A Multicenter, Prospective, Randomized, Double-Blind, Placebo Controlled, Phase 2 Study to Assess the Safety and Efficacy of ANG 3777 in Patients Developing Acute Kidney Injury after Cardiac Surgery

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Background

Acute kidney injury (AKI) is an abrupt decrease in kidney function resulting from an insult to the kidney [1]. It is a broad clinical syndrome encompassing various etiologies. Its clinical features include apoptotic cell death in proximal and distal tubules, resulting in tissue damage that reduces renal clearance. AKI is a frequent complication of cardiac surgery (CS) requiring cardiopulmonary bypass, causing renal ischemia reperfusion injury. [2-4] CS-AKI increases the risk for chronic kidney disease, and when severe can require renal replacement therapy. CS-AKI increases morbidity and mortality, and increased healthcare resource use and cost.[5-9]

ANG-3777 (formerly BB3), is a small molecule hepatocyte growth factor mimetic. In animal models of renal injury, ANG-3777 binds to the c-Met receptor, triggering a cascade that reduces apoptosis; increases proliferation and cell scatter; and stimulates angiogenesis, ultimately leading to tissue regeneration and return of renal function. In a Phase 2 study in AKI of renal transplantation, ANG-3777 increased urine output and hastened the resolution of oliguria; decreased serum creatinine (sCr) and increased eGFR, shortened duration of dialysis, and reduced hospital stay compared to placebo.

Objective

The objective of the GUARD (Guard Against Renal Damage) study is to assess the safety and efficacy of ANG-3777 in patients at risk for developing acute kidney injury following cardiac surgery (CS-AKI) involving cardiopulmonary bypass (CPB).

Design

This is a randomized, prospective, parallel-group, double-blind, placebo-controlled, multicenter Phase 2 study. Thirty participating sites are located in the US, Canada and Brazil.

Methods

Population: Adults undergoing cardiac surgery involving CPB (N=240).

Inclusion Criteria:

1. Male or female ≥18 years.
2. Scheduled for and undergo a non-emergent cardiac surgical procedure involving CPB, including coronary artery bypass graft (CABG), valve repair or replacement, or CABG with valve repair/replacement.
3. Patient must have risk factor(s) for AKI prior to surgery, including:
   - Estimated glomerular filtration rate (eGFR) of ≥20 and <30 ml/min/1.73m2, or
   - eGFR ≥30 and <60 mL/min/1.73m2 and ONE additional risk factor other than age ≥75 years (see 4), or
   - eGFR ≥60 ml/min/1.73m2 and TWO additional risk factors (see 4)
4. Additional risk factors:
   - Combined valve and coronary surgery
   - Previous cardiac surgery with sternotomy
   - Left ventricular ejection fraction <35% within 90 days prior to surgery
   - Diabetes mellitus requiring insulin treatment
   - Non-insulin-requiring diabetes with documented presence of at least moderate (+2) proteinuria
   - Documented NYHA Class III or IV within 1 year prior to index surgery.
   - Age ≥75 years can be considered an Additional Risk Factor only for patients with eGFR ≥60 ml/min/1.73m^2
5. No acute rise in sCr >0.3 mg/dL or 50% increase in sCr between the time of Screening and pre-surgery.
6. Body mass index (BMI) <40 at Screening.
7. Written informed consent, willing/able to comply with the requirements of study.

Exclusion Criteria:

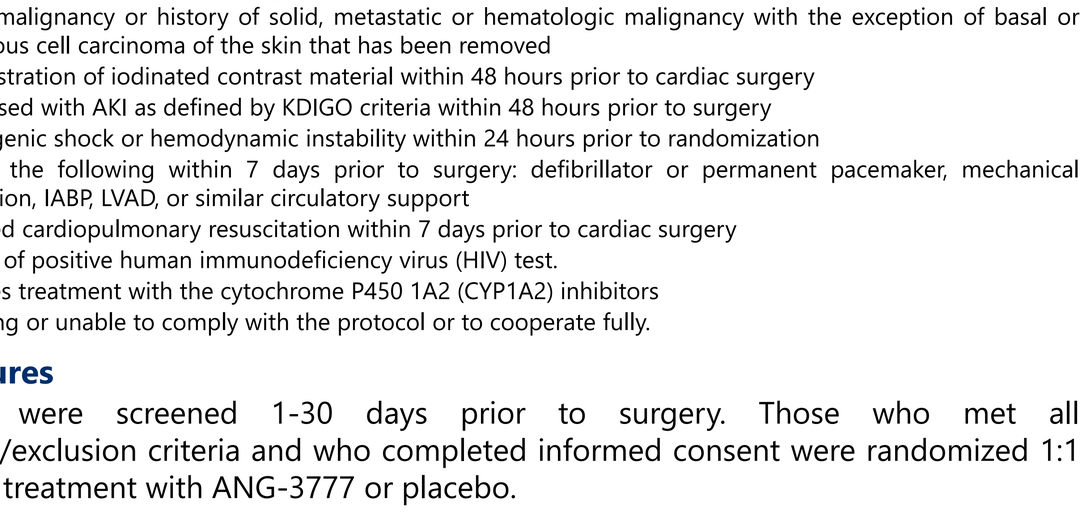
1. eGFR <20 mL/min/1.73 m2 within 48 hours pre-surgery
2. Ongoing sepsis or partially treated infection
3. Currently active infection requiring antibiotic treatment
4. Active malignancy or history of solid, metastatic or hematologic malignancy with the exception of basal or squamous cell carcinoma of the skin that has been removed
5. Administration of iodinated contrast material within 48 hours prior to cardiac surgery
6. Diagnosed with AKI as defined by KDIGO criteria within 48 hours prior to surgery
7. Cardiogenic shock or hemodynamic instability within 24 hours prior to randomization
8. Any of the following within 7 days prior to surgery: defibrillator or permanent pacemaker, mechanical ventilation, IABP, LVAD, or similar circulatory support
9. Required cardiopulmonary resuscitation within 7 days prior to cardiac surgery
10. History of positive human immunodeficiency virus (HIV) test.
11. Requires treatment with the cytochrome P450 1A2 (CYP1A2) inhibitors
12. Unwilling or unable to comply with the protocol or to cooperate fully.

Procedures

Patients were screened 1-30 days prior to surgery. Those who met all inclusion/exclusion criteria and who completed informed consent were randomized 1:1 to active treatment with ANG-3777 or placebo.

Within 4 hours after completing CPB, patients were administered study drug or placebo. Patients in the active treatment arm were administered ANG-3777, 2 mg/kg intravenously over 30 minutes via infusion pump. Patients received 3 additional doses at 24 ± 2 hours after the respective previous dose. The overall duration of administration is 4 days. Patients in the placebo group received normal saline provided by IV infusion. Patients in the placebo group received a volume of normal saline equivalent to that containing active drug on a mL/kg basis.

Schematic of trial design



Schedule of Assessments

Patients will be followed for safety and efficacy up to Day 90 post infusion, Patients will be assessed daily through Day 7 and then on Days 14, 30 and 90 as shown in the schedule of assessments below. A subset with be followed for pharmacokinetic assessment.

Study Day	Screening 1-30 Days Prior to Surgery	Day 1 (Day of Surgery) Pre-Surgery	Day 1 Post Surgery (Day CPB Ends)	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 14 ±2	Day 30 ±5	Day 90 ±10
Informed Consent	X											
Eligibility criteria	X	X										
Randomization		X										
Demographics	X											
Medical history	X	X										
Physical examination[2]	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs[3]	X	X	X	X	X	X	X	X	X	X	X	X
Height and weight	X	X										
12-lead ECG	X	X	X	X	X	X					X	X
Serum Creatinine	X	X	X	X	X	X	X	X	X	X	X	X
Hematology parameters	X	X	X	X	X	X				X	X	X
Chemistry parameters	X	X	X	X	X	X	X			X	X	X
Hepatic panel	X				X					X	X	X
Coagulation panel[7]	X	X	X	X	X	X	X			X		X
Urinalysis	X	X			X	X				X		X
Serum pregnancy test[14]	X	X										
Surgical information[8]		X	X									
Biomarkers (blood[15] and urine)		X	X	X	X	X	X	X	X	X	X	X
12-hour urine output[13]			X	X	X	X	X					
Administer study drug[9]			X	X	X	X						
PK samples[10]			X			X						
Dialysis session record[11]			X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X

Primary Efficacy Endpoint

The primary endpoint is the mean area under the curve of the percent increase in sCr above baseline over time, starting from 24 hours after the end of CPB, through Day 6

Secondary and Exploratory Endpoints

Secondary endpoints include:

- eGFR at Day 30
- Proportion of subjects diagnosed with AKI per KDIGO criteria through Day 5
- Length of hospitalization starting from 24 hours after the end of CPB

Exploratory endpoints which include:

- Maximum % increase in sCr from baseline from 24 hours after the end of CPB and Day 6
- Mean AUC of the % increase in sCr above baseline over time
- Mean percent increase of sCr above baseline, at 24 hours after CPB, Day 3, Day 4, Day 5, and Day 7
- Proportion of subjects diagnosed with AKI per KDIGO criteria through Day 7
- Proportion of patients by severity of renal injury using KDIGO AKI staging, at 24 hours after the end of CPB, Day 3, Day 4, Day 5, Day 7, Day 14, and Day 30
- Proportion of patients with AKI at 24 hours after the end of CPB, Day 3, Day 4, Day 5, Day 7
- Time in days from end of CPB to occurrence of AKI within Days 1-5 and within Days 1-7.
- Time in days from the occurrence of AKI diagnosed postoperatively through Day 5 to recovery from AKI and through Day 7 to recovery from AKI.
- Time in days to improvement in renal function from the day of occurrence of AKI through Day 5 and Day
- Among patients with AKI diagnosed postoperatively through Day 5, the proportion of patients with renal function recovery, progression, or stabilization at Day 30
- Slope of decline of the creatinine curve from the day of peak sCr through Day 5, Day 7, Day 14 and Day 30
- Proportion of patients requiring initiation of any form of renal replacement therapy through Day 30
- Proportion of patients developing a composite endpoint of: death, ≥ 25% decrease in eGFR from baseline, or receiving renal replacement therapy through Day 90 (ie, MAKE90)
- Change from baseline in eGFR at Days 4, 7, 14, 30 and 90
- Proportion of patients with ≥ 20 % reduction from baseline in eGFR at Days 2, 3, 4, 7, 14, and 30 and 90
- Maximal change from baseline in eGFR and sCr through Day 90
- Changes in circulating or urinary biomarkers: C-reactive protein, neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 [KIM-1], S-cystatin C)
- Urine output over 12-hour periods for the first 72 hours post-CPB

Safety

All patients randomized and receiving any part of at least one infusion of study treatment will be evaluated for safety. Safety analyses will include evaluation of the incidence of adverse events (AEs), treatment-emergent AEs, serious AEs, treatment emergent serious AEs, AEs rated by severity, and AEs leading to discontinuation. Laboratory and vital sign assessments will be evaluated over time on study. Shift analyses of relevant clinical laboratory parameters will be produced showing shifts across low, normal, and high categories.

Ethics and Study Conduct

This study is being performed in accordance with ICH-GCP guidelines and with appropriate federal or national regulations including FDA investigational new drug regulations (21 CFR 312). The Principal Site Investigators obtained Institutional Review Board (IRB) / Independent Ethics Committee (IEC) approval for the investigation. A Data and Safety Monitoring Board (DSMB), composed of individuals not affiliated with the study is monitoring subject safety and is formally reviewing safety data at regular intervals during the study.

References

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