therapy, and mortality is high among those who require dialysis.⁹ Patients with CSA-AKI have longer hospital stays and are more likely to require intensive care.¹⁰ Even a small increase in SCr (< 0.3 mg/dl) is associated with higher mortality, progression of chronic kidney disease, and requirement for renal replacement therapy.^{1,11–15} The longer the duration of

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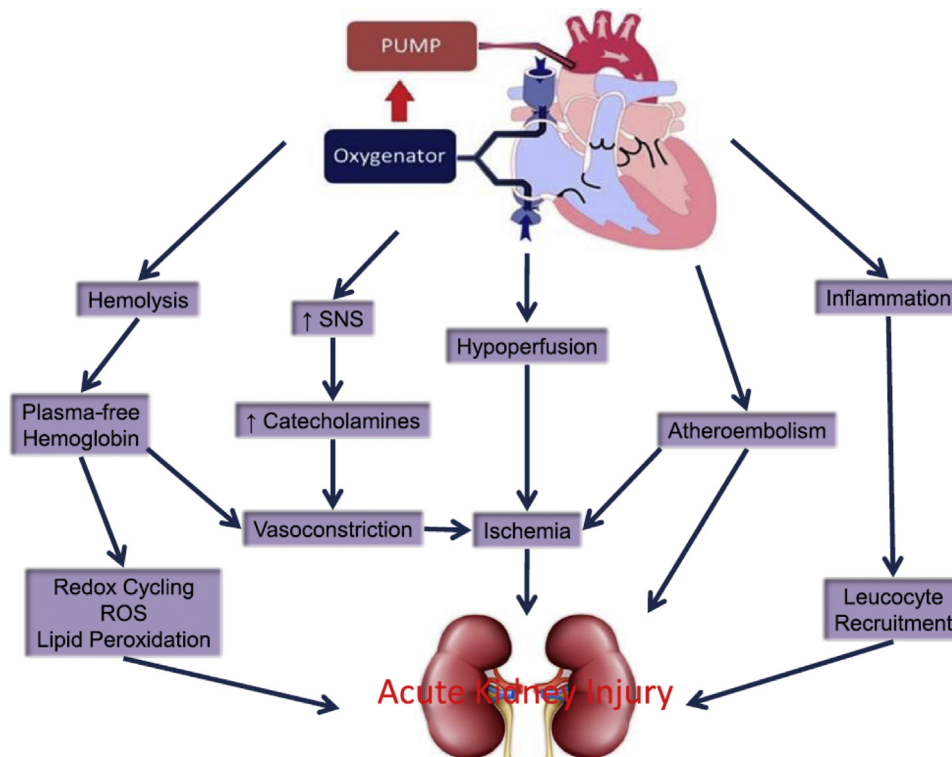


Figure 1. Pathophysiology of acute kidney injury after cardiac surgery. Reprinted from O'Neal JB, Shaw AD, Billings FT. Acute kidney injury following cardiac surgery: current understanding and future directions. *Crit Care*. 2016;20:187.⁹ © 2016 The Author(s), <http://creativecommons.org/licenses/by/4.0/>. ROS, reactive oxygen species; SNS, sympathetic nervous system.

elevated SCr, the greater the risk of significant morbidity and mortality. Compared to patients without AKI, those with a diagnosis lasting 1 to 2 days had increased risk for mortality hazard ratio (HR) of 1.66; at 3 to 6 days the HR risk increased to 1.94; and at ≥ 7 days the incremental HR risk was 3.40.¹⁶ This association has been independently replicated.¹⁷ The incremental cost of CSA-AKI is considerable, including \$16,000 to \$22,000 in initial hospital costs alone.^{10,14} Treatment for the underlying cause of AKI and supportive care remain the mainstay of clinical management.¹

Common risk factors for AKI include older age, hypertension, diabetes mellitus, heart failure, chronic kidney disease, sepsis, chronic obstructive pulmonary disease, use of nephrotoxic drugs, and use of vasopressors/inotropes.^{18–20} More than 50% of all cardiac surgery patients may have one or more of these risk factors, and a combination of CPB with one or more of these risks probably increases the incidence of AKI more than 50%. Given the related adverse clinical and cost consequences of CSA-AKI, an effective treatment for patients at high risk would address a significant unmet clinical need.

KIDNEY INJURY ASSOCIATED WITH CARDIAC SURGERY

There are several mechanisms by which AKI occurs secondary to cardiac surgery. The contrast medium used

in cardiac imaging is known to be directly cytotoxic to renal tubular cells, and can also induce medullary vasoconstriction and hypoxia, increase blood and renal tubular viscosity, impair tubuloglomerular feedback, and increase oxidative stress.²¹ The switch from high osmolal to low-osmolal and iso-osmolal contrast medium has reduced but not eliminated the AKI risk of contrast media,²¹ and has been shown by the Preserve Trial.²² O'Neal *et al.*⁹ has outlined additional mechanisms underlying CSA-AKI (Figure 1).⁹ Although oxidative stress, vasoconstriction, and thromboembolic events all play a role, ischemia reperfusion injury associated with CSA-AKI appears to be a significant cause, with time on CPB, return to CPB, hypovolemia, and hypoperfusion among the contributing factors.

Although no systematic studies of the pathologic changes in the kidney have been undertaken in patients with AKI associated with CPB, it is largely assumed that the pathologic lesion is acute tubular necrosis.²³ In a physiologic study of 10 patients with protracted severe AKI after CPB, the transmembrane gradient for glomerular ultrafiltration was significantly diminished, likely from intratubular obstruction and hypertension due to sloughing from injured tubular epithelial cells.²⁴ In addition, significant transtubular back-leak of glomerular ultrafiltrate across the injured epithelium was observed. The pathology is similar to other, better studied causes of AKI, such as AKI of transplantation.²⁵

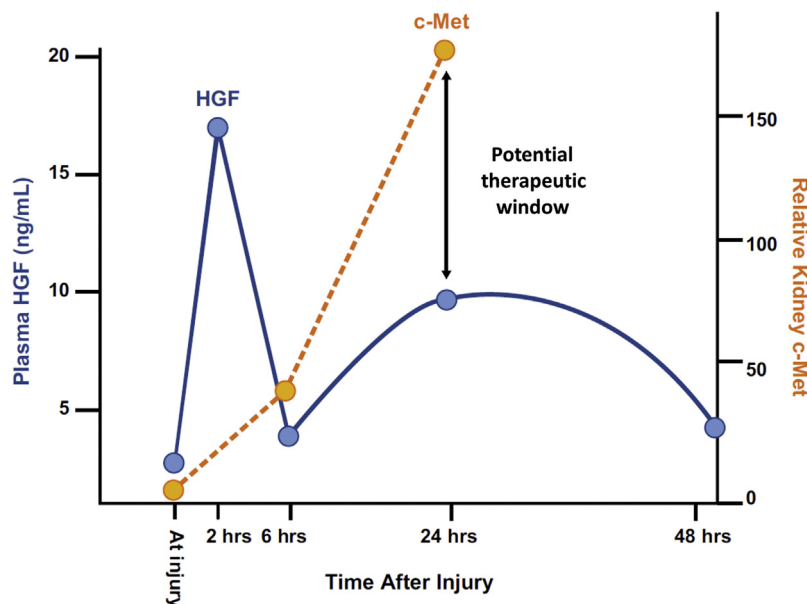


Figure 2. Hepatocyte growth factor (HGF) plasma levels and c-Met receptor expression levels.

THE ROLE OF HEPATOCYTE GROWTH FACTOR AND ANG-3777 IN RENAL REPAIR

One of the primary mechanisms of solid organ tissue repair is the hepatocyte growth factor (HGF)/c-Met pathway. HGF binds exclusively with its receptor, c-Met, initiating a cascade that decreases apoptosis and increases proliferation, migration, morphogenesis, and angiogenesis.^{26–29} When tissue is damaged, chemokines stimulate the proximal and distal release of HGF.^{30,31} In the kidney, HGF reduces tubular necrosis, decreases renal epithelial apoptosis, and augments renal regeneration, ultimately attenuating renal dysfunction.^{32–36} There is, however, a mismatch in the upregulation of HGF and c-Met. HGF levels increase within minutes of tissue damage and peak at approximately 2 hours, with a second, smaller peak at 24 hours.³⁷ c-Met receptor expression is also upregulated shortly after injury, however, the surface density of c-Met peaks at 24 hours, leaving a mismatch between peak surface receptor expression and ligand levels.³⁷ This presents a potential therapeutic window for exogenous stimulation (Figure 2).

ANG-3777 is a small molecule HGF mimetic. *In vivo* studies have shown that it binds to renal c-Met receptors, producing the same decreases in apoptosis and increases in proliferation induced by endogenous HGF. In a series of pre-clinical studies, Narayan *et al.*³⁸ induced renal ischemia reperfusion injury in rats and randomized animals to receive 2 mg/kg of ANG-3777 or placebo at 24 hours after injury. Compared to vehicle, ANG-3777 reduced tubular epithelial apoptosis preserving nephron mass, and also reduced hemorrhage, tubular dilation, and acute tubular necrosis. Additionally, animals treated

with ANG-3777 showed increased urine output, decreased SCr and blood urea nitrogen, and reduced mortality.³⁸ In a phase 2 randomized placebo-controlled double-blind proof-of-concept study in renal transplantation patients showing signs of delayed graft function (a form of AKI in kidney transplantation), patients treated with ANG-3777 showed improvements in multiple endpoints compared to placebo. ANG-3777-treated patients had higher urine output over 28 days after transplantation, lower SCr, higher estimated glomerular filtration rate (eGFR) up to 1 year, greater reduction in markers of renal damage (C-reactive protein and neutrophil gelatinase-associated lipocalin), and shorter duration of dialysis and transplant hospitalization.³⁹

With approximately 50% of patients undergoing cardiac surgery at high risk of AKI, and with the significant increase in morbidity and mortality among those who experience AKI, there is a significant unmet need for preventive treatment.

RATIONALE AND DESIGN FOR A RANDOMIZED CONTROLLED TRIAL IN CSA-AKI: THE PREVENTION AND AMELIORATION OF CSA-AKI

The goal of this phase 2 proof-of-concept study is to assess the safety and efficacy of ANG-3777 in patients at high risk for AKI undergoing cardiac surgery involving cardiopulmonary bypass.

Trial Name

The trial name is Guard Against Renal Damage (GUARD); Angion study 002-15; [Clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02771509) identifier NCT02771509.

Table 1. Patient population

Inclusion criteria	Exclusion criteria
≥18 years of age undergoing CPB surgery ^a	Emergency cardiac surgery
eGFR ≥20 and <30 ml/min per 1.73 m ²	AKI or significant renal impairment within 24 hours of surgery: a diagnosis of AKI as defined by KDIGO criteria or
eGFR ≥30 and <60 ml/min per 1.73 m ² and one additional risk factor from Table 2 (other than age ≥75 years) or	eGFR <20 ml/min per 1.73 m ² or
eGFR ≥60 ml/min per 1.73 m ² and two additional risk factors from Table 2	An acute rise in SCr >0.3 mg/dl or
	50% increase in SCr between the time of screening visit and pre-surgery
	Patients receiving iodinated contrast material within 24 hours of surgery
	Active sepsis or current active infection requiring antibiotic treatment
	Treatment with cytochrome P450 1A2 (CYP1A2) inhibitors;
	HIV seropositivity
	Active malignancy or history within the previous 5 years before screening visit
	Cardiogenic shock or hemodynamic instability within 24 hours before randomization
	Use of a pacemaker, mechanical ventilation, any form of mechanical circulatory support, or cardiopulmonary resuscitation 7 days before surgery
	Clinical or laboratory diagnosis of shock liver
	BMI >40 kg/m ² at screening

AKI, acute kidney injury; BMI, body mass index; CPB, cardiopulmonary bypass; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes; SCr, serum creatinine.

^aAge ≥75 years can be considered an additional risk factor only for patients with eGFR ≥60 ml/min per 1.73 m².

Study design

This is a randomized, double-blind, placebo-controlled, multicenter phase 2 trial.

Patient population

Participants are male and female patients 18 years of age or older undergoing a non-emergent cardiac surgical procedure involving CPB. Inclusion and exclusion criteria were selected to first enrich the sample for risk of CSA-AKI, then to minimize confounders that could obscure efficacy signal detection and safety assessment (Table 1). The first set of inclusion criteria are specific to the AKI risks of cardiac surgery itself. The requirement for CPB was based on its association with significant increased risk for CSA-AKI: 24% to 26%.^{3,4} The cardiac procedures were selected based upon the requirement for CPB, as well as their own associated risk of AKI: CABG; aortic, mitral, tricuspid, or pulmonary valve replacement or repair; valve repair/replacement with concurrent CABG. Emergency cardiac surgery was excluded as it introduces significant confounding clinical complications, including acute cardiac ischemia.

The second set of enrichment criteria involved pre-surgical patient characteristics associated with AKI. The first risk factor was eGFR ≥20 and <30 ml/min per 1.73 m². In a study of CSA-AKI risk factors, Hsu *et al.*⁴⁰ reported that, after controlling for other patient and surgical risk factors, a pre-surgery eGFR 15 to <30 ml/min per 1.73 m² was associated with an HR of 20.4 to 28.5 for AKI (the reference group was eGFR ≥60 ml/min per 1.73 m²). Thus, an eGFR indicative of chronic kidney disease stage 4 is highly predictive of CSA-AKI. The decision to reduce the lower bound to 20 ml/min per 1.73 m² was

made to avoid the enrollment of patients on the cusp of requiring renal replacement therapy, where advanced chronic kidney disease would significantly confound CSA-AKI-specific treatment effects.

Patients with an eGFR ≥30 and <60 ml/min per 1.73 m² had an HR of 1.7 to 6.5 for CSA-AKI compared to eGFR ≥60 ml/min per 1.73 m².⁴⁰ Although this represented significant incremental risk, the decision was made to further enrich this population by requiring at least one additional AKI risk factor. Those risk factors and associated HRs are shown in Table 2.

Patients with eGFR ≥60 ml/min per 1.73 m² were required to have at least two additional risk factors shown in Table 2. For these patients, age ≥75 years was also considered an additional risk factor, as it is generally accepted that advanced age is a risk factor for AKI,^{1,41-43} and there is an increased risk of AKI for those who are ≥75 years compared to those who are younger than 75 years.^{41,44,45}

Exclusion criteria were established to ensure that AKI was associated with cardiac surgery and no other causes, in other words, to reduce confounding factors that would unnecessarily interfere with efficacy signal detection and safety assessment. To ensure AKI was

Table 2. AKI risk factors

Risk (enrichment) factors	HR
Combined valve and CABG surgery ^{5,7,8}	>3
Previous open heart surgery ⁵⁻⁸	1.8
Left ventricular ejection fraction <35% ^{5,6,8}	1.5
Diabetes mellitus requiring insulin or with at least moderate (+2) proteinuria ^{7,8,13}	1.8; 2.0
NYHA functional class IV ⁵	1.55

AKI, acute kidney injury; CABG, coronary artery bypass graft; HR, hazard ratio; NYHA, New York Heart Association.

Table 3. KDIGO AKI stages¹

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline or ≥ 0.3 mg/dl increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ≥ 12 hours
3	3.0 times baseline or Increase in serum creatinine to ≥ 4.0 mg/dl (≥ 353.6 $\mu\text{mol/l}$) or Initiation of renal replacement therapy or In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m ²	< 0.3 ml/kg/h for ≥ 24 hours, or; Anuria for ≥ 12 hours

AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; KDIGO, Kidney Disease: Improving Global Outcomes.

associated with cardiac surgery and not existing renal insufficiency, patients were excluded who had existing AKI or significant renal impairment within 24 hours of surgery: a diagnosis of AKI as defined by Kidney Disease: Improving Global Outcomes criteria or eGFR <20 ml/min per 1.73 m², or; an acute rise in SCr >0.3 mg/dl or 50% increase in SCr between the time of screening visit and pre-surgery. Patients receiving iodinated contrast material within 24 hours of surgery are also excluded for the reasons previously discussed.

To reduce confounding, patients with the following comorbidities were excluded: active sepsis or current active infection requiring antibiotic treatment; treatment with cytochrome P450 1A2 (CYP1A2) inhibitors; HIV seropositivity; active malignancy or history within the previous 5 years before screening visit; cardiogenic shock or hemodynamic instability within 24 hours prior to randomization; use of a pacemaker, mechanical ventilation, any form of mechanical circulatory support or cardiopulmonary resuscitation 7 days before surgery; clinical or laboratory diagnosis of shock liver; and body mass index >40 kg/m² at screening.

Treatment

Patients are randomized 1:1 to placebo or ANG-3777. This study uses the same 2-mg/kg ANG-3777 dose as the phase 2 trial in delayed graft function,³⁹ which was determined based upon pre-clinical and phase 1 studies showing efficacy and safety at this dose. The study drug is administered via peripheral venous infusion over a period of 30 minutes (± 5 minutes), with initial dose administered within 4 hours after CPB (i.e., at the time the patient is taken off pump). The second dose is administered 24 \pm 2 hours after CPB, and the third and fourth doses 24 \pm 2 hours after the previous dose.

Selection of primary endpoint

The primary endpoint is the percent increase in SCr above baseline (24 hours after end of CPB) area under the curve from days 2 through 6. This is calculated as: area under the curve = ($\frac{1}{2}$ day 2 + day 3 + day 4 + day 5 + $\frac{1}{2}$ day 6)/number of non-missing days. The selection of this endpoint reflects SCr as a fundamental

criteria in the Acute Kidney Injury Network diagnostic criteria, and allows for the assessment of change in SCr both as a continuous measure, and as categorical stage as defined by Kidney Disease: Improving Global Outcomes (Table 3).¹

The primary endpoint will be analyzed as a between group difference using an analysis of variance.

Selection of secondary endpoints

There are three secondary efficacy endpoints: (i) change in eGFR from baseline to day 30; (ii) proportion of patients diagnosed at each AKI stage per Kidney Disease: Improving Global Outcomes criteria through day 5 (see Table 2); and (iii) length of hospitalization starting from 24 hours after end of CPB.

Twenty-eight-day eGFR was an endpoint in the phase 2 delayed graft function trial, and 12-month eGFR is the primary endpoint in the phase 3 delayed graft function trial. eGFR was selected both for clinical meaningfulness and to allow for comparison of data across AKI indications. The choice of AKI stage is self-evident. The choice of hospital length of stay was selected to begin to understand the potential cost offsets associated with treatment efficacy in this population.

Safety

Safety will be assessed through physician- and patient-reported adverse events, physical examination and vital signs, clinical laboratory tests (hematology, serum chemistry, coagulation profile, and hepatic profile), and electrocardiogram. A Data and Safety Monitoring Board is undertaking ongoing monitoring of the safety data for this trial.

PROCEDURES

The GUARD study will enroll approximately 240 eligible subjects at 30 sites in the United States, Canada, and Brazil over approximately 4 years. With 90 days of follow-up, total study time will be ~ 4.5 years. As shown in Figure 3, subjects are screened for eligibility, consented, and enrolled up to 30 days before surgery. Baseline demographics, height and weight, medical history, concomitant medications, vital signs, physical examination, and all safety measures are assessed at this time. On the day of surgery, eligibility is confirmed and all safety measures are again collected, as well as baseline SCr for calculation of the primary endpoint. Patients then undergo cardiac surgery. Within 4 hours of the completion of CPB, patients receive the first dose of study drug, and receive their second dose 24 (± 2) hours after CPB. Two additional doses are administered at subsequent 24 (± 2)-hour intervals, for a total of 4 doses. SCr is measured daily though day 7, and again at days 14, 30, and 90, as are adverse events and vital

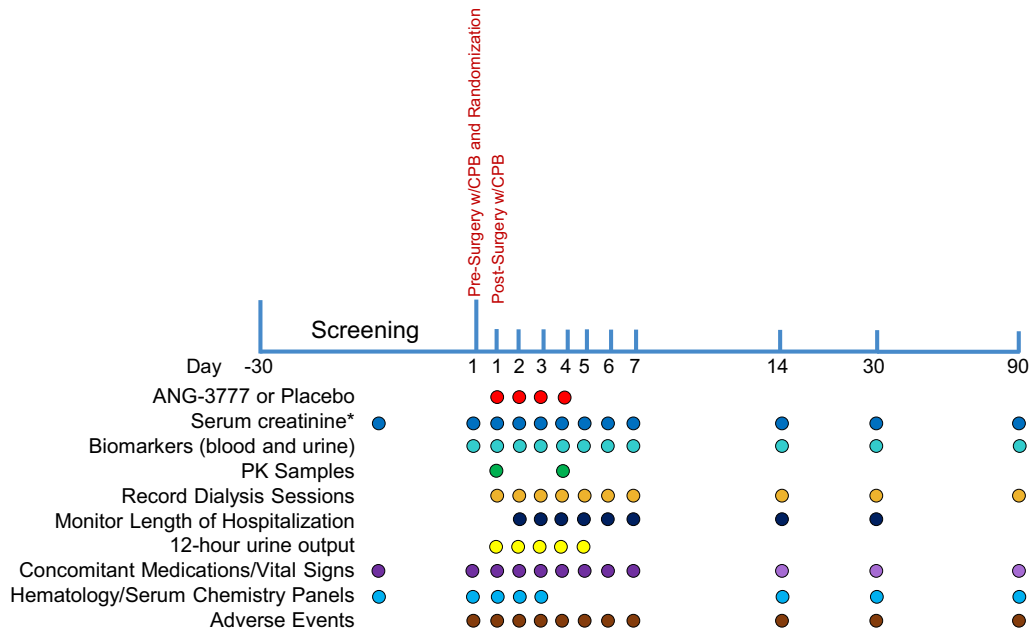


Figure 3. Study schematic. *Serum creatinine (Scr) must be captured twice prior to surgery and after patient goes off cardiopulmonary bypass (CPB). A sample for SCr must be obtained after the patient goes off CPB and before the first administration of the study drug, then at 12 ± 2 hours, at 24 hours ± 2 hours, and at 48 ± 2 hours after the patient has gone off CPB. PK, pharmacokinetics.

signs. Full hematology and serum chemistry panels are conducted on days 1, 2, 3, 14, 30, and 90.

This study is being conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use/good clinical practice, applicable regulatory requirements and the sponsor policy on bioethics. All sites received Institutional Review Board/Institutional Ethics Committee approval before screening and enrolling into the study.

DISCUSSION

Cardiac surgery is a life-saving procedure, with 470,000 coronary bypass and valve replacement surgeries performed each year.^{9,46} These procedures include the use of CPB, which is required for these surgeries, but also runs the risk of inducing ischemia reperfusion injury in the kidney. CSA-AKI is associated with renal tubular damage, and treatment largely consists of supportive care. More than half of patients undergoing cardiovascular surgery have one or more risk factors for CSA-AKI, and those diagnosed have significantly increased morbidity and mortality and associated health care resource use and cost.

An endogenous mechanism by which renal tissues repair and regenerate is through the HGF/c-Met pathway. Released soon after renal injury, HGF binds

to c-Met on renal cells, stimulating a cascade that decreases apoptosis and increases proliferation, migration, morphogenesis, and angiogenesis. However, HGF peaks 2 hours after injury whereas c-Met surface receptor density peaks at 24 hours. This timing mismatch represents a potential therapeutic window for exogenous c-Met stimulation.

ANG-3777 is an HGF mimetic that *in vitro* induces the same c-Met cascades and cellular effects as endogenous HGF. In animals, ANG-3777 stimulates tubular repair and regeneration, resulting in improved renal function following ischemia reperfusion injury. In humans, ANG-3777 has been shown to improve renal function up to 1 year after kidney transplantation in patients with signs of delayed graft function.

This study will test the hypothesis that ANG-3777 improves renal function and reduces AKI in patients undergoing cardiac surgery. Inclusion criteria were selected to enrich the sample for risk for AKI. It will include patients undergoing CABG and or valve replacement/repair requiring CPB, as this increases the risk for renal ischemia reperfusion injury. Inclusion criteria also include patient-levels factors known to increase risk for CSA-AKI. An eGFR >20 to 30 ml/min per 1.73 m² represents sufficient incremental risk; an eGFR >30 to 60 ml/min per 1.73 m² requires at least one additional risk factor; and eGFR >60 ml/min per 1.73 m² requires two or more additional risk factors. Conditions known to introduce significant clinical risk beyond CSA-AKI, such as active viral or bacterial

infection or active malignancy, were excluded. The primary endpoint is percent change from baseline SCr, using mean area under the curve from days 2 through 6 post-surgery. SCr is a primary sign of AKI, and change in SCr defines AKI stage which is a secondary endpoint in this study. Additional endpoints include renal function at day 30 measured via eGFR, as well as length of hospital stay, which will provide data to begin to understand the cost-offsets associated with this treatment. It is hoped that GUARD produces incremental efficacy with no associated difference in safety, which will progress to a phase 3 registrational study in this costly and medically complex condition.

DISCLOSURE

SA and MS are both principal investigators for the GUARD study. DG and TJM were employees of Angion Biomedica at the time of writing and original submission. JN is an employee of Angion Biomedica and owns stock/stock options.

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