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CLINICAL RESEARCH

Phase 3 trial Design of the Hepatocyte Growth Factor Mimetic ANG-3777 in Renal Transplant Recipients With Delayed Graft Function

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Introduction: One-third of kidney transplantation patients experience acute kidney injury (AKI) resulting in delayed graft function (DGF), associated with increased risk of graft failure and mortality. Preclinical and phase 2 data indicate that treatment with ANG-3777 (formerly BB3), a hepatocyte growth factor (HGF) mimetic, may improve long-term kidney function and reduce health care resource use and cost, but these data require validation in a phase 3 randomized controlled trial.

Methods: The Graft Improvement Following Transplant (GIFT) trial is a multicenter, double-blind randomized controlled trial, designed to determine the efficacy and safety of ANG-3777 in renal transplantation patients showing signs of DGF. Subjects are randomized 1:1 to ANG-3777 (2 mg/kg) administered intravenously once daily for 3 consecutive days starting within 30 hours after transplantation, or to placebo.

Results: The primary endpoint is estimated glomerular filtration rate (eGFR) at 12 months. Secondary endpoints include proportion of subjects with eGFR >30 at days 30, 90, 180, and 360; proportion of subjects whose graft function is slow, delayed, or primary nonfunction; length of hospitalization; and duration of dialysis through day 30. Adverse events are assessed throughout the study.

Conclusion: GIFT will generate data that are important to advancing treatment of DGF in this medically complex population.

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End-stage renal disease (ESRD) is a critical public health concern, with more than 750,000 patients requiring renal replacement therapy at substantial cost to patients, caregivers, and society.[1–3] Kidney transplantation is acknowledged as the "dominant strategy" for treatment of ESRD, in that it produces better clinical outcomes at less cost than dialysis.[4,5] However, only ~20,000 kidney transplantation surgeries occur each year in part because of a high discard rate of kidneys at the upper end of the Kidney Donor Profile Index (KDPI) score based on perceptions of poorer long-term survival.[2,6] For these reasons, HHS has adopted a national initiative to maximize renal transplantation, increasing both the number of transplants and the longevity of grafted organs.[1]

An important factor that affects both the viability of a kidney for transplantation and the longevity of the graft is AKI in the donor organ. Recipient and donor variables, such as comorbid conditions, as well as organ procurement factors, particularly cold ischemia time, play critical roles in AKI of transplanted organs.[7–11] Whether AKI is due to recipient, donor, or procurement factors, it can result in slow or delayed graft function in which initial post-transplantation renal function is suboptimal. In the case of DGF, which affects approximately 30% of deceased donor renal transplantation recipients, this requires supportive renal replacement therapy in the first week after

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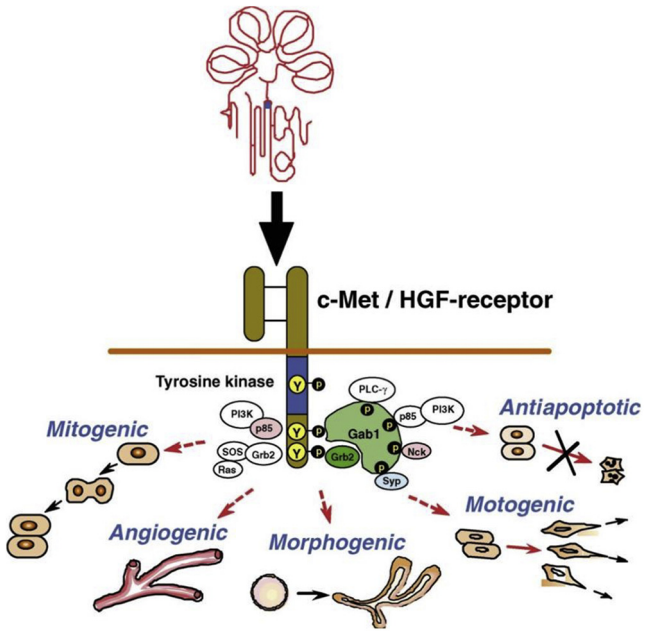

Figure 1. Structure and biologic function of HGF: HGF/c-MET signaling pathways are associated with angiogenesis as well as cell survival, proliferation, mobility, and cytoskeletal changes. Reprinted with permission, Nakamura T, Mizuno S. The discovery of hepatocyte growth factor (HGF) and its significance for cell biology, life sciences and clinical medicine. *Proc Jpn Acad Ser B Phys Biol Sci.* 2010;86:588-610. ©2010 The Japan Academy.

transplantation.[11] There are currently no approved treatments for DGF, and numerous studies have shown that DGF has long-term negative consequences including less robust graft function measured via serum creatinine and eGFR, increased risk of graft failure and mortality, and significant incremental health care costs.[12–15]

There are several physiologic cellular pathways that promote recovery from ischemia reperfusion injury. One is through the HGF, the natural ligand of the c-Met receptor. ANG-3777 (formerly BB3) is an HGF mimetic that in preclinical and phase 2 studies has demonstrated the ability to activate the c-Met receptor and the pathways associated with that activation, improving renal function in induced-AKI in animals and long-term graft function occurring in renal transplantation recipients with signs of DGF.

The purpose of this article was to review the role of HGF and ANG-3777 in AKI, to provide the rationale for conducting a phase 3 randomized controlled trial to test the hypothesis that treatment with ANG-3777 improves long-term renal function in patients who have undergone kidney transplantation with signs of DGF, and to review the design of the GIFT study.

The Role of HGF and ANG-3777 in Kidney Repair

HGF, also named scatter factor, was simultaneously discovered in 2 laboratories in the 1980s.[16,17] Bottaro *et al.* subsequently identified c-Met, a tyrosine kinase receptor, as the exclusive receptor for the HGF ligand.[18] As reviewed by Nakamura and Mizuno and by Matsumoto *et al.*, damaged tissues release signaling proteins, such as injurin, which trigger release of HGF into circulation. Injured tissues also upregulate c-Met expression on cell surfaces.[19,20] As shown in Figure 1, HGF binds to c-Met initiating a cellular cascade that decreases apoptosis and increases cell proliferation, migration, morphogenesis, and angiogenesis. In the kidney, HGF regulates a variety of physiological processes that include renal development, compensatory growth, and tubule repair and regeneration following acute injury.[21,22] In renal epithelial cells, HGF is cytoprotective and antiapoptotic.[23] Several lines of evidence show that the HGF/c-Met pathway plays a key role in renal regeneration and recovery after an acute insult. For example, renal HGF and c-Met mRNA levels increase significantly in animals in AKI induced by ischemia or administration of a nephrotoxin.[24,25] Nephrectomy or ischemic renal insults lead to a markedly increased expression of HGF, not only in the kidneys but also in other organs such as the liver.[25] Urinary HGF excretion is elevated in patients with AKI.[26] Administration of exogenous HGF attenuates renal dysfunction, reduces tubular necrosis, decreases renal epithelial apoptosis, and augments regeneration in *in vivo* models of renal injury due to ischemia or nephrotoxin administration.[24,27] Simultaneous increases in HGF gene expression in multiple organs provides abundant HGF to the damaged tissue.

A series of experiments (Supplementary Table S1) characterized the interaction between ANG-3777 and the c-Met receptor. *In vivo*, ANG-3777 results in dimerization and phosphorylation, and thus activation of the c-Met receptor, followed by activation of c-Met signaling cascades. The presence of c-Met is needed for ANG-3777 activity, and ANG-3777 selectively phosphorylates c-Met. Furthermore, c-Met phosphorylation induced by ANG-3777 occurs in a dose- and time-dependent manner with selective phosphorylation of c-Met and its downstream effector of ERK. No phosphorylation of IFGR, Tie2, EGFR, or FGFR occurs.

Results from nonclinical *in vivo* models of kidney injury, summarized in Table 1, demonstrate that ANG-3777 ameliorates renal dysfunction regardless of the cause of injury. These models included renal damage induced by toxins and ischemia-reperfusion.

In a phase 2 trial, patients with signs of DGF post–renal transplantation (low urine output: ≤50 ml/h for 8 consecutive hours in the first 24 hours post-transplantation) were randomized to 2 mg/kg IV ANG-3777, administered in the first 36 hours post-transplantation and at 2 subsequent 24-hour intervals, or to placebo. Data from the 28 patients enrolled show that compared to placebo, patients

Table 1. Studies of ANG-3777 in animal models of renal injury

Study	Methods in brief	Dose/route/duration	Results
$HgCl_2$-induced toxicity models			
$HgCl_2$-induced mortality	Male SD rats, pretreat with ANG-3777, next day expose to $HgCl_2$	ANG-3777 2 mg/kg i.p. immediately before and 18 h after $HgCl_2$ (5.0 mg/kg, i.p.)	ANG-3777 decreased mortality
$HgCl_2$-induced mortality and renal dysfunction	Male SD rats, pretreat with ANG-3777, next day expose to $HgCl_2$	ANG-3777 2 mg/kg i.p. immediately before and once daily after $HgCl_2$ (3.0 mg/kg, i.p.)	ANG-3777 decreased mortality and attenuated renal dysfunction
$HgCl_2$-induced renal dysfunction (dose response)	Male SD rats, pretreat with ANG-3777, next day expose to $HgCl_2$	ANG-3777 0-, 0.22-, 0.66-, 2-, 4-, or 12-mg/kg i.p. on day 0, 1, and 2; $HgCl_2$ (3.0 mg/kg, i.p.) on day 1	ANG-3777 doses of 0.66 mg/kg and above were effective
Renal ischemia reperfusion models			
Post-ischemic renal injury (male rats)	Male SD rats, 60-min left renal occlusion, remove other kidney, kill 24 h later; determine renal function and renal epithelial apoptosis	ANG-3777 2 mg/kg i.v. immediately before ischemia and at 18-h reperfusion	ANG-3777 attenuated renal dysfunction (blood urea nitrogen [BUN] and serum creatinine [sCr]) and renal epithelial apoptosis
Post-ischemic renal injury (female rats)	Female SD rats, 60-min left renal occlusion, remove other kidney, kill 24 h later	ANG-3777 2 mg/kg i.v. immediately before ischemia and at 18-h reperfusion	ANG-3777 attenuated renal dysfunction (BUN and sCr)
Post-ischemic renal injury (male rats)	Male SD rats, 60-min left renal occlusion, remove other kidney, kill 72-96 h later; determine renal function	ANG-3777 2 mg/kg i.v., once daily starting at 24-h reperfusion	ANG-3777 attenuated mortality and renal dysfunction (BUN and sCr) and improved urine output.
Post-ischemic renal injury (dogs)	Adult dogs subjected to 120-min left renal occlusion, remove other kidney, kill 1 wk later	ANG-3777 2 mg/kg i.v., once daily at onset of reperfusion or at 24-h reperfusion	ANG-3777 attenuated renal dysfunction (BUN and sCr)

treated with ANG-3777 were more likely to achieve the primary endpoint of 1200 ml urine over 24 hours by 28 days post-transplantation (83.3% vs. 50% placebo; log-rank test: $\chi^2 = 2.799$, $P = 0.09$).[28] Median number of days from transplantation to production of ≥1200 ml of urine over 24 hours was 5 for ANG-3777 (95% confidence interval: 2.4, 12.0) and 14 for placebo (95% confidence interval: 2.44, –). Patients in the ANG-3777 arm also showed numerically better outcomes on all secondary endpoints: daily urine output, serum creatinine, C-reactive protein and neutrophil gelatinase–associated lipocalin, number of dialysis sessions, and duration of transplant hospitalization.

In consideration of the release of the 2017 US Food and Drug Administration Draft Guidance for Industry Delayed Graft Function in Kidney Transplantation: Developing Drugs for Prevention, 3 post hoc analyses were conducted to explore possible primary endpoints and associated power for the phase 3 trial. The US Food and Drug Administration guidance specified that 12-month eGFR, graft failure, and duration of dialysis were considered appropriate endpoints for a phase 3 registrational trial in DGF.[29] Analysis of these 3 endpoints in the phase 2 trial showed that patients in the ANG-3777 arm had statistically significantly better graft survival: 0 graft failures in the ANG-3777 arm versus 2 (22%) graft failures in placebo arm 1 year post-transplant ($\chi^2 = 4.66$, $P = 0.03$). The ANG-3777 arm also had a numerically shorter duration of dialysis: least squares mean days = 7.6, standard error = 2.0; placebo least squares mean days = 10.0, standard error = 3.9. As shown in Figure 2, patients in the ANG-3777 arm showed improvements in eGFR relative to placebo starting at day 7, which reached statistical significance on day 14 and year 1. Figure 2 shows the eGFR group means when eGFR was set to the prespecified 0 ml/min per 1.73 m^2 for patients with graft failure, as well as a sensitivity analysis that set eGFR to 10 ml/min per 1.73 m^2 as per the Clinical Trials in Organ Transplantation convention.[30]

There were no deaths or discontinuations due to study drug in the phase 2 study. ANG-3777 was well tolerated and similar to placebo in terms of proportion of patients experiencing adverse events (89.5% vs. 88.9%), treatment-emergent adverse events (78.9% vs. 88.9%), and treatment-emergent serious adverse events (42.1% vs. 44.4%). No serious adverse events were assessed as related to study drug.

Rationale for a Randomized Controlled Trial in DGF: An Opportunity to Improve Long-term Renal Transplantation Outcomes

With approximately 20% of deceased donor kidneys discarded because of measures indicating

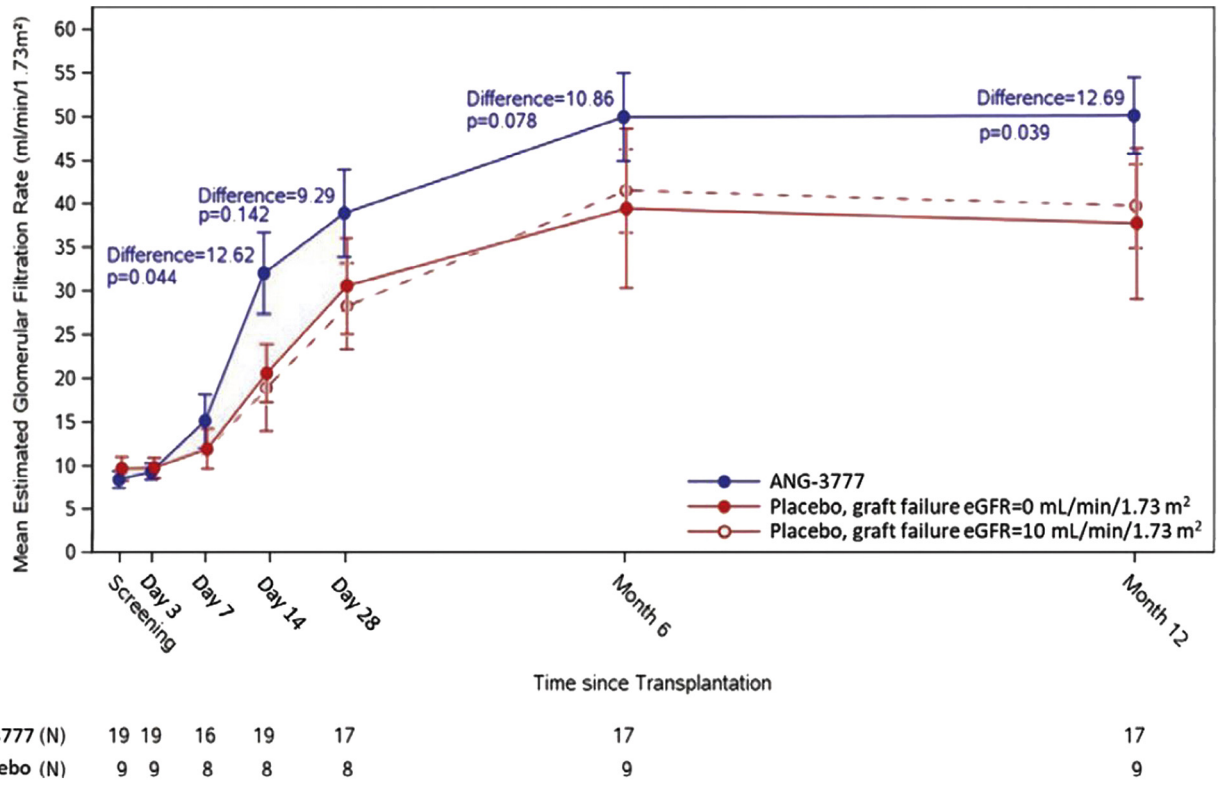

Figure 2. Estimated Glomerular Filtration Rate Over Time by Study Arm: Results from phase 2 randomized controlled trial indicating improvements in eGFR beginning 14 days post-transplant. Reprinted with permission, Bromberg JS, Weir MR, Gaber AO, Yamin MA, Goldberg ID, Mayne TJ, Cai W, Cooper M. Renal function improvement following ANG-3777 treatment in patients at high risk for delayed graft function after kidney transplantation. *Transplantation*. 2021;105:443–450. Copyright 2020 The Authors. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY).

decreased viability, and one-third of renal transplantation patients experiencing DGF, and given the significant increase in adverse clinical outcomes and cost associated with the resumption of dialysis, the need for an effective treatment for DGF is clear and immediate. Although several drugs have been tested in clinical trials to prevent the occurrence of DGF, ANG-3777 is the first drug developed for use after transplantation in patients with signs of DGF to induce faster and better recovery of renal function.

METHODS

Trial Name

Graft Improvement Following Transplant (GIFT); Angion study 001-15; Clinicaltrials.gov identifier NCT02474667

Study Design

The study design was selected as the gold standard for regulatory approval: a randomized, double-blind, placebo-controlled, multicenter phase 3 trial.

Patient Population

The patient population was selected to be comparable to the population in the phase 2 trial. Patients are adults (≥18 years) with renal failure and <200 ml of urine output per day who have been on renal replacement therapy for ≥3 months (thus excluding pre-emptive transplantation) who are receiving their first renal transplantation with a deceased donor kidney. Donation after brain death and cardiac death donor (DCD) are both eligible and stratified at randomization. Recipients of DCD kidneys are capped at 20%, as some studies have shown that DCD kidneys may be prone to worse outcomes,[31–33] though this observation remains controversial.[34,35] Although differing outcomes across studies may be due to magnitude of ischemic reperfusion injury, generally greater in DCD kidneys, versus the increased propensity for repair, generally improved in the typically younger DCD donor organs, we sought to approximate current clinical practice by the cap on DCD kidneys. Kidneys may be preserved by static cold storage or cold pulsatile machine perfusion, with the latter capped at 40% to reflect current practice as

quantified in the Organ Procurement and Transplantation Network (OPTN) database. Recipients of normothermic pulsatile machine perfused kidneys, which is still an emerging technology, are excluded.

Patients must show signs of DGF in the first 24 hours post-transplantation based on an average urine output of <50 ml/h over any 8 consecutive hours. The criterion parallels the phase 2 trial and was selected based on previous research showing that patients producing urine output <50 ml/h for 6 consecutive hours post–renal transplantation were 13 times more likely to require dialysis than those without oliguria.[36] As low urine output should be a reflection of impaired intrinsic renal function, patients with structural or vascular abnormalities, confirmed with a renal ultrasonography with Doppler and/or other imaging studies, are excluded.

Treatment

This study uses the same dose and administration as the phase 2 trial, which was determined based on preclinical and phase 1 studies demonstrating efficacy and safety at this dose. Patients are randomized 1:1 to placebo or 2 mg/kg of ANG-3777. Three doses of the study drug are administered via peripheral venous infusion over a period of 30 minutes (±5 minutes), with initial dose administered within 30 hours after transplantation and subsequent doses administered 24 ± 2 hours after the previous dose.

Selection of Primary Endpoint

The primary endpoint was selected based on the US Food and Drug Administration DGF Guidance, the phase 2 trial results, as well as the clinical meaningfulness of the endpoint to practicing clinicians. In examining duration of dialysis, we conducted a literature search to understand the clinical meaningfulness of the 3-day between-group difference in duration of dialysis observed in the phase 2 study. Although there is a published literature quantifying the relationship of pretransplantation duration of dialysis and outcomes, and many studies examining whether post-transplantation dialysis measured dichotomously (any dialysis vs. no dialysis) is associated with outcomes, we were unable to identify any studies defining the relationship between post-transplantation duration of dialysis and outcomes that allowed for an understanding of a 3-day difference. Therefore, duration of dialysis was rejected as a primary outcome for lack of defined clinical meaningfulness, but was included as a secondary endpoint.

In the phase 2 trial, both eGFR and graft failure had effect sizes sufficient to reach statistical significance. In attempting to anchor graft failure to epidemiologic studies, the 0% 12-month graft failure in the treatment arm is less than what one would normally observe in a non-DGF patient population, which is 2%–3%. The graft failure incidence of 22% in the placebo arm has been reported in some studies of DGF patients[14,37,38] but is higher than observed in most.[39,40] Given the risk of regression to the mean requiring a significantly larger and longer trial, and the availability of eGFR as an acceptable surrogate (discussed next), this endpoint was rejected.

The 12-month eGFR endpoint was selected for several reasons. First, the difference between the ANG-3777 and placebo groups in 12-month eGFR (8-12 ml/min per 1.73 m^2) is similar to the difference observed between DGF and non-DGF patients in the OPTN database. Thus, the difference observed in the phase 2 trial is grounded in a known group difference. Second, eGFR is closely monitored in clinical practice as an index of post-transplantation graft function, making it an inherently clinically meaningful measure.[4] Third, at 12 months post-transplantation, eGFR is the single best predictor of graft survival, making it a highly meaningful surrogate for an important clinical outcome.[41] Therefore, a between-group difference in 12-month eGFR was chosen as the primary endpoint. The primary endpoint will be analyzed using a Mixed Model Repeated Measures approach, and significance testing will represent the difference between treatments at 12 months as estimated by the model.

Sample Size and Power

In the phase 2 trial, the between group differences in eGFR from Day 14 to 1-year post transplantation ranged from 8 to 12 ml/min per 1.73 m^2, with a standard deviation on the order of 21. Setting alpha at $P \leq 0.05$ (2-sided) with a total sample size of 253 subjects randomized 1:1, power ranged from 87% at 8 ml/min per 1.73 m^2 to >99% at 12 ml/min per 1.73 m^2. Therefore, the trial is adequately powered to detect an effect of the magnitude observed in the phase 2 trial.

Secondary Endpoints

Secondary endpoints include the proportion of subjects with eGFR >30 on days 30, 90, 180, and 360; proportion of subjects categorized as primary graft nonfunction, DGF, slow graft function, or normal graft function; length of transplant hospitalization; and duration of dialysis

A Data and Safety Monitoring Board (DSMB) is undertaking ongoing monitoring of the safety data for this trial.

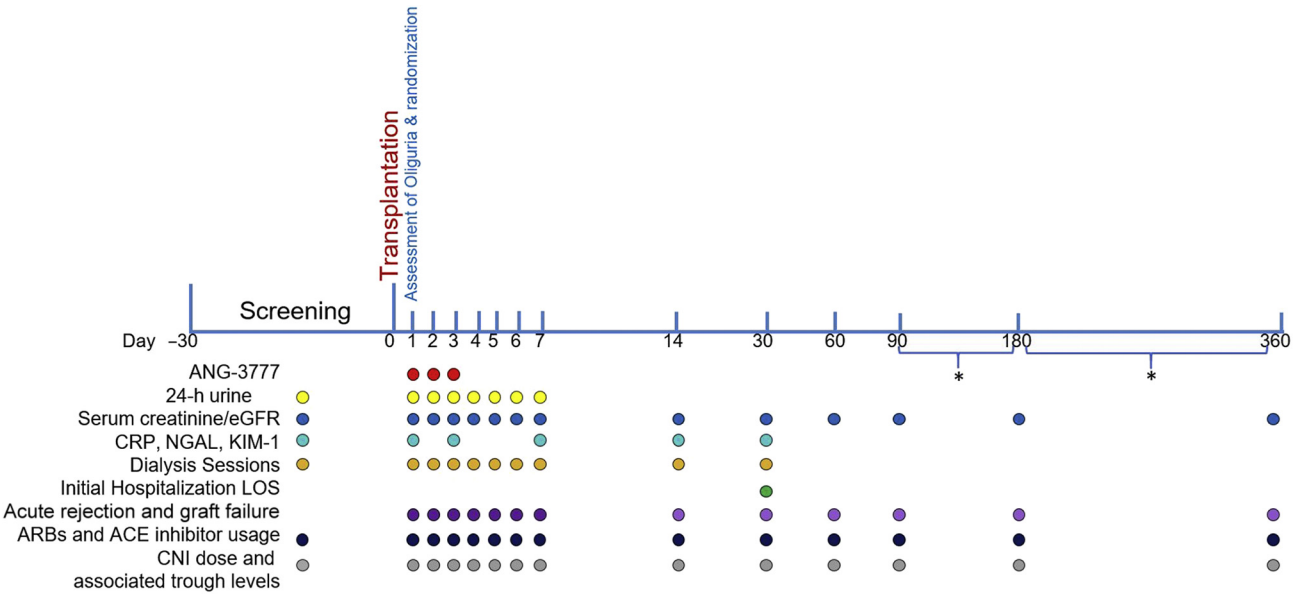

Figure 3. Study schematic depicting randomization, intervention, and schedule of assessments. *Review of medical records between study visit days for eGFR, CNI dose and trough, adverse events, and select concomitant medications. ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; *CNI,* calcineurin inhibitor; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; KIM-1, kidney injury molecule–1; LOS, length of stay; NGAL, neutrophil gelatinase–associated lipocalin.

PROCEDURES

The study is being conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH-GCP (International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use–Guideline for Clinical Practice), applicable regulatory requirements, and the sponsor policy on Bioethics. All sites have provided institutional review board / institutional ethics committee approval.

GIFT will enroll 253 eligible subjects over 5 years with 1 year of follow-up, for a total study time of 6 years. Subjects are being recruited at 32 sites in the United States. As shown in Figure 3, subjects are screened for inclusion/exclusion in the 24 hours after transplantation. Eligible subjects are enrolled and randomized to placebo or ANG-3777. Subjects receive their first dose of study medication within 30 hours of transplantation, with 2 doses administered at subsequent 24±2-hour intervals. Safety and efficacy measures are collected at regular intervals up to 12 months post-transplantation.

CONCLUSION

In the course of deceased donor kidney transplantation, ischemia reperfusion injury commonly occurs. Cell death, particularly in the tubular epithelium, can be sufficiently severe to compromise post-transplant kidney function. An important endogenous pathway by which the body recovers from this injury is through the release of HGF and activation of the c-Met receptor on injured tissue, which initiates a cascade that reduces apoptosis and stimulates proliferation, migration, morphogenesis and angiogenesis. The exogenous supplementation of ANG-3777, timed to peak c-Met receptor expression, has been shown *in vivo* to mimic the effects of HGF—in animal models to accelerate organ recovery and in humans with signs of DGF to result in incremental post-transplant graft function up to 1 year post-transplantation.

DGF requiring supplementation with renal replacement therapy affects approximately 30% of patients undergoing renal transplantation. DGF is associated with a significant increase in adverse clinical outcomes, including graft failure and death, as well as incremental health care cost. The lack of effective treatment represents a significant unmet medical need.

This study will test the hypothesis that ANG-3777 improves renal function 12 months post-transplantation relative to placebo in patients with signs of DGF. It is the first study to examine a drug for the treatment of DGF, as opposed to prevention. The primary outcome of interest is graft function at 1 year, with additional endpoints examining other clinical outcomes and associated health care resource use. Angion Biomedica looks forward to continued collaboration with the transplant community on this landmark clinical trial. It is hoped that GIFT will serve as an example of a robust randomized controlled trial that can support evidence-based practice patterns to improve outcomes in patients undergoing renal transplantation.

DISCLOSURE

FV and JK have received research funding related to this study from Angion Biomedica and are both principal investigators for this study. DG and TJM were employees of Angion Biomedica at the time of writing. GP and JFN are employees of Angion Biomedica and own stock/stock options.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Table S1. Studies characterizing ANG-3777 interaction with c-MET receptor

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