ANG-3777, a Hepatocyte Growth Factor (HGF) Mimetic, Significantly Improves Outcomes in Patients with Delayed Graft Function (DGF): Results from A Randomized Double-blind Placebo Controlled Phase 2 Trial with 12-month Follow-up

Jonathan Bromberg[1], Matthew Weir[1], Osama Gaber[2], Barry Brown[3], Itzhak Goldberg[4], Michael Yamin[4], Tracy Mayne[5], Matthew Cooper[6]

University of Maryland School of Medicine, Baltimore, MD[1]; The Houston Methodist Hospital, Houston, TX[2]; Balboa Nephrology Medical Group, Inc., San Diego, CA[3]; Angion Biomedica, Uniondale, NY[4]; Angion Biomedica, San Francisco, CA[5]; Medstar Georgetown Transplant Institute, Washington, DC[6]

Background

Kidney transplantation is the preferred treatment for patients with end stage renal disease (ESRD) due to increased survival, improved quality of life, and lower cost compared to dialysis. Delayed graft function (DGF) is a form of acute kidney injury. Contributing factors include patient age, quality of the donor kidney, and transplantation factors such as cold ischemia time and ischemia reperfusion injury.[1] DGF is most commonly defined as the need for dialysis in the first week after transplantation. Patients with DGF are at increased risk for graft failure and death, as well as increased healthcare resource utilization and cost.[2,3] To date, there is no effective treatment for DGF, only supplementation via dialysis. ANG-3777 is an HGF mimetic shown in animal models to enhance tissue repair & function in damaged kidneys.

Study Design

Design: Randomized, double blind, placebo controlled multi-center Phase 2 trial (**Figure 1**)

Population: Patients undergoing kidney transplantation with signs and symptoms of DGF

Study Drug: ANG-3777 2 mg/kg; 30 min IV infusion; 1st dose 24-36 hours post transplantation, with 2 subsequent doses at 24 and 48 (± 2) hours.

Inclusion Criteria:

- Males and females ≥18 years of age
- Renal transplantation due to end stage disease requiring chronic dialysis
- Donor terminal serum creatinine (sCR) ≤2.2 mg/dL
- Dry weight ≤120 kg, body mass index (BMI) <35
- <50cc urine/hr. for any 8 consecutive hrs. and/or creatinine reduction rate <30%, within first 24 hrs. post-transplant

Exclusion Criteria:

- Signs and symptoms of volume depletion
- Recipient of multiple organ transplantation
- Recipient of kidney with cold ischemia time >40 hr.
- Active malignancy or history of solid, metastatic or hematologic malignancy
- Concurrent sepsis or active bacterial infection
- +HIV test

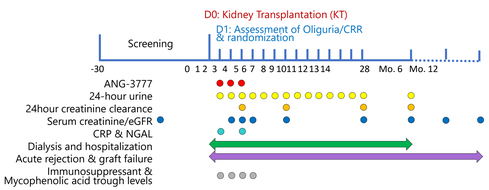
Primary Endpoint: Time to ≥ 1200 cc urine/24 hr.

Secondary Endpoints:

- Daily 24-hour urine production on post-transplantation Days 1 to 14
- Change from Baseline (Day 1) urine production on post-transplantation Days 2 to 14
- Mean sCR at Screening and post-transplantation Days 3, 7, 14, 28, Month 6 and Month 12
- Mean 24-h creatinine clearance on post-transplantation Days 3, 7, 14, and 28
- CRP and NGAL on post-transplantation Days 1 and 3
- Incidence of DGF, defined as dialysis during the first 7 days post-transplantation
- Number of dialysis sessions through Day 28 post-transplantation
- Number of acute rejection episodes from transplantation through 12 months
- Length of hospitalization following transplantation

Post-hoc Analysis: Time to graft failure; eGFR at screening to Month 12; duration of dialysis to Day 28

Figure 1: Trial Schematic



Abbreviations: eGFR, estimated glomerular filtrate rate; CRP, C-reactive protein; NGAL, neutrophil gelatinase-associated lipocalin

Figure 2: Subject Disposition

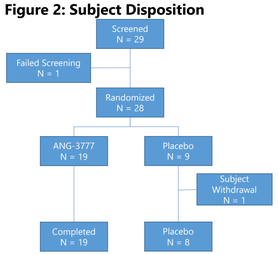


Table 1: Patient Clinical Characteristics

	ANG-3777 (N = 19)	Placebo (N = 9)
Height (cm), n	19	9
Mean (SD)	173.5 (9.3)	168.2 (7.2)
Median (Min, Max)	173 (157, 191)	168 (154, 180)
Body Weight (kg), n	19	9
Mean (SD)	90.9 (17.1)	79.8 (16.2)
Median (Min, Max)	88.6 (51.3, 124.2)	76.2 (57.1, 108)
Dry Weight (kg), n	15	6
Mean (SD)	86.9 (16.6)	80.85 (17.9)
Median (Min, Max)	87.9 (51.3, 118)	82.1 (57.1, 108)
BMI (kg/m^2), n	19	9
Mean (SD)	30.1 (4.7)	27.9 (3.9)
Median (Min, Max)	30.7 (19.3, 36.4)	27 (23.2, 33.3)

Table 2: Patient Demographics

	ANG-3777 (N = 19)	Placebo (N = 9)
Age at signing informed consent (years)		
Mean (SD)	54.7 (13.7)	65.7 (12.8)
Median (Min, Max)	52.0 (29, 75)	65.0 (46, 84)
Gender, n (%)		
Male	15 (78.9)	8 (88.9)
Female	4 (21.1)	1 (11.1)
Race, n (%)		
White	9 (47.4)	5 (55.6)
Black or African American	8 (42.1)	2 (22.2)
Asian	1 (5.3)	1 (11.1)
American Indian or Alaska Native	1 (5.3)	0 (0.0)
Other	0 (0.0)	1 (11.1)

Table 3: Donor/Kidney and Renal Transplantation Characteristics

	ANG-3777 (N = 19)	Placebo (N = 9)
Donation Type, n (%)		
Donor after Brain Death	13 (68.4)	7 (77.8)
Donor after Cardiac Death	4 (21.1)	1 (11.1)
Live donor	2 (10.5)	0
Unknown	0	1 (11.1)
History of DM or HTN		
Yes	12 (63.2)	7 (77.8)
No	7 (36.8)	2 (22.2)
Donor Age (years), n	19	8
Mean (SD)	43.0 (21.2)	56.3 (10.8)
Median (Min, Max)	49.0 (0, 72)	59.0 (37, 68)
Hours from Procurement to Transplantation		
n (%)	17 (89.5)	8 (88.9)
UK/non-calculable, n (%)	2 (10.5)	1 (11.1)
Mean (SD)	23.3 (9.18)	23.7 (10.32)
Median (Min, Max)	27.1 (6, 36)	25.2 (10, 37)
Total Transplantation Time (hours)		
n (%)	16 (84.2)	8 (88.9)
UK/non-calculable, n (%)	3 (15.8)	1 (11.1)
Mean (SD)	3.2 (1.59)	3.0 (0.94)
Median (Min, Max)	2.9 (1, 7)	3.0 (1, 4)

Abbreviations: SD, standard deviation; Min, minimum; Max, maximum; cm, centimeters; kg, kilograms; DM, diabetes mellitus; HTN, hypertension; UK, unknown. Data shown are n (%). Percentages are based on N. Source: Table 14.4.1 and Table 14.7.1

Figure 3: Time to 1200 cc Urine/ 24 Hours

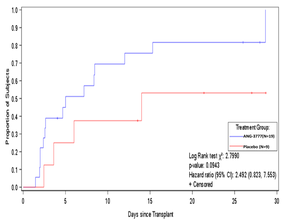


Figure 4: Change from Baseline (Day 1) Urine Vol. (in cc)

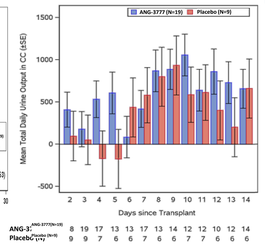
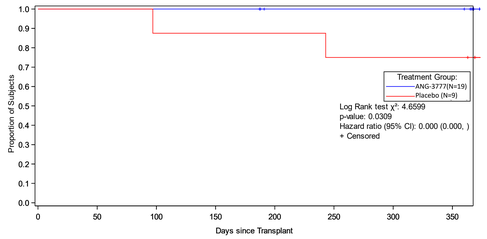


Figure 5: Incidence of Graft Failure



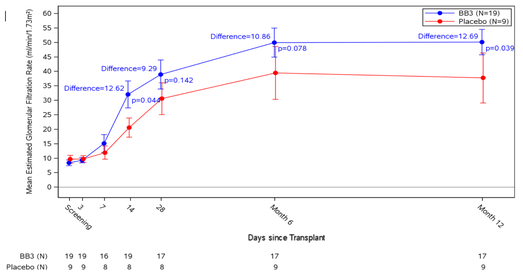


Table 3: Adverse Events Summary

	ANG-3777 (N = 19)		Placebo (N = 9)	
	n (%)	Events	n (%)	Events
At least one AE	17 (89.5)	99	8 (88.9)	89
At least one TEAE	15 (78.9)	83	8 (88.9)	78
TEAEs related to IMP	3 (15.8)	6*	0	0
At least one severe TEAE	6 (31.6)	11	1 (11.1)	1
At least one SAE	8 (42.1)	16	4 (44.4)	17
At least one TESAE	8 (42.1)	16	4 (44.4)	17
With TESAEs related to IMP	0	0	0	0
Deaths – All Causes	0	0	0	0

**All 6 TEAEs related to IMP occurred in 3 subjects; 2 infusion site reactions, 2 nausea and vomiting, 1 decreased blood phosphorus and potassium*

Abbreviations: AE, adverse event; TEAE, treatment emergent adverse event; IMP, investigational medical product; SAE, severe adverse event; TESAE, treatment emergent severe adverse event

Results

Subject Disposition: 28 patients were randomized. One patient in the placebo arm withdrew; withdrawal was not associated with the study drug (**Figure 2**).

Patient characteristics: While study arms were balanced on many measures, there were some imbalances on variables known to be associated with transplant outcomes (**Tables 1, 2, 3**). Compared to ANG-3777, the placebo arm was older (mean=65.7, SD=12.8 vs mean=54.7, SD=13.7); had higher prevalence of CVD (100% vs 78.9%); received kidneys from older donors (mean=56.3 years, SD=10.8 vs mean=43.0 years, SD=21.2); and donors with DM/HTN (77.8% vs 63.2%). Compared to placebo, ANG-3777 arm was more likely to be black (42.1% vs 22.2%), have higher BMI (mean=30.1 kg/m^2, SD=4.7 vs mean=27.9 kg/m^2, SD=3.9), to receive a DCD kidney (21.1% vs 11.1%), have a higher incidence of DGF (73.7% vs. 66.7%) and had higher CRP (LS mean=7.5, SE=0.9 vs LS mean=5.7, SE=1.8 mg/dL), NGAL (LS mean=1152, SE=121 vs (LS mean = 646, SE=102 ng/mL) and sCR (mean=7.23, SE=0.50; vs LS means = 6.90, SE = 0.73) immediately post-transplantation. Thus, while there were imbalances on factors associated with poor transplant outcomes, they did not systematically favor one arm.

Efficacy Outcomes: The ANG-3777 arm was more likely to attain 1200 cc urine/24 hr. by Day 28 vs placebo (79% vs 44%); at a median of 5 days for ANG-3777 vs 14 days for placebo (**Figure 3**). The time to event log-rank test: χ^2=2.799; *p=0.094*. While Day 1 urine was similar (ANG-3777=690 cc; placebo=600 cc), patients in the ANG-3777 had greater increases from baseline urine for 10 out of the following 13 days (**Figure 4**). Serum creatinine was higher at Screening and Day 3 in the ANG-3777 arm, and lower at all other timepoints (data not shown). eGFR was similar at Screening and Day 3, and higher in the ANG-3777 arm at all other timepoints, reaching statistical significance on Day 14 and Month 12 (**Figure 6**). Incidence of DGF was slightly higher in the ANG-3777 arm (73.6% vs 66.6%). Subjects in the ANG-3777 arm had 1 less day of dialysis (mean=2.8 sessions, SE=0.6 vs mean=3.8 sessions, SE=1.4), 2.4 days shorter duration of dialysis (mean=7.6 days, SE=2.0 vs mean=10 days, SE=3.9) and 4 fewer hospital days (mean=7.6 days, SE=0.53 vs mean=11.4, SE=3.44). Two placebo patients experienced graft failure; versus none in the ANG-3777 arm (χ^2=4.66; *p=0.03*) (**Figure 5**).

Safety Outcomes: There were no deaths, and no discontinuations of study drug due to adverse events. In the ANG-3777 arm, there was a total of 99 AEs reported in 17 subjects (89.5%), an average of 5.8 events per subject. In the placebo arm, there was a total of 89 AEs reported in 8 subjects (88.9%), an average of 11.1 events per subject. In the ANG-3777 arm, 83 TEAEs were reported in 15 subjects (78.9%), an average of 5.5 TEAEs per subject. In the placebo arm, 78 TEAEs were reported in 8 subjects (88.9%), an average of 9.8 TEAEs per subject. Six of these TEAEs in the ANG-3777 arm, occurring in three subjects, were assessed by the Principle Investigator (PI) as related to study drug: 2 infusion site reactions in one subject, 2 instances of nausea and vomiting in one subject, and 1 instance of decreased blood phosphorus and potassium in one subject. None of the TEAEs in the placebo arm were assessed by the PI as related to study drug. There were 11 TEAEs in the ANG-3777 arm rated as severe, compared with 1 in the placebo arm. All severe TEAEs were assessed as SAEs. All SAEs were treatment emergent. In the ANG-3777 arm, 8 subjects (42.1%) reported a total of 16 TESAEs, an average of 2.0 TESAEs per subject. In the placebo arm, 4 subjects (44.4%) reported 17 TESAEs, an average of 4.3 TESAEs per subject. None of the TESAEs in either study arm was assessed by the Investigator as related to study drug.

Conclusion

In this Phase 2 trial, there was a signal for improved renal function in subjects treated with ANG-3777 relative to placebo, which manifested across both laboratory and clinical treatment measures. ANG-3777 had similar safety to placebo.

References

1. Pallardó-Mateu LM, Calabuig AS, Plaza LC, Esteve AF. Acute rejection and late renal transplant failure: Risk factors and prognosis. Nephrology Dialysis Transplantation. 2004; 19(3): 38–42.
2. Gueler F, Gwinner W, Schwarz A, Haller H. Long-term effects of acute ischemia and reperfusion injury. Kidney International. 2004; 66(2): 523-527.
3. Mohan S, Corvino FA, Dillon AL, Wang W, Mayne TJ Delayed Graft Function (DGF) in Kidney Transplantation Patients: An Analysis of Disease Burden. Presented at American Society for Nephrology, 2019. Washington, DC.