CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase I/II, Double-Blind, Placebo-Controlled Study: Assessing Safety and Efficacy of Preoperative Renal Allograft Infusions of C1 Inhibitor (Berinert®) (Human) (C1INH) vs. Placebo Administration in Recipients of a Renal Allograft from Deceased High Risk Donors and its impact on Delayed Graft Function (DGF) and Ischemia/Reperfusion Injury (IRI)
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Glossary and Abbreviations

AE	Adverse Event
CRF	Case Report Form (either paper or electronic)
EC	Ethical Committee
GCP	Good Clinical Practice
IRB	Institutional Review Board
MRR	Medical Research Report
SAE	Serious Adverse Event
SOC	Standard of Care
DGF	Delayed Graft Function
EGF	Early Graft Function
CVA	Cerebral Vascular Accident
DCD	Donation after Cardiac Death
ECD	Extended Criteria Donor
GFR	Glomerular Filtration Rate
UNOS	United Network for Organ Sharing
SCD	Standard Criteria Donor
OPTN	National Organ Procurement and Transplantation Network
ACR	Acute Cellular Rejection
C1INH	C1 inhibitor (Berinert®)
CMV	Cytomegalovirus
IRI	Ischemia-Reperfusion Injury
USRDS	The United States Renal Data System
WFI	Water for Injection

1.0 Introduction

Delayed graft function (DGF), defined as the need for dialysis in the first week after kidney transplant, is estimated to occur in over 20% of deceased donor kidney transplants (1). Its development is associated with an increased risk of rejection, poorer long-term kidney allograft function, and lower patient and graft survival (2,3). This association is modified by the severity of DGF, as indicated by the duration of dialysis-dependence after transplant, where longer periods of dialysis-dependence are associated with progressively higher risks of rejection and graft failure (4). Not surprisingly, kidneys at higher risk for DGF are more likely to be discarded in the United States despite the well-documented shortage in donor organ supply (5,6).

The predominant mechanism of DGF is ischemia-reperfusion injury. This is marked by an alloantigen-independent inflammatory response, characterized by influx of pro-inflammatory cells early after ischemic injury (7). Additionally, the complement cascade can be activated in response to ischemia-induced membrane changes (8). Although the alternative pathway has historically been thought to play the major role in ischemia-reperfusion injury, evidence suggests that the classical and mannose binding lectin (MBL) pathways are also important (9,10). Damage-associated molecular patterns (DAMPs), polysaccharides, and intracellular antigens exposed during ischemic injury can activate both the classical and MBL pathways (11). C4-deficient mice, who cannot activate the classical pathway C3 convertase (C2aC4b), were less susceptible to ischemia-induced injury compared to wild-type mice and antibodies against mannan-binding lectin-associated serine protease (MASP)-2 were protective against ischemia-reperfusion injury in the murine gastrointestinal tract and myocardium (11,12). Recent data from an animal model of heart transplant ischemia-reperfusion injury demonstrated that ischemia-reperfusion injury was largely prevented in animals that were genetic knockouts for the MBL collectin-11 but not for Factor B (alternative pathway) knockouts (10). In addition, wild-type mice treated with C1 esterase inhibitor were protected from ischemia-reperfusion injury, similar to collectin-11 (-/-). Thus, mounting experimental evidence suggests blockade of the classical and MBL complement pathways is a potentially attractive approach for prevention or mitigation of DGF caused by ischemia-reperfusion injury. Of interest is recent data linking IRI/DGF to induction of B-cell injury and DSA generation post-transplant. This is discussed below:

Evidence for B-cell Activation in Allografts Experiencing IRI/DGF

Cippa et al (13) in an elegant article published in *Nature* demonstrated a causal relationship between IRI/DGF and subsequent B-cell activation in the allografts. This clearly differed from allografts not experiencing IRI/DGF as no B-cell signals were demonstrated on protocol biopsies. The authors showed that production of DSAs post-transplant was a late event reflecting irreversible organ damage due to IRI/DGF. The authors conclude that their findings point to new opportunities for early diagnosis and novel therapeutic interventions that could prevent or alter IRI/DGF induced immune

activation events in the allograft. Here, early ischemic events incite innate immune systems (complement activation) that ultimately leads to chronic injury and activation of B-cells through exposure to cryptic antigens resulting in DSAs. Prevention of this early IRI/DGF damage should limit immune activation of B-cells and DSA inducted injury later post-transplant. See Figures 1A and 1B for the data presented in this manuscript.

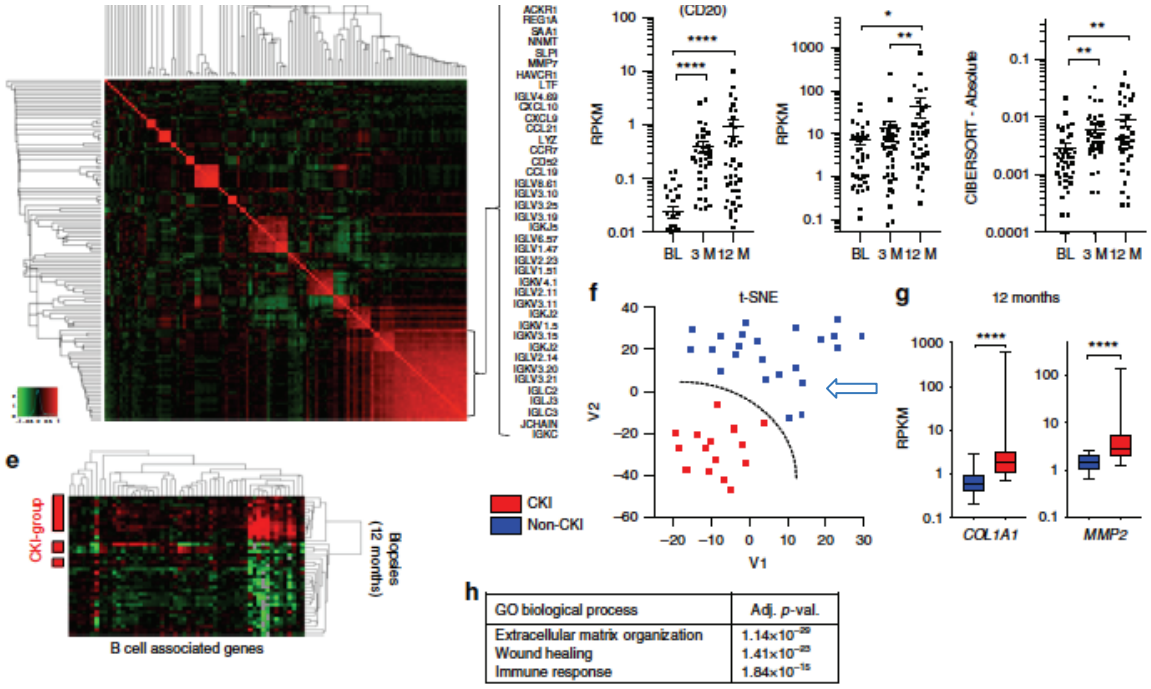

*Fig. 1A Chronic kidney injury and B cell immunity in human allografts. Heatmap showing the gene expression correlation of the 120 most variably expressed genes across kidney biopsies collected at 3 and 12 months after transplantation (N =80). The names of the genes included in the cluster in the bottom right corner are shown. b, c RPKM values of MS4A1 (CD20) and IGKC over time in human kidney allograft biopsies. BL: baseline. N= 39–42 for each time point. Wilcoxon matched-pairs signed rank test, ****P < 0.0001, **P < 0.01, *P < 0.05. d Semi-quantitative evaluation of immune cell infiltrates in the kidney at different time points after transplantation as determined by CIBERSORT analysis on RNAseq data. N = 39–42 for each time point. Wilcoxon matched-pairs signed rank test, **P < 0.01. e Cluster analysis based on the expression of B cell-associated genes including kidney biopsies collected at 12 months after transplantation (N= 39). Patients classified in the CKI group are indicated on the left. f t-SNE analysis on RNAseq data from kidney biopsies collected 12 months after transplantation defining the classification of patients in the CKI group. The boundary was determined by visual examination of the t-SNE plot. N = 39. g RPKM values of COL1A1 and MMP2 shown as examples of genes differentially expressed in CKI and non-CKI. Mean value and standard error (SE) are shown. Mann–Whitney test, ****P < 0.0001. (13)*

Data presented in this manuscript also demonstrated increased allo- and auto-antibody production in microarray analysis of blood from patients experiencing IRI/DGF post-transplant.

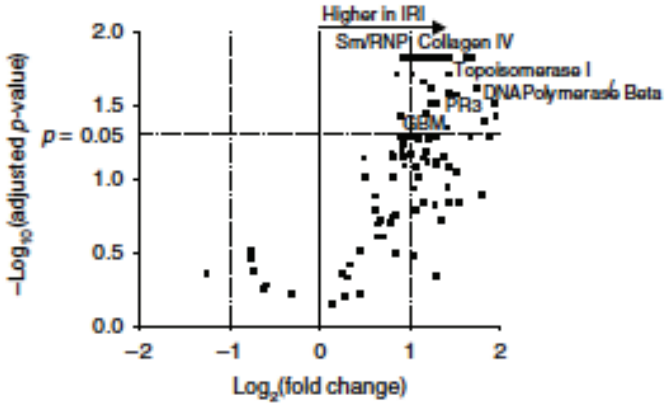

Figure 1B: *Volcano plot comparison of signal-to-noise ratio in IgG reactivity in plasma samples collected 16–18 months after IRI (n = 6) and in age-matched controls (n= 6) on microarray of autoantigens, with indication of log2-fold change on the x-axis (>0 indicates higher in IRI) and significance level. (13)*

1.1 Criteria for Defining IRI/DGF in Human Kidney Transplants

Historically DGF has been defined as the requirement for dialysis during the first week after renal transplantation, however the postoperative requirement of hemodialysis or peritoneal dialysis is not standardized and the decision to dialyze varies from center to center and among consultants (14). Efforts have been made to scientifically quantify DGF in a more stringent manner with various alternative definitions of DGF including; (14) the number of days to achieve a creatinine clearance of >10 mL/min, calculated by the Gault-Cockroft formula (15) a serum creatinine level of >3 mg/dL on the fifth day post-transplant (16) the need for dialysis within 72 hours after transplantation (17) serum creatinine level changes, including an increase, remaining unchanged, or decreasing by less than 10% per day immediately after surgery during three consecutive days for >1 week (18) a rising serum creatinine level above that before surgery, or urine output of <300 mL within 6 hours of transplantation, despite diuretics and adequate volume (19) urine output of <1 L in the first 24 hours or a decrease in serum creatinine of <20-30% reflected in a poor glomerular filtration rate (GFR) (20) and calculating the creatinine reduction ratio on day two following surgery (21). However, despite these alternative suggestions, the conventional definition of "requirement for dialysis in the first week post-transplant" remains the most utilized and published definition for DGF, with "need for dialysis" being easily measured and clinically relevant. However, recent data from the FDA indicate that more relevant end points for clinical trials of agents aimed at reducing IRI/DGF would be need for dialysis in the first month post-transplant and eGFR at 1year (https://www.fda.gov/media/103928/download.

1.2 The Kidney Donor Profile Index (KDPI)

Key to the success of any study aimed at evaluating efficacy against IRI/DGF is the reasonable stratification of risk for said event. In recent years this has been codified using the KDPI index. The Kidney Donor Profile Index (KDPI) is a numerical measure that combines ten donor factors, including clinical parameters and demographics, to summarize into a single number the

quality of deceased donor kidneys relative to other recovered kidneys. The KDPI is derived by first calculating the Kidney Donor Risk Index (KDRI) for a deceased donor.

Kidneys from a donor with a KDPI of 90%, for example, have a KDRI (which indicates relative risk of graft failure) greater than 90% of recovered kidneys. The KDPI is simply a mapping of the KDRI from a relative risk scale to a cumulative percentage scale. The reference population used for this mapping is all deceased donors in the United States with a kidney recovered for the purpose of transplantation in the prior calendar year. Lower KDPI values are associated with increased donor quality and expected longevity. This is shown in figure 2 below:

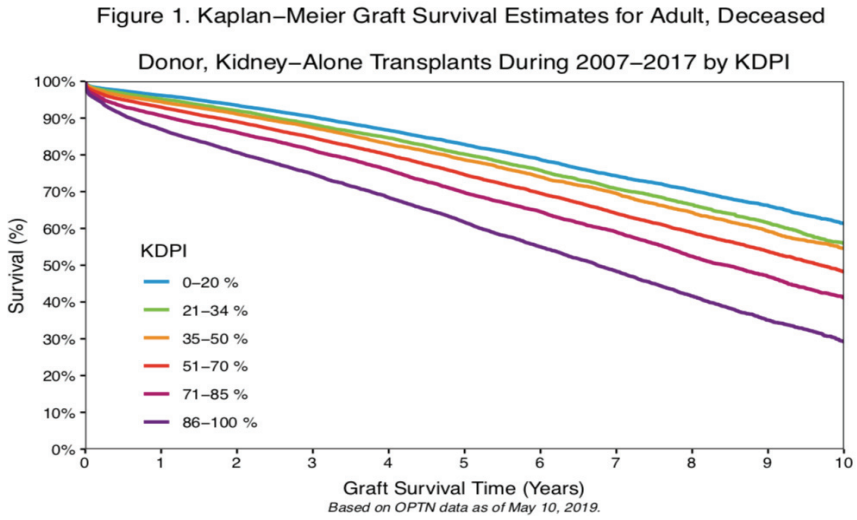

Figure 2: *This figure shows the outcomes of kidney transplants performed 2007-2017 based on KDPI scores. Here, the patients with the highest scores (86-100%) experienced the worst outcomes over time. This would suggest that kidneys donated from patients with high risk for IRI/DGF are unlikely to provide long-term benefits to patients, thus may be discarded.*

1.3 Complement as a Mediator of Ischemia Reperfusion Injury (IRI)

The complement system in humans exists as a system of recognition molecules, proteolytic enzymes and receptors for activated complement components that are responsible for host defense. The complement system can be activated in at least 3 separate ways; first, the classical pathway which depends on antibody binding to antigen targets and binding complement components (i.e. C1q) to ultimately activate C3 and initiate terminal complement component activation of C5b-C9 (see figure 3). Binding of lectins (i.e. mannose binding lectin and mannose binding lectin serine protease (MBLSP) activate the C3 convertase without activation of C1->4->2 (C3 convertase). In addition, the alternative pathway is activated by interaction with H_2O or activating surfaces. The deposition of complement on bacteria or sites of injury signal initiation of an inflammatory response and tags complement bound targets for elimination through apoptosis or phagocytosis by macrophages. The complement system also contains a number of receptors that

modify or abate complement-mediated inflammation. Complement also exists in two distinct compartments (central and local). The central compartment of complement is produced in the liver and is responsible for all circulating complement factors. The peripheral compartment included complement generated locally in organs such as the CNS and kidneys (22) Activation of complement in the peripheral compartments appears to be regulated primarily by IRI. Figure 2 below describes the importance of complement activation in initiation of renal tubular cell (RTC) injury with reference to induction by IRI. Briefly, IRI stimulates C3 production in the RTCs that is subsequently cleaved by the MBL/MBLSP or alternative pathway (22). C3b generated then activates C5 to C5a and C5b. C5b forms the C5b-C9MAC which induces cell death and cytokine (IL-6) release. C5a interacts with the C5aR to induce apoptosis and cell death. Data from have also shown that kidneys from C3 deficient mice are resistant to IRI. Other investigators have also shown that expression of C3 and other complement components in human donor kidneys before transplantation had a negative impact on graft outcome at 2-3 years (23). Thus there is significant support for a role of complement activation in inducing RTC injury and ultimately DGF and it would be reasonable to assume that administration of complement inhibitors would be of potential benefit in prevention or amelioration of RTC injury and possibly improve outcomes in kidneys at high risk for development of DGF.

As previously mentioned, this field has evolved considerably in the past 2-3 years. Recent data from a small consortium trial examined the utility of eculizumab (anti-C5) for prevention of IRI/DGF in a protocol similar to the one we previously reported with C1INH.(24) Here, the investigators showed no benefit on prevention of IRI/DGF and no long term benefit in improving eGFR in treated v. placebo patients. This would seem to challenge the findings of our larger study with C1INH v. placebo where significant benefits in reducing IRI/DGF were seen early that translated into long-term benefits in graft survival and renal function (24, 25). The differences seen in the two trials may be explained by two important papers recently published. Data summarizing this information is shown below. Briefly, data from Sacks et al (26) (27) have recently demonstrated that the lectin pathway of complement activation is critical to IRI/DGF injury in animal models. This finding implicated IRI induced expression of fucose on renal tubular cells that directly binds to the MASP collectin-11. The binding of this serine protease activates complement through the lectin pathway resulting in C5b-C9MAC and C5a induced ischemic injury to tubules. This is shown in Figure 4 below. These authors also found that collectin-11 was critical to the induction of interstitial fibrosis and tubular atrophy in experimental models. The conundrum regarding the differences in complement inhibitors used in the two studies discussed above may be resolved by a study reported by (10) Using a heart transplant model of IRI/DGF injury, these investigators examined the role of complement using specific knock-out mice. Here, Factor B (-/-) animals showed no benefit in prevention of IRI/DGF suggesting that the omission of the alternative complement activating pathway had no impact on prevention of IRI/DGF (10). This is important since the alternative pathway is best inhibited by eculizumab. In addition, the investigators performed similar experiments using collectin-11 (-/-) mice. Here dramatic differences were seen with knock-out of the collectin-11 gene expression resulting in a significant inhibition of

IRI/DGF injury to allografts. This data would tend to confirm the importance of the interactions of collectin-11 with fucose moieties on ischemic cells as a critical pathway for IR injury. Further support for this contention was shown when the investigators used C1INH treatment in this model. Here, results recapitulated those seen in the collectin-11 (-/-) experiments suggesting that C1INH treatment may have unique benefits in preventing IRI/DGF injury to allografts (10). The complement activation pathways and their roles in IRI/DGF are shown in Figure 4 below. In addition, Figure 4 shows the points of inhibition by C1INH that could have significance in prevention of IRI/DGF, specifically, the role in inhibiting collectin-11 binding to fucose moieties on renal tubular cells.

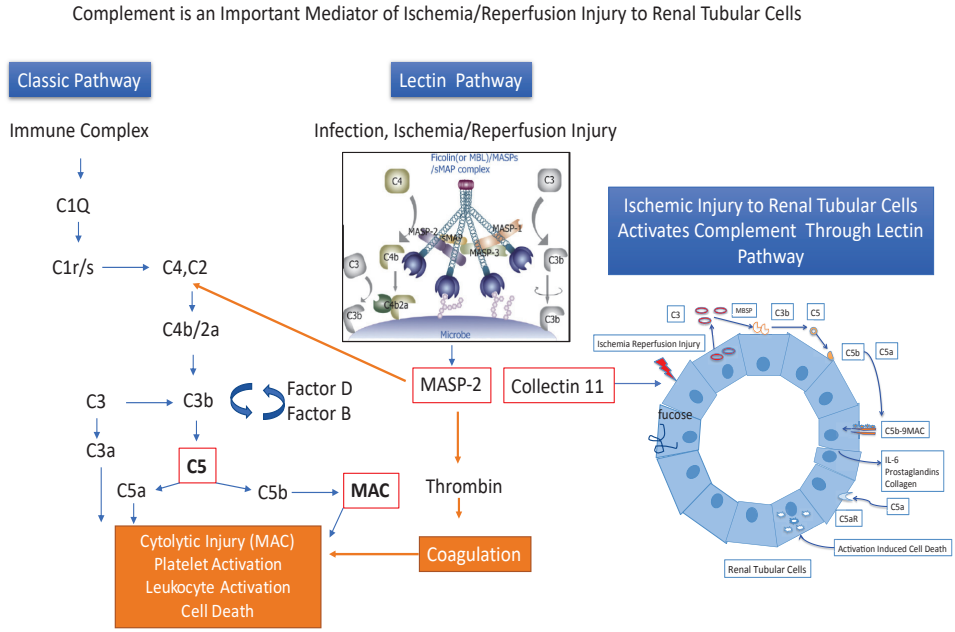

Figure 3: *This figure shows the impact of ischemic injury on RTCs. Ischemia induces complement activation through the lectin pathway (MASP-> Collectin-11) binding to fucose moieties expressed on injured tubular epithelial cells. Complement injury proceeds with damage to RTC epithelium manifest as renal ischemia injury with long-term implications.*

C1 Esterase Inhibitor: A Potential Inhibitor of IRI to Renal Tubular Cells

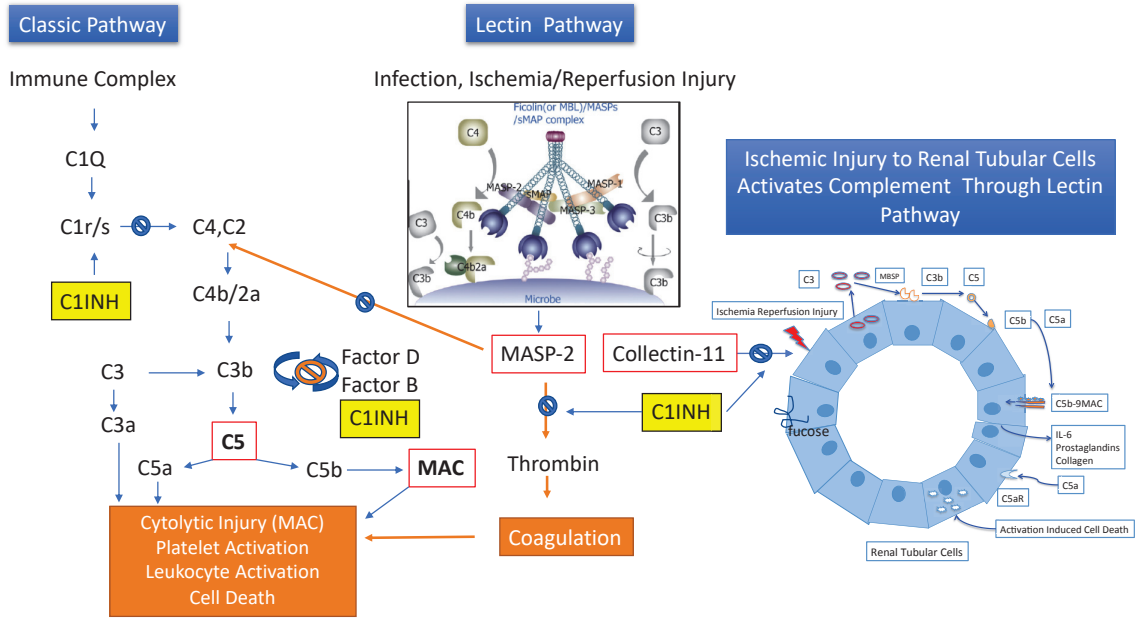

Figure 4 *shows the importance of C1INH in this process. Briefly, C1INH inhibits early complement activation by blocking C1QRS apposition. More importantly, C1INH inactivates collectin-11 and other Mannose binding serine proteases, inhibiting their ability to bind to fucose moieties and activate the lectin pathway. These findings distinguish the mechanisms of action of anti-C5 v. C1INH and are supported by the findings of Heeger et al. who demonstrated that the beneficial effects of collectin-11 (-/-) could be recapitulated by using C1INH treatment.*

1.4 Evidence for C1INH Prevention of IRI in Animal Models

Although limited, there are recent investigations which show dramatic results in prevention of IRI after C1INH treatment. (28) investigated the ability of recombinant C1INH (rC1INH) to alter tissue injury in a porcine model of controlled hemorrhage. In this model, the administration of 100U/kg or 250U/kg rC1INH significantly reduced IRI injury to kidneys, lungs, intestine and liver. The animals treated with 250U/kg also showed significant reductions in TNF-α levels and severity of metabolic acidosis. The significant beneficial effects of rC1INH administration were found to be related to the ability of C1INH to reduce IRI induced complement activation in tissue. All treated animals also showed reduced immune cell infiltration and cytokine production. The authors felt that the use of rC1INH would have significant benefits in patients with hemorrhagic shock in prevention of IRI and organ failure (29). In a comprehensive analysis of rC1INH use in an IRI model of kidney injury in the swine model found that IRI was associated with significant C3 activation, primarily through the MBL/MBLSP-2 pathway. The infusion of rC1INH led to significant reductions in peritubular capillary C4d deposition, and C5b-C9MAC. Complement inhibition with rC1INH also reduced the numbers of infiltrating CD163+, CD4+ and CD8+ T-cells. Animals

treated with rC1INH had significantly less RTC injury and renal damage. The authors conclude that the use of C1INH may represent a novel therapeutic approach in the prevention of DGF that would have particular relevance to kidney transplantation. Data from animal models of stroke induced by middle cerebral artery (MCA) occlusion showed that significant benefits in reducing infarct size were obtained with C1INH given at 20U/kg. Here, C1INH was shown to bind to microvasculature in the brains of animal who showed protection, presumable through prevention of IRI induced complement activation. (30), C1-inhibitor protects from brain ischemia-reperfusion injury by combined anti-inflammatory and antithrombotic mechanisms.

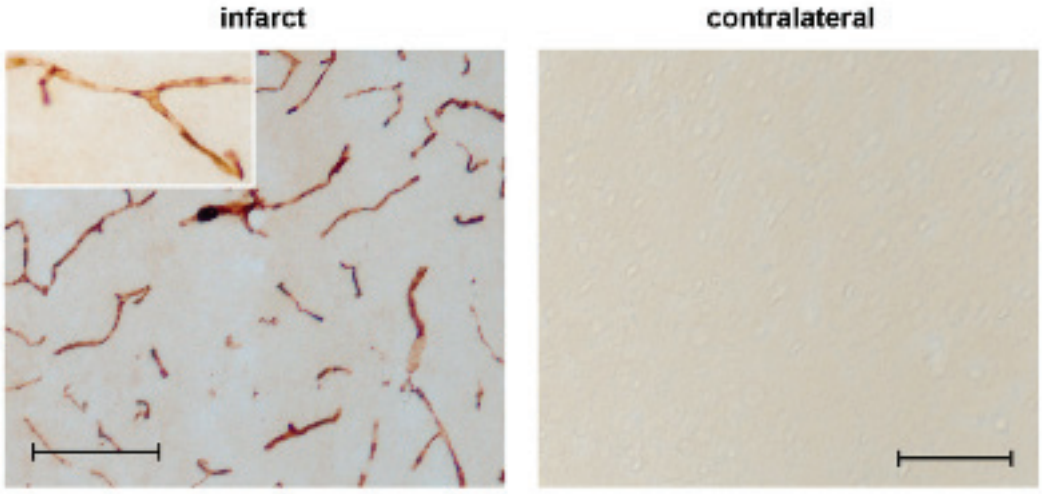

Figure 5: *Immunohistochemistry for human C1-INHin an infarcted (left) and healthy contralateral (right)rat hemisphere 30 minutes after reperfusion. C1-INH immunoreactivity is predominantly located within brain capillaries after stroke. This suggest the protective effect is related to C1INH inhibition of complement activation on the capillary walls.*

1.5 Evidence for Efficacy of C1INH in Preventing IRI/DGF in Human Kidney Transplant Recipients

C1 esterase inhibitor was approved by the United States Food and Drug Administration in 2009 for the treatment of hereditary angioedema. C1 esterase inhibitor is a serine protease inhibitor targeting C1s and C1r in the classical pathway and MASP-1 and MASP-2 in the MBL complement pathway and is therefore a relevant intervention to test the impact of complement inhibition on short- and long-term kidney function among allografts with ischemia-reperfusion injury. Our group recently reported twelve-month outcomes of a double-blind, randomized, placebo-controlled study investigating the safety and efficacy of C1 esterase inhibitor among deceased donor kidney transplant recipients at high-risk for DGF (25). Salient findings from this study were a shorter duration of DGF and higher estimated glomerular filtration rate (eGFR) at twelve months among patients treated with C1 esterase inhibitor compared to placebo. From our initial report we showed that C1INH was associated with a ~50% reduction in need for dialysis in the first month post-transplant in high risk patients and a clinically significant improvement in eGFR at 1 year. This is shown in

figure 6 below. For more details please see the referenced manuscript that is attached as an appendix.

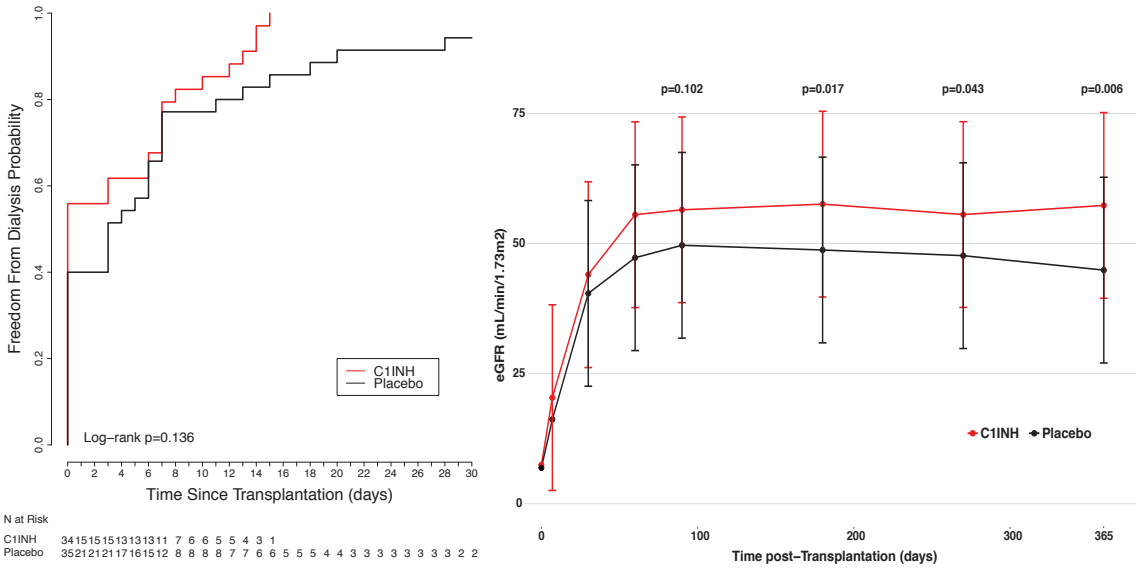

Figure 6: *This figure demonstrates that giving C1INH 50U/kg at time of transplant and @24 hrs post-transplant was associated with a near significant reduction in need for dialysis during the 1st month post-transplant and a significant improvement in eGFR at 1 year compared to placebo. The at risk population was balanced for risk factors associated with IRI/DGF being enriched for the risk. This data would suggest that prevention of early IRI/DGF has long-term implications for improving kidney function.*

We have subsequently assessed the long-term (3.5 year) outcomes of patients treated with C1INH v. placebo and saw that the results for improvements in eGFR have been sustained over the 3.5 year follow up.(31)This is also associated with an improved graft survival in the C1INH group and is shown in figures 7B and 8 below. Briefly, in figure7A, we show that in the C1INH group, the eGFR is maintained at +0.5 cc/min/1.73m^2/year for 3.5 years. However, the placebo group showed a decline of - 4.1cc/min/1.73m^2/year (p=0.03). We also saw that the graft survival was significantly decreased in the patients receiving placebo (p=0.007), again suggesting that prevention of early IRI/DGF is associated with a beneficial long-term survival and function of the kidney allografts. Although not statistically significant, there was a numerically important reduction in DSA generation post-transplant in the C1INH treated patients. This may be related to benefits in reducing ischemia-related activation of B-cells with subsequent DSA generation.(31)

C1INH v. Placebo for Prevention of IRI/DGF in Kidney Transplantation: Results

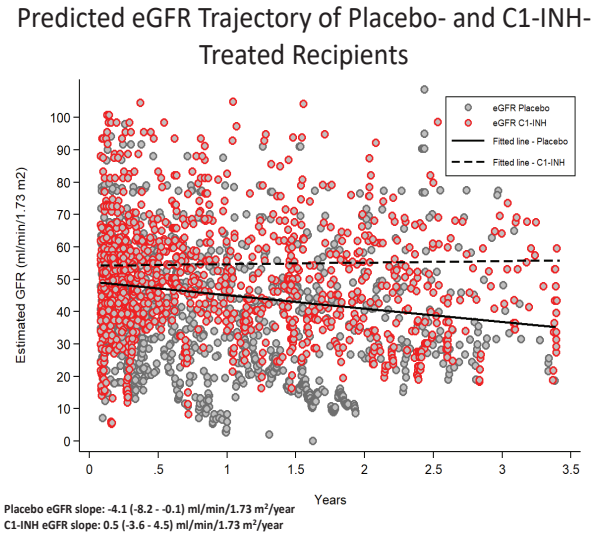

Figure 7A: *Data from our randomized placebo-controlled trial show that at 3.5 years C1INH treatment at transplant results in a significant improvement in eGFR compared to placebo treatment. The slope of eGFR was -4.1 cc/min/1.73m2/year in placebo v. +0.5cc/min/1.73m2/year in C1INH p=0.03.*

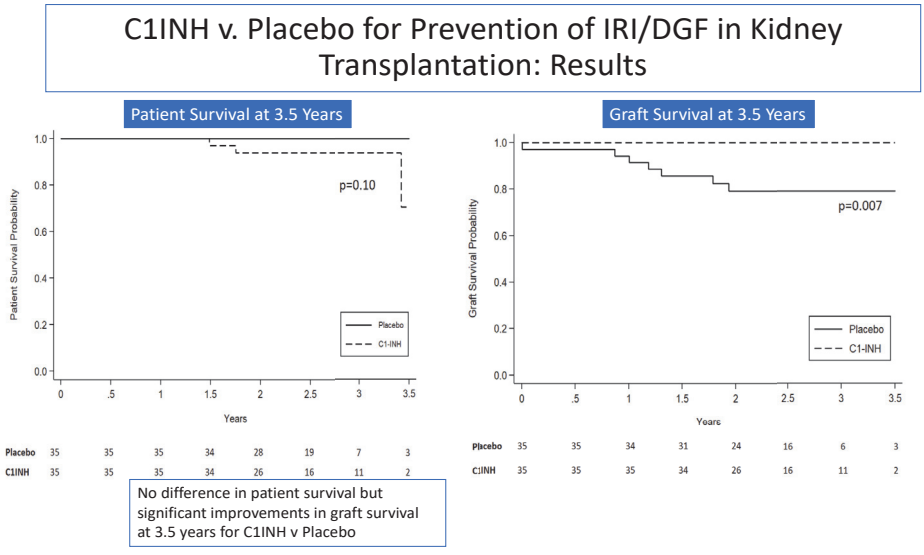

Figure 7B: *This figure shows the patient and graft survival at 3.5 years post-C1INH. Here, we see a significant benefit in prolonging graft survival if C1INH was given at time of transplant. There were 3 deaths that occurred in the C1INH group at 2-3 years post-transplant that were not related to C1INH administration.*

A summary of the data generated from our 3.5 year follow up study is shown below and will be published soon in the *Clinical Journal of the American Society of Nephrology*.

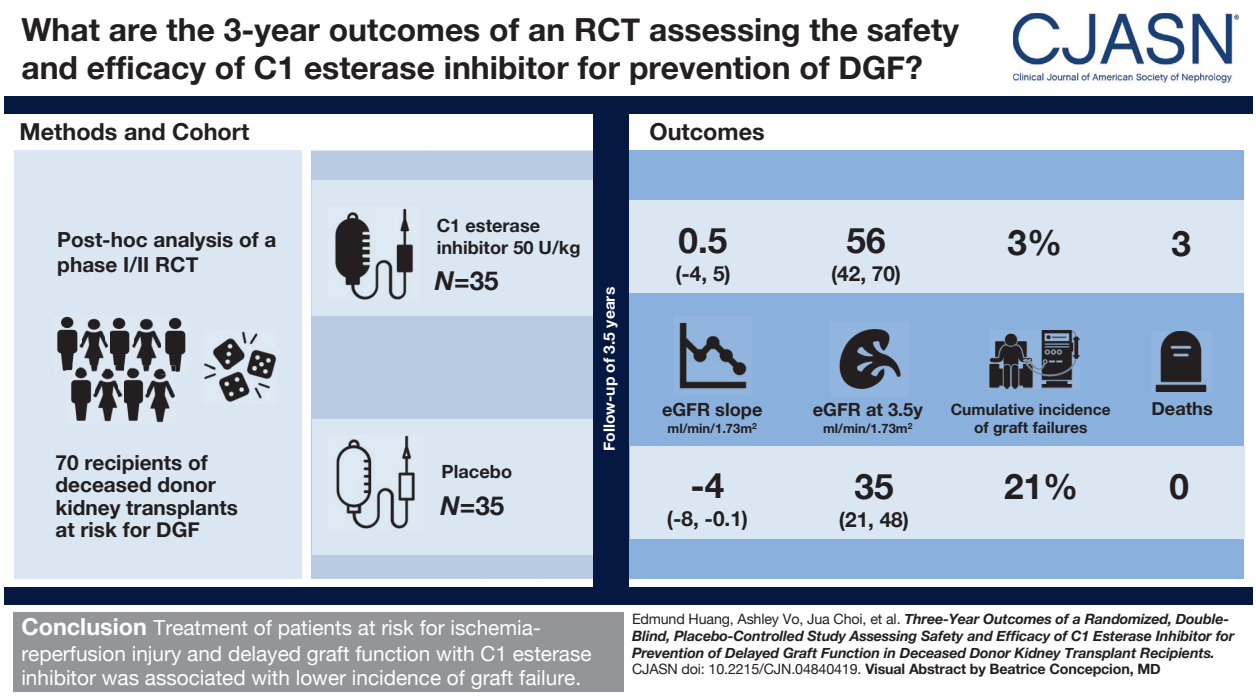

Figure 8: *A summary of the data from our 3.5 year follow-up of C1INH treatment of high-risk kidney allograft recipients is shown. Briefly the study was a placebo-controlled, blinded trial of C1INH v. placebo administered to a total of 70 (35 placebo & 35 C1INH) patients at risk for IRI/DGF. Data at 3.5 years show that C1INH treatment was associated with a significant improvement in eGFR and reduction in graft loss compared to placebo treated patients.*

2.0 Hypothesis

Since complement activation is detectable in animal models of IRI and in human kidneys after IRI, experimental data suggests that use of C1INH prior to induction of IRI shows significant beneficial effects on reducing IRI as well as inflammatory cell infiltrates, and since clinical data from humans indicate significant benefits in reducing dialysis at 1M post-transplant and, more importantly, significant improvements in renal function and graft survival 3.5 years after intravenous C1INH infusion, we hypothesize that the use of C1INH perfused into the kidney prior to transplant in patients receiving deceased donor (DD) kidney transplants with high risk for DGF (KDPI >80) will also show significant reductions in DGF and improved outcomes post-transplant compared with patients receiving KDPI >80 DD transplants receiving placebo treatment.

2.1 Study Objectives

In this study, we propose to investigate the application of pre-operative doses of C1INH (Berinert®)administered by infusion into the renal artery vs.

placebo, 1-2 hours prior to implantation, in adult subjects receiving a deceased donor renal allograft considered at high-risk for IRI and DGF (KDPI>80). We hypothesize that C1INH treated patients will demonstrate improved function of the kidney allograft compared to placebo, with equivalence in safety. **The primary objectives of this study are, using a double blinded, placebo controlled format, we will:**

1. Evaluate and compare the safety of C1INH (500U/kidney) administered pre-transplant by surgeons in the operating room in recipients of KDPI >80 kidney allografts from high risk deceased donors.

The secondary objectives are to:

1. Determine if Berinert® (C1INH) study dose 500U/kidney results in benefits of reducing need for dialysis in the 1st month post-transplant.
2. Determine if Berinert® (C1INH) study dose 500U/kidney results in benefits in improving long-term patient & graft survival and results in improved kidney function at 1 year compared to placebo infusions in the kidney.

2.2 Study Synopsis

TITLE	A Phase I/II, Double-Blind, Placebo-Controlled Study: Assessing Safety and Efficacy of Intraoperative Intrarenal Infused C1 Inhibitor(Human) (C1INH)vs. Placebo in Recipients of a Kidney Allograft from Deceased High Risk Donor (KDPI >80)and its impact on Risk for Delayed Graft Function (DGF)
INVESTIGATIONAL AGENT	C1INH (Berinert® [human][C1INH])
HYPOTHESIS	Pre-operative, infusion of C1INH into the renal allograft artery 1-2 hours prior to implantation will improve early graft function and reduce the rate of DGF, requirements for dialysis, graft survival and eGFR in patients receiving kidney allografts from high risk deceased donor compared to placebo.
RATIONALE	Early graft function has a long-term effect on graft survival. Poor early graft function and DGF contributes to decreased short- and long-term patient and graft survival, increased incidence of acute rejection, prolonged hospitalization, and higher costs of transplantation. Although multiple factors contribute to the impaired graft function, ischemia-reperfusion injury (IRI) is the underlying pathophysiology leading to poor early graft function and DGF. A >35% incidence of DGF has remained constant over time despite significant improvements in immunosuppressive strategies and patient management. This may be due to increased use of kidneys from "extended-criteria" and/or non-heart-beating donors, where even greater rates (>60%) of DGF have been reported.

	More than 94,653 people are currently waiting for a kidney transplant in the United States (UNOS.org 9/30/2019). Of the 19,360 kidney transplants performed in the US in 2018, 20% were from DCD donors and 9% from donors of KDPI>85. The USRDS reports that more than 50% of patients on the waiting list are willing to accept a kidney from an expanded-criteria donor (KDPI >85). This study will seek to expand the use of high KDPI kidneys and reduce wastage by showing improved function after C1INH treatment.
NUMBER OF PATIENTS AND CENTERS	40 patients will be enrolled into the study (20 C1INH and 20 Placebo). The study will be performed at Cedars-Sinai Medical Center. In 2018, we transplanted 38 kidneys into patients with KDPI > 85%. We anticipate the rate of offers from OneLegacy will continue at that rate. However, we would propose that 18-20 months will be required to complete study entry given the vagaries of acceptable offers and willingness of individual patients to participate in clinical trials.
INVESTIGATOR / CLINICAL TRIAL LOCATION	Stanley C. Jordan, M.D. Cedars-Sinai Medical Center
STUDY OBJECTIVES	• To evaluate and compare the safety of Berinert® (C1INH) 500U/kidney in recipients of a kidney allograft from high KDPI donors (KDPI >80) receiving kidneys infused with Berinert® (C1INH) 500U/kidney or placebo pre-operatively. • To evaluate early kidney function in recipients of a kidney allograft from a high KDPI donors following the intra-renal administration of Berinert® (C1INH) pre-operatively compared to placebo.
STUDY DESIGN	Patients who fulfill all I/E criteria will be eligible to be enrolled into Study **I Study Group (40 patients):** *Treatment Arm* I – KDPI >80 kidneys will be infused with one intrarenal dose of 500U of Berinert® in OR prior to implantation into the recipient. *Control Arm* – KDPI >80 kidneys will be administered one intrarenal dose of normal saline (NS) in the OR in a volume identical to the volume of the dose of Berinert® before implantation of kidney into the patient. Drug v. placebo administration will be randomized 1:1. Drug preparation and randomization will be carried out in a blinded fashion by research pharmacist.
STUDY POPULATION	**Inclusion Criteria:**

1) Adult men or women (18-77 years of age) who are on chronic dialysis therapy and acceptable candidates for receipt of a kidney transplant.
2) Recipients who are ABO compatible with donor allograft (A2 to B offers allowable)
3) Understand and sign a written inform consent prior to any study specific procedure
4). AND one of the below criteria:

a) Recipients of kidney allograft from KDPI >80 donors
b) Recipients of kidney allograft from DCD donors
c) Recipients of kidney allograft with CIT > 24 hours
d) Recipients of kidney allograft from donor on HD/CRRT prior to death/procurement
e) Recipients of kidney allograft with donor terminal creatinine SCr ≥3.0 mg/dL
f) Patient risk a total risk index score of ≥3 based on the following:

Table 1. Characteristics	Risk Index
Donor Age (years)	
<40	0
41-49	1
50-54	2
55-59	3
>60	6
Cold Ischemia Time (hours)	
0-12	0
13-18	1
19-24	2
24-30	3
31-36	4
>37	6
Recipient Race	
Non-black	0
Black	1
Recipient with Diabetes	
Has diabetes	1
Donor cause of death due to CVA	
Donor age >50 years	3
Donor Terminal Cr	
TCr >4	3
TCr ≥2-4	2
Tcr <2	0

Exclusion Criteria:

1) Patients with a known pro-thrombotic disorder. (eg. Factor V Leiden)
2) Patients with a history of thrombosis or hypercoagulable state, excluding access clotting.
3) Patients with a history of administration of C1INH containing products or recombinant C1INH within 15 days prior to study entry.
4) Patients with a known hypersensitivity to treatment with C1INH.
5) Patients with an abnormal coagulation function. (INR ≥2, PTT> 50, PLT<60,000) who are not on anti-coagulation.

	6) Patients with known active presence of malignancies. 7) Patients who are PCR positive for Hep B, Hep C, or HIV. 8) Recipients of pre-emptive kidney transplantation (unless baseline SCr is ≥4 mg/dL, making minimal urine output) 9) All zero mismatch kidneys. 10) Recipients of multi-organ transplants. (kidney and any other organ) 11) Recipients of kidney allograft that was arriving on pump preservation 12) Recipients of kidney allograft from a living donor. 13) Female subjects who are pregnant or lactating.
STUDY ENDPOINTS	**SAFETY:** • Overall incidence of adverse events and serious adverse events and relationship of AE and SAEs to the study treatment • Need for HD in the 1st month post-transplant. • eGFR at 1M, 3M, 6M Patient and graft survival at Day 180 • Rate of acute cellular rejection (ACR) and antibody mediated rejection at 6M **EFFICACY ASSESSMENTS:** **Primary Endpoints** ***Need for Dialysis in the 1st Month Post-Transplant:*** *(Excluding patients who get dialysis for hyperkalemia)* • The proportion of patients enrolled who require at least one session of dialysis in the first 30 days post transplant. • Number of dialysis sessions per patient in the first 30 days post transplant. **Renal Function and Graft Survival 6M** • eGFR at 6M post-transplant • Patient & Graft survival 6M post-transplant **Secondary Endpoints** • Rate of acute cellular and antibody mediated rejection episodes by day 180 • Calculated creatinine clearance at 1M, days 90, 180days post transplant. • Development of DSAs at 6M • SOC biopsies will be assessed at time of implantation and 6M post implantation.
IMUNOSUPPRESSION REGIMEN	• Induction therapy using Thymoglobulin in divided doses (total of 6mg/kg) or Campath 1H 30mg SQ x 1. • Calcineurin inhibition (Tacrolimus or Cyclosporine) will be initiated as per standard practice

	• MMF will be started per standard of care (SOC). • Corticosteroids will be used per SOC. • Valgancyclovir will be used as the prophylaxis for CMV for a minimum of 6 months. • Prophylaxis for bacterial and fungal infection will be per institutional SOC. • Diagnosis and treatment of acute cellular or antibody-mediated rejection will be per institutional SOC.
STATISTICAL ANALYSIS	Descriptive and comparative statistics will be used to evaluate results
Study Timelines	**Phase 1:** *Patient Entry*. Once the study is approved by CSMC IRB and contracting, we anticipate a study entry period of up to 18-20 months to complete study entry. **Phase 2:** *Follow Up to Study Completion*. The next phase of the study will be having each subject complete the study which is 6 months. Depending on our rate of entry, this means the study could last an additional 6 months from completion of patient entry. **Phase 3:** *Data collection, analysis and preparation of manuscript*. Once every patient has completed the study, we anticipate an additional 6M to complete data collection, analysis and preparation of abstract presentations and manuscript. **Total Study Time:** 36-40M (estimated)

3. Investigator(s) And Other Study Participants

Information regarding additional key personnel involved in the conduct of the study, including names and contact details of participating investigators, monitors, clinical laboratories, technical departments, as well as information on members of additional study committees, will be found in the study files of the sponsor and on site if requested.

A Data Safety Monitoring Board (DSMB) committee will review safety data. Quarterly assessment of AEs & SAEs will be performed and reported to FDA and Cedars-Sinai IRB. In addition, DSMB must be informed and may be convened at any time questions about safety arise and/or thromboembolic events occur. Please see appendix E FDA Guidance for Clinical Trial Sponsors.

4. Investigational Plan

4.1 Study Design And Plan

This is a Phase I/II double-blind, randomized, placebo-controlled study assessing safety and limited efficacy of intraoperative C1INH (500U/kidney) vs. Placebo administered into the graft renal artery 1-2 hours prior to implantation in adult subjects receiving a deceased donor kidney allograft considered high-risk for development of DGF (KDPI>80). Once eligible patients are identified, consented, and have an acceptable kidney transplant offer, they will be randomized by the Cedars-Sinai Research Pharmacy to

receive study drug vs. placebo. Drug and placebo will be prepared by the Cedars-Sinai Research Pharmacy and conveyed to the operating room in a blinded manner. The drug will be administered by the transplant surgeon in the OR in a blinded manner.

4.1.1 Study Drug Administration Timing

In consideration of the latest time point of treatment application before graft reperfusion (ie. beginning of renal vein anastomosis), study treatments will be administered pre-operatively, 1-2 hours **before graft reperfusion.** Due to the biologic half-life of C1INH (approximately 2.5 to 3.8 days), the time difference between early and late intraoperative treatment application, is thought to be negligible; however, we will administer the C1INH or placebo product at 1-2 hours prior to implantation for dosing consistency. This will constitute the entirety of C1INH vs. placebo administration. The study format is shown below in figure 9.

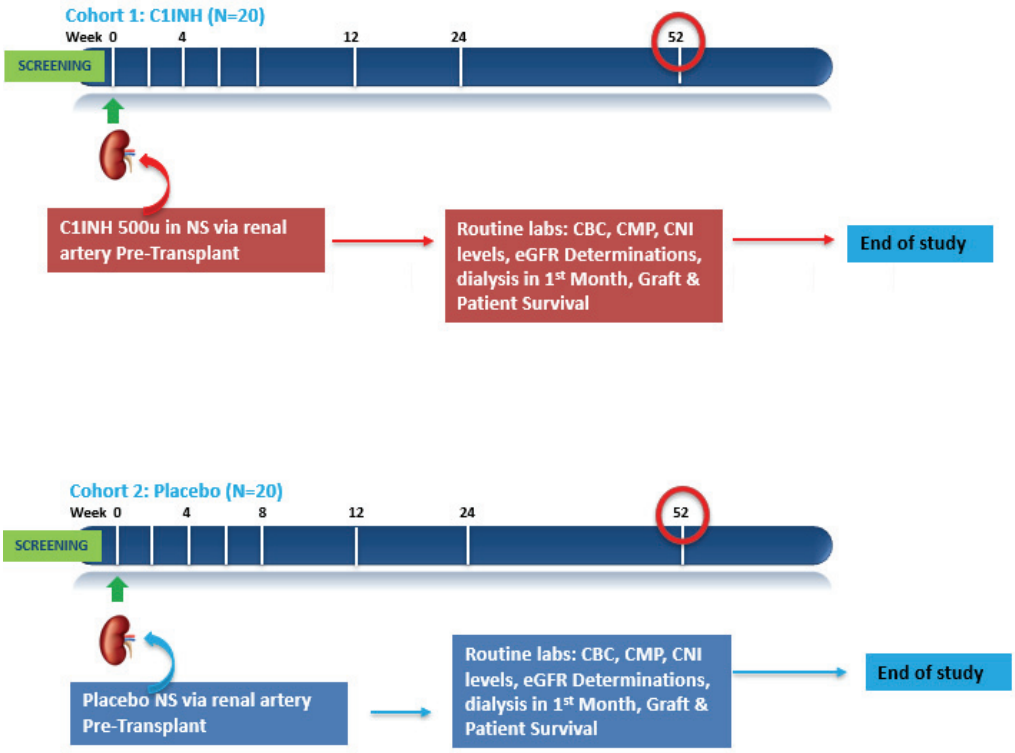

Figure 9: *Study format to evaluate C1INH in DGF.*

4.2 Selection Of Study Population

Persons legally incompetent to provide informed consent include, but may not be limited to, minors (children), individuals who are mentally incapable of understanding the implications of the PI/IC, and those who are physically unable, by any written, physical or verbal means, to confirm their understanding and consent to take part in the study. Our policy is not to

enter adult patients who are mentally incompetent to give informed consent. Exceptions must be approved by the Study Director.

Up to 40 adult men and women (18-77 years of age) who are recipients of a kidney transplant and only a kidney allograft from a deceased donor who is high risk for DGF will be enrolled in the study (KDPI >80).

4.2.1 Inclusion Criteria

Recipient Inclusion Criteria

1). Adult men or women (18-77 years of age) who are on chronic dialysis therapy and acceptable candidates for kidney transplant.
2). Understand and sign a written informed consent prior to study specific procedures.
3). Recipients who are ABO compatible with donor allograft. (A2 to B offers allowable)
4). AND one of the below criteria:

a) Recipients of kidney allograft from **KDPI >80** donors
b) Recipients of kidney allograft from DCD donors
c) Recipients of kidney allograft with CIT > 24 hours
d) Recipients of kidney allograft from donor on HD/CRRT prior to death/procurement
e) Recipients of kidney allograft with donor terminal creatinine SCr ≥3.0 mg/dL
f) Patient risk a total risk index score of ≥3 based on the following:

Table 1. Characteristics	Risk Index
Donor Age (years)	
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50-54	2
55-59	3
>60	6
Cold Ischemia Time (hours)	
0-12	0
13-18	1
19-24	2
24-30	3
31-36	4
>37	6
Recipient Race	
Non-black	0
Black	1
Recipient with Diabetes	
Has diabetes	1
Donor cause of death due to CVA	
Donor age >50 years	3
Donor Terminal Cr	
TCr >4	3
TCr ≥2-4	2
Tcr <2	0

4.2.2 Exclusion Criteria

1) Patients with a known pro-thrombotic disorder. (eg. Factor V Leiden)

2) Patients with a history of thrombosis or hyper-coagulable state, excluding access clotting.
3) Patients with a history of administration of C1INH containing products or recombinant C1INH within 15 days prior to study entry.
4) Patients with a known hypersensitivity to treatment with C1INH or blood products.
5) Patients with an abnormal coagulation function. (INR ≥2, PTT> 50, PLT<60,000) who are not on anti-coagulation.
6) Patients with known active presence of malignancies.
7) Patients who are positive for Hep B, Hep C, or HIV PCR test.
8) Recipients of pre-emptive kidney transplantation. (unless baseline SCr is ≥4 mg/dL, making minimal urine output)
9) All zero mismatch kidneys.
10) Recipients of multi-organ transplants. (kidney and any other organ)
11) Recipients of kidney allograft that was arriving on pump preservation
12) Recipients of kidney allograft from a living donor.
13) Female subjects who are pregnant or lactating.

4.3 Removal Of Subjects From Study

A subject who is withdrawn is one who discontinued in the clinical study for any reason. Subjects may be withdrawn from the study for the following reasons:

- At their own request or at the request of their legally acceptable representative.
- If, in the investigator's opinion, continuation in the study would be detrimental to the subject's well-being.
- At the specific request of the sponsor.

In all cases, the reason for withdrawal must be recorded in the case report form and in the subject's medical records.

Patients have the right to withdraw from the study at any time for any reason without penalty or prejudice. The Investigator also has the right to withdraw patients from the study if he/she feels it is in the best interest of the patient or if the patient is uncooperative or non-compliant. It is understood by all concerned that an excessive rate of withdrawals can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided. Should a patient decide to withdraw, all efforts will be made to complete and report the observations, and early withdrawal procedures, as thoroughly as possible.

The Investigator should contact the patient either by telephone or through a personal visit to determine as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the patient’s withdrawal should be made with an explanation of why the patient is withdrawing from the study. If the reason for removal of a patient from the study is an adverse event or an abnormal laboratory test result, the principal specific event or test will be recorded on the CRF. For all patients who are withdrawn pre-maturely, every attempt should be made to assess the patient’s status (i.e. patient and graft survival, malignancies, etc.) at 30 days after administration of the last dose of study medication.

4.4 Premature Termination Of Study/Closure Of Center

The sponsor has the right to close this study at any time, although this should occur only after consultation between involved parties. The Ethics Committee/Institutional Review Board (EC/IRB) must be informed. Should the study/center be closed prematurely, all study materials (except documentation that has to remain stored at site) will be retained on site by the sponsor/investigator.

4.5 Treatments

4.5.1 Treatments To Be Administered

This study is designed with two blinded treatment groups (C1INH vs. Placebo). Each group will include 20 patients in a treatment arm and 20 patients in a placebo arm.

This design is not statistically powered to show significant differences if there is a 30-50% reduction in the treatment group but may trend towards positive treatment effect since extensive DGF (40-50%)is expected in KDPI >80 recipients. The dose of C1INH chosen is (500U/kidney) which should be sufficient to bind all endothelial surfaces in the transplanted kidney. This is based on our observations from our experience using C1INH vs. placebo to prevent antibody-mediated rejection in humans. In those randomized to placebo, an equivalent volume of placebo (0.9% normal saline) will be administered prior to graft reperfusion. Both groups (C1INH or placebo) will receive an intrarenal administration of heparinized normal saline before study drug administration.

Patients who fulfill all I/E criteria will be eligible to be enrolled into this Phase I/II study.

4.5.2 Identity Of Investigational Product(s)

Medication will be labeled according to the requirements of local law and legislation. Label text will be approved according to agreed CSMC Research Pharmacy procedures.

Product name: Berinert® / C1INH (Human)

Chemical name: Complement Factor 1 Inhibitor (C1INH)

Study Medication & Dosing: Berinert® is available in a single-use vial that contains 500 units of C1 esterase inhibitor as a lyophilized concentrate. Each vial must be reconstituted with 10 mL of diluent (sterile water) provided. Prior to reconstitution, Berinert® should be stored at 2° to 25°C. After reconstitution, administration may begin within 8 hours provided the solution has been stored at up to 25°C. Berinert® is dosed as a 500U/kidney infusion 1-2 hours prior to implantation of the KDPI >80 kidney. Participating patients will receive 500U/kidney C1 INH vs placebo (0.9% NS) prior to implantation, (see Appendix A). The C1INH or placebo dose will be preceded by an intrarenal administration of heparinized normal saline.

4.5.3 Method Of Assigning Subjects To Treatment Groups

Patients will be randomized into treatment/placebo arms in a 1:1 ratio. Randomization will be completed prior to patient entering the operating room for transplantation.

This study is a double-blind, placebo-controlled study. The clinical pharmacist will maintain the randomization assignment. The Investigators, other study personnel, patients, and the Sponsor will be blinded to treatment assignment.

4.5.4 Selection Of Doses In The Study

4.5.4.1 Berinert® (C1INH Dosing)

For the planned study, subjects will receive C1NH 500U/kidney infused into the renal artery pre-operatively 1-2 hours before graft reperfusion. For all dose reconstitutions, Berinert® is provided in single dose vials of 500 units. Each vial will be reconstituted in 10 ml sterile water for injection. Placebo will be administered in an identical volume. C1INH will be preceded by an intrarenal administration of heparinized normal saline prior to renal vein anastomosis.

4.5.4.2 Placebo Dosing

The placebo used in this study will be 0.9% normal saline administered as a single dose into the renal artery, 1-2 hours before graft reperfusion. The total volume will be identical to that calculated for Berinert® infusions. Placebo will be preceded by an intrarenal administration of heparinized normal saline prior to renal vein anastomosis.

4.5.5 Immunosuppression

Immunosuppression regimen is an important part of the care for recipients of kidney transplantation. The regimen to be used in this study is reflecting the fact that the patients enrolled into this study are at high risk for developing poor or delayed graft function.

4.5.5.1 Induction Antibody Therapy

All patients enrolled into this study will be treated with induction antibody therapy with Thymoglobulin® OR Campath 1H. For Thymoglobulin®, the first dose will be given immediately after the transplantation procedure to follow with additional doses so that patients receive up to 6 mg/kg (1.5mg/kg/dose) using standard institutional treatment guidelines for use of this agent in this patient population. Campath 1H will be administered in a single 30 mg subcutaneous dose post-transplant. No induction administration of IL-2 receptor inhibitors is permitted in this protocol.

4.5.5.2 Maintenance Immunosuppression

4.5.5.2.1 Calcineurin Inhibitors (Tacrolimus or Cyclosporine)

Tacrolimus (Prograf) and Cyclosporine (Neoral) are indicated for the prophylaxis of organ rejection in patients receiving allogeneic kidney transplants. Tacrolimus or Cyclosporine will be initiated and monitored with trough levels using standard institutional treatment guidelines for use of these agents in this patient population. If conversion to belatacept is deemed necessary per SOC process, this is allowable during study participation

4.5.5.2.2 Mycophenolate Mofetil(MMF)

Mycophenolate mofetil (MMF, CellCept), the morpholinoethylester of mycophenolic acid, has been shown to have antiproliferative effects on lymphocytes by blocking proliferation of T- and B-lymphocytes. MMF will be dosed using standard institutional treatment guidelines for use of these agents in this patient population. Myfortic can be used instead of CellCept and will be dosed using standard institutional treatment guidelines for use of these agents in this patient population.

4.5.5.2.3 Corticosteroids

Corticosteroids will be administered using standard institutional treatment guidelines for use of these agents in this patient population.

4.5.6 Anti-infective Prophylaxis

Valgancyclovir for the prophylaxis of CMV infection will be used for a minimum of 6 months. If PO administration of valgancyclovir is not possible, the use of ganciclovir while the patient is inpatient is also permissible.

Local standards of care for post-transplant bacterial and fungal prophylaxis will be applied using standard institutional treatment guidelines for use of these agents in this patient population.

4.5.7 Selection And Timing Of Dose For Each Subject

The active treatment arm (Berinert® 500U/kidney) will be compared to a placebo control treatment arm, with a total of 20 adult subjects in each study group. A total of 40 adult subjects will be enrolled in the study and additional subjects will not be enrolled to replace dropouts. This design is not statistically powered to show differences in DGF; a 30-50% reduction in DGF predicted for the Berinert® study group. Treatment effect will be investigated following renal artery infusion with Berinert® or an equivalent volume of placebo (0.9% normal saline) pre-operatively prior to graft reperfusion. The C1INH or placebo dose will be preceded by an intrarenal administration of heparinized normal saline.

If a patient is enrolled into the study but the transplant does not occur as planned (e.g. transplant is cancelled due to donor organ quality at time of transplant), the patient will be considered a "screening without transplant". The patient will be maintained on the study ID # that was assigned

at enrollment but will not be followed past the screening day. IF the patient receives another transplant offer (at any time while study enrollment is still open), the patient will be allowed to continue with the study protocol, with Day of Transplant = Day 0, as if the screening and consenting occurred during the current admission.

4.5.8 Blinding

The investigational drug pharmacist will be contacted by the study staff and informed of a patient's eligibility. The pharmacist will prepare the blinded study medication or placebo. The study treatment will be prepared according to a pharmacist-supplied randomization code (blinded from all other study personnel). The study treatment will be prepared in a non-siliconized sterile syringe (Berinert® {500U} for all individuals) and labeled with:

- Protocol Number
- Screening number
- Randomization number.

The pharmacist will check the non-siliconized IV syringe for potential particulates. If none are found, the blinded syringe of study treatment, labeled as stated above, will be transported to the surgical suite and matched with the matching patient chart. For the placebo arm, an equivalent volume of normal saline will be prepared in an identical dispensing medium as the C1INH product, labeled as stated above, and transported to the surgical suite and matched with the matching patient chart. Before the study treatment (Berinert or placebo), heparinized normal saline will be administered to the allograft. This method of drug administration has not been FDA approved and may have unforeseen risks

In case of a medical emergency, the study drug assignment for a particular patient may be unblinded. Unblinding study drug assignment will only be necessary if knowledge about treatment is needed for the medical management of the patient. The patient's treatment assignment can be identified for unblinding purposes by calling the Investigational Pharmacist (310-423-6580). When this is necessary, the investigator must immediately notify the IRB, and document the reason and date of the un-blinding. The event must also be documented on the study termination record, the AE page of the CRF, and in source documents. Additionally, the Principal Investigator will submit to the IRB a written explanation describing the event within 5 working days. The procedures for un-blinding study drug treatment will be provided to the Principal Investigators prior to study implementation.

4.5.9 Treatment Compliance

There is only one application of the drug, which takes place approximately 60-120 minutes prior to graft reperfusion administered pre-operatively.

4.6 Study Variables

4.6.1 Efficacy Variables

4.6.1.1 Primary Efficacy Endpoints

For patients who require dialysis in the first 30 days: (*Excluding patients who get dialysis for hyperkalemia)*

- The proportion of patients enrolled who require at least one session of dialysis in the first 30 days post transplant.
- Number of dialysis sessions per patient in the first 30 days post-transplant.

Renal function and graft survival 6M

- **eGFR at 6M post-transplant**
- **Patient and graft survival at 6M post-transplant**

4.6.1.2 Secondary Efficacy Endpoints

- Calculated Creatinine Clearance obtained at 1M, 3M, 6M post-transplant.
- Rate of acute cellular and antibody mediated rejection episodes by day 180
- Development of DSAs at 6M
- Analysis of renal transplant biopsies at time of implantation and at 6M as clinically indicated.

4.6.2 Safety Variables

4.6.2.1 *Adverse Drug Reactions*: The most serious adverse reaction reported in subjects in clinical studies who received Berinert® was an increase in the severity of pain associated with hereditary angioedema. In a placebo controlled clinical study, the incidence of adverse events occurring in more than 4% of subjects (n = 43) receiving Berinert® up to 72 hours after infusion was nausea (7%), headache (7%), abdominal pain (7%), dysgeusia (4.7%), vomiting (2.3%), pain (2.3%), and muscle spasms (2.3%). Adverse reactions can persist 7-9 days after infusion and have been reported to be abdominal pain (6.5%), diarrhea (4.6%), nausea (6.5%), vomiting (4.6%), headache (11.1%), hereditary angioedema recurrence (11.1%), muscle spasm (5.6%), and pain (5.6%). Subjects were tested at baseline and after 3 months for exposure to parvovirus B19, HBV, HCV, and HIV-1 and HIV-2. No subject who underwent testing evidenced seroconversion or treatment-emergent positive polymerase chain reaction testing for the above pathogens. Post-marketing reports from Europe since 1979 in patients receiving Berinert® for treatment of HAE include hypersensitivity/anaphylactic reactions, a few suspected cases of viral transmission, including cases of acute hepatitis C, injection-site pain, injection-site redness, chills, and fever. See Novation Drug Monograph for Berinert®. Berinert® was well tolerated with minimal AE/SAE profile in our kidney transplant studies (Appendix B).

4.6.2.2 Assessment of Risk for Thrombotic Events with C1INH Administration: Patients with known risk factors for thrombotic events will be monitored for signs and symptoms of thrombosis, such as new onset swelling and pain in the

limbs or abdomen, new onset chest pain, shortness of breath, loss of sensation or motor power, or altered consciousness, vision, or speech. Patients will be assessed for evidence of DVT or other TEs per the usual standard process. Routine measurements of coagulation factors to evaluate DIC (D-Dimers, fibrinogen, PT, PTT) will be performed per standard process.

4.6.2.3 Evidence of a Thrombotic Effect of C1INH Administration when Given in Supraphysiologic Dosages to Humans: The German Medical Profession's Drugs Committee (AkdÅ) reported on 13 cases of severe thrombus formation after Berinert® infusions. These infusions were given to neonates undergoing cardiac surgery and doses of Berinert® were given at exceedingly high doses (~500U/kg) without control studies (see Appendix C). Nine of these infants died of this complication. The conclusions from this report are as follows:

- There are no studies to support the use of C1INH outside of those with hereditary angioneurotic edema.
- The use of C1INH in patients who do not have C1INH deficiency may result in abnormal coagulation parameters with propensity to thrombosis.
- There are no controlled studies that suggests a benefit of C1INH therapy in conditions other than C1INH deficiency.
- Any proposed uses outside of C1INH deficiency should be conducted in a controlled manner to monitor for unexpected or unanticipated side effects of C1INH therapy.

Clearly, this is a serious and unanticipated complication of C1INH therapy that could potentially limit its use in patients with other conditions where complement inhibition would be desirable. This is the case with our proposal. Inhibition of complement activation post-transplant has great potential for prevention of complement-dependent DGF. In addition, there is an important unmet need for new therapeutics in the prevention and treatment of DGF. Despite this, it is important to assess the tolerability and safety of C1INH therapy in this patient population. Although the C1INH dosing proposed in our study is much less than that reported to be associated with TE and well below therapeutic dosing recommendations (20-50U/kg) (500U/kidney once on Day 0), and will be administered intra-renally, there is still a possibility that increasing C1INH levels above normal baseline could have deleterious effects and induce coagulation abnormalities. Recent safety data from clinical trials of C1INH for use in C1INH deficiency have not reported TE with one exception of a basilar artery thrombosis in a patient treated for C1INH deficiency (Appendix C). This event was deemed unrelated to C1INH therapy. As previously indicated if significant coagulation abnormalities or TE events are seen in any study patient, the study will be terminated. *However, data from our recently completed study of C1INH in prevention of antibody-mediated rejection (NCT01134510) in a randomized placebo controlled study showed no evidence of thrombotic events in any patient treated with Berinert® at 20U/kg x 8 doses given during the first month post-transplant. In addition, recent reports from the FDA (Gandhi et al) suggests that thrombotic events do occur with C1INH therapy, but most cases are associated with the product (Cinryze®).*

4.6.2.4 Evidence of a Thrombotic Effect of C1INH Administration when Given in Supra-physiologic Dosages to Animals: Data on C1INH transgenic mice show that blood levels as high as 2mg/ml (NL 25 μg/ml) are produced without reported effects (34)(Appendix D). Other investigators have shown that ischemia-reperfusion injury is reduced in animals transgenic for C1INH expression (Appendix D). Data provided by CSL Behring (Appendix D) shows that administration of Berinert® up to 200U/kg daily for 14 days had no deleterious effects and did not induce coagulation abnormalities.

4.6.2.5 Therapy Stopping Points

As indicated previously, the study will be halted and re-evaluated by the DSMB if any patient in the study group develops thrombosis of the allograft, thromboembolic events (TE) or evidence of coagulation abnormalities that would suggest impending TE. In addition, the study will be halted or stopped if any other known or unexpected AEs attributable to C1-inhibitor occur. Reassessment of the study goals and complications will be done and discussed with the DSMB prior to proceeding. A summary report will be submitted to the IRB and FDA.

4.6.2.6 Primary Safety Endpoints

- Overall incidence of adverse events and serious adverse events and relationship to the study treatment including but not limited to, occurrence of infections, thrombosis of the allograft, vascular thromboses, bleeding, death, vital signs, and abnormal lab values.

4.6.2.7 Secondary Safety Endpoints

- Chemistry and coagulation parameters
- eGFR at 1M, 3M, 6M
- Patient survival at day 180
- Graft survival at day 180
- Rate of acute cellular and antibody mediated rejection episodes at day 180
- Rate of de novo Donor Specific Antibody (DSA) development

4.6.3 Assessment Periods

4.6.3.1 Screening Procedure –Day 0

Prior to screening activities, each patient must be given an opportunity to ask questions and to understand the details of study participation. This consent process must be documented in the patient's source documents and evidenced by the patient signing the informed consent form.

After signing the ICF, each patient will be assigned a patient identifier number that will be used on all subject documentation. Numbers will be assigned in ascending sequential order. This number will also correspond to the patient number entered on study materials.

The Principal Investigator or qualified and assigned Sub-investigator will review the inclusion and exclusion criteria and laboratory test data to confirm eligibility of each subject.

The screening procedures will include the following:

- Informed consent
- Medical history
- Inclusion/Exclusion criteria review
- Vital signs/weight
- Complete physical examination
- Hematology & chemistry profile
- Record PT, PTT, INR collected by SOC
- Review historical serologies for HIV, HBV, HCV, CMV and EBV, collected by SOC
- Concomitant medications
- Review of previous Pneumococcal vaccination
- Review of Pregnancy test (for WOCP, Age 12-55 years old)

4.6.3.2 Day 0 – Day of Transplantation

- Vital signs (pre- and post-transplant)
- Physical examination (pre- and post-transplant)
- Randomization (pre-transplant)
- Hematology & chemistry profile (pre- and post-transplant)
- Record PT, PTT and INR collected by SOC (pre-transplant)
- Concomitant medications (pre- and post-transplant)
- ECG (pre-transplant)
- Chest x-ray (pre-transplant)
- Serum Creatinine (pre-and post-transplant)
- Berinert vs. Placebo infusion (on call to OR) with heparinated saline
- Campath 1H or Thymoglobulin administration
- Assessment of implantation biopsy (if collected)
- Urine output measurement if producing urine (post-transplant)
- Adverse event assessment
- Dialysis assessment

4.6.3.3 Day 1-7 Assessments measured on days 1, 3 and 7 (or until discharge)

- Concomitant medications
- Serum creatinine measurements through Day 7 or until discharge.
- Dialysis assessment
- Physical examination
- Vital Signs/weight
- Calculated estimated GFR
- Record Urine output measurement if producing urine
- Adverse event assessment
- Hematology & chemistry profile
- Urinalysis if producing urine. Urinary IL-18 to be collected on two days, between day 1 to 7, if producing urine and testing is available

4.6.3.4 Day 30 ± 7 days

- Concomitant medications
- Physical examination (may occur as a video visit)
- Vital Signs/weight
- Dialysis assessment
- Adverse Event Assessment
- Calculated estimated GFR
- Hematology & chemistry profile
- Urinalysis

4.6.3.5 Days 90, 180 ±30 days

- Concomitant medications
- Physical examination(may occur as a video visit)
- Dialysis assessment
- Vital Signs/weight
- Adverse Event Assessment
- Calculated estimated GFR
- Hematology & chemistry profile
- Urinalysis
- ACR assessment on Day 180
- Assessment of SOC biopsies on Day 180
- Patient survival assessment on day 180
- Graft survival assessment on day 180
- Donor Specific Antibody (DSA) assessment at Day 180

4.6.4 Observations And Measurements—see Appendix A.

4.6.4.1 Physical Examination

A complete physical examination will include; the examination of the following body systems: general appearance, skin, HEENT (head, ears, eyes, nose, throat), cardiovascular, pulmonary, abdomen, neurological, lymph nodes, spine and extremities (skeletal). Patient visits may occur as video visits with the MD as per standard of care procedures.

4.6.4.2 Vital Signs

Vital signs; including blood pressure, heart and respiratory rate will be measured using clinically acceptable methods and devices at each clinic visit. Height will be measured at the screening visit only.

4.6.4.3 Serum Creatinine

Serum creatinine levels will be measured per institutional SOC.

4.6.4.4 Calculated GFR

Estimated GFR will be calculated using the MDRD formula.

4.6.4.5 Urine Output

Urine output will be collected and recorded for the first 0-7 days post-transplant, until patient discharge.

4.6.4.6 PT, PTT and INR Tests

PT, PTT and INR tests will be performed per institutional SOC.

4.6.4.7 Hematology and Chemistry Profile

Hematology and Chemistry profile performed per institutional SOC

4.6.4.8 ECG Testing

An ECG will be performed per institutional SOC.

4.6.4.9 ACR Assessment

An acute rejection assessment will be recorded on patients who were diagnosed with an ACR grade ≥ Grade 2 per the Banff grading system and received anti-rejection therapy.

4.6.4.10 Rate and Duration of Dialysis

Duration of dialysis will be measured by the number of sessions of dialysis treatment needed in the first 30 days post transplant. As for rate of dialysis, one dialysis session will represent the need for dialysis treatment.

4.7 Data Quality

Monitoring and auditing procedures defined/agreed by the sponsor will be followed, in order to comply with Good Clinical Practice (GCP) guidelines. Our center will be monitored at quarterly to ensure compliance with the study protocol, GCP and legal aspects. This will include on-site checking of the case report forms (CRF) for completeness and clarity, cross checking with source documents, and clarification of administrative matters.

4.8 Documentation

Entries made in the CRF must be either verifiable against source documents, or have been directly entered into the CRF, in which case the entry in the CRF will be considered as the source data. The source data parameter to be verified and the identification of the source document must be documented. The study file and all source data should be retained until notification given by the sponsor for destruction.

5 Ethical And Legal Aspects

5.1 Ethics Committee (EC) Or Institutional Review Board (IRB)

Documented approval from appropriate IRBs will be obtained prior to study start, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IRB approval must be obtained and retained in site files. IRB must supply to the sponsor, upon request, a list of the IRB Committee members involved in the vote and a statement to confirm that the IRB Committee is organized and operates according to GCP and applicable laws and regulations.

5.2 Ethical Conduct Of The Study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by *GCP Guidelines* and under the guiding principals detailed in the 1989 version of the *Declaration of Helsinki*. The study will also be carried out in keeping with applicable local law(s) and regulation(s). This may include an inspection by the sponsor representatives and/or Regulatory Authority representatives at any time. The investigator agrees to the inspection of study-related records by the Regulatory Authority/sponsor representatives, and must allow direct access to source documents to the Regulatory Authority/sponsor representatives.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator may implement a deviation form, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IRB/Sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IRB/Sponsor. Any deviations from the protocol must be fully explained and documented by the investigator.

5.3 Regulatory Authority Approvals/Authorizations

Regulatory Authority approvals/authorizations/ notifications, where required, must be in place and fully documented prior to study start.

5.4 Subject Information And Consent

The Informed Consent Form (ICF) will be provided. Prior to the beginning of the study, the investigator must have the IRB written approval/favorable opinion of the written Informed Consent Form and any other written information to be provided to subjects. The written approval of the IRB together with the approved subject information/ICF must be filed in the study files.

Written informed consent must be obtained before any study specific procedure takes place. Participation in the study and date of informed consent given by the subject should be documented appropriately in the subject’s files.

Discussion of the study with the patient will occur in person or via phone. While patients may be approached soon after their visit and/or admission begins, they can take time to consider and discuss participation with others before deciding. All questions will be answered by an investigator prior to signing the consent form. In rush/emergency transplant cases, the study will not be offered. If the patient wishes to enroll in the study, consenting will occur in person with a paper ICF or via phone conversation using DocuSign. The process followed will be fully documented with a consent progress note.

5.5 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number and subject initials will be recorded in the case report form, and if the subject name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The subjects will be informed in writing that representatives of the sponsor, EC/IRB, or Regulatory Authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects' records to be identified.

6 Statistical Methods And Determination Of Sample Size

6.1 Statistical And Analytical Plans

6.2 Determination of Sample Size

Since this pilot study will be looking at feasibility and safety of a novel method of administration of C1INH, sample size determination was not performed.

7 Adverse Events (AEs)

7.1 Adverse Event (AE) Monitoring

7.2 Adverse Event (AE) Definitions

7.2.1 Adverse Events (AEs)

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered with a pharmaceutical product. The AE does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the medicinal product.

Adverse events associated with the use of a drug in humans, whether or not considered drug related, include the following:

- An AE occurring in the course of the use of a drug product in professional practice,
- An AE occurring from an overdose whether accidental or intentional,
- An AE occurring from drug abuse,
- An AE occurring from drug withdrawal.

- An AE where there is a reasonable possibility that the event occurred purely as a result of the subjects participation in the study (e.g. adverse event or serious adverse event due to discontinuation of anti-hypertensive drugs during wash-out phase) must also be reported as an adverse event even if it is not related to the investigational product.

The clinical manifestation of any failure of expected pharmacological action is not recorded as an AE if it is already reflected as a data point captured in the CRF. If, however, the event fulfills any of the criteria for a "serious" AE (SAE), it must be recorded and reported as such.

7.2.2 Serious Adverse Event (SAE)

An SAE is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability or incapacity
- is a congenital anomaly or birth defect
- is an important medical event

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.

Hospitalization: Any AE leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following exceptions are met:

- The admission is pre-planned (i.e., elective or scheduled surgery arranged prior to the start of the study)

OR

- The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care)

However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability: a substantial disruption of a person's ability to conduct normal life's functions.

Important medical event: Any adverse event may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events refer to the "*WHO Adverse Reaction Terminology – Critical Terms List*". These terms either refer to or might be indicative of a serious disease state.

Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

SAE medwatch reports **WILL NOT** be filled out for any prolonged hospital admissions or readmissions that are related to expected complications of the patients' primary disease (ESRD). For example, prolonged admissions for dialysis or readmission for fluid overload as a consequence of ESRD since this this is an expected complication of the patients' disease state and not related to study drug. These events will be adjudicated by the PI. Otherwise, all SAEs medwatch reports will be submitted to the IRB, and FDA.

7.2.3 Unexpected Adverse Event (AE)

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current Investigator Brochure (or Package Insert for marketed products). Also, reports which add significant information on specificity or severity of a known, already documented adverse event constitute unexpected AEs. For example, an event more specific or more severe than described in the Investigator Brochure would be considered "unexpected". Specific examples would be; (a) acute renal failure as a labeled adverse event with a subsequent new report of interstitial nephritis and (b) hepatitis with a first report of fulminant hepatitis.

7.2.4 Relationship Of Adverse Event To Investigational Product

The assessment of the relationship of an AE to the administration of study drug is a clinical decision based on all available information at the time of the completion of the case report form.

An assessment of 'No' would include:

1. The existence of a clear alternative explanation, e.g., mechanical bleeding at surgical site; or

2. Non-plausibility, e.g., the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of 'Yes' indicates that there is a reasonable suspicion that the adverse event is associated with the use of the investigational drug.

Factors to be considered in assessing the relationship of the adverse event to study drug include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event
- Recovery on discontinuation (de-challenge), recurrence on reintroduction (re-challenge): Subject's response after drug discontinuation (de-challenge) or subject's response after drug re-introduction (re-challenge) should be considered in the view of the usual clinical course of the event in question

- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question
- The pharmacology and pharmacokinetics of the test drug: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the test drug(s), coupled with the individual subject's pharmacodynamics should be considered.

7.2.5 Severity Of The Adverse Event (AE)

The following classification should be used:

The severity of AEs should be graded as follows:

- Mild – usually transient in nature and generally not interfering with normal activities
- Moderate – sufficiently discomforting to interfere with normal activities
- Severe – prevents normal activities.

7.2.6 Adverse Event (AE) Documentation

All AEs occurring after the subject has signed the informed consent must be fully recorded in the subject's case record form.

Documentation must be supported by an entry in the subject's file. A laboratory test abnormality considered clinically relevant, e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, or judged relevant by the investigator, should be reported as an AE. Each event should be described in detail along with start and stop dates, severity, relationship to investigational product, action taken and outcome.

7.3 Reporting of Serious Adverse Events (SAEs) or Pregnancy

Serious adverse events (SAEs), including laboratory test abnormalities fulfilling the definition of serious, after signing the informed consent and during follow-up period must immediately (within 24 hours of the investigator's awareness) be reported to the person detailed in the study file. A *Serious Adverse Event Form* must also be completed within 24 hours of the investigator awareness and forwarded to the designated person as detailed in the study file. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated person.

When required, and according to local law and regulations, SAEs must be reported to the IRB and Regulatory Authorities.

All AEs, SAEs, and SUSARs believed or possibly attributable to the investigational product must be reported to the IRB and FDA in accordance

with the signed Pharmacovigilance Agreement, which will also be included in the study file and regulatory binder.

Pregnancy occurring during a clinical investigation, although not considered an SAE, must be reported to the IRB within the same timelines as an SAE on a *Pregnancy Monitoring Form*. The outcome of a pregnancy should be followed up carefully and any abnormal outcome of the mother or the child should be reported. This also applies to pregnancies following the administration of the investigational product to the father prior to sexual intercourse.

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9 Appendices

Appendix A

Study visit	Screening [a]	Transplant Day 0 (C1INH vs Placebo)[a]	Day 1 ±6 hrs	Day 3±6 hrs	Day 7 -2 days/+6 hrs[1]	Day 30 ±7 days	Day 90 ± 30 days	Day 180 ± 30 days
Informed Consent	X							
Inclusion/exclusion criteria	X							
Randomization		X						
Medical History	X	X	X	X	X	X	X	X
Complete Physical Exam	X	X	X	X	X	X	X	X
Vital signs/weight	X	X	X	X	X	X	X	X
12-lead ECG[2]		X						
Chest X-ray[2]		X						
Safety laboratory tests (CBC, BMP)	X	X	X	X	X	X[3]	X[3]	X[3]
Record PT, PTT, INR	X[2]	X						
Review Historical Serologies for HIV, HBV, HCV, CMV EBV[2]	X							
Record Pregnancy test (for WOCP)[3]	X							
Record UA, Urine Output Measurement[b]		X	X	X	X	X	X	X
Estimated GFR (MDRD equation)			X	X	X	X	X	X
Campath/Thymoglobulin		X						
Review Pneumococcal Vaccination	X							
Berinert® vs Placebo Infusion		X						
Heparin in Normal Saline		X						
Lab: cytokines[4]			X					
Urinary IL18[4,b]			X					
Dialysis Assessment		X	X	X	x	X	X	X
Concomitant medications	X	X	X		X	X	X	X
Adverse Event Monitoring		X	X	X	X	X	X	X
Acute Rejection Assessment								X
Donor specific antibody[3]								X
Assess SOC biopsy		X						X

1 Day 7 assessment performed until the patient is discharged. 2. If a recent test is not on file, this will be collected via SOC 3. Within 30 days prior 4. May be collected on any two days from day 1 to 7; if testing is available a. If screening and transplant day 0 occur on the same day, duplicate study items will be omitted b. collected in those producing urine

Appendix B

Novation®

Human C1 Esterase Inhibitor

(Berinert®—CSL Behring)

December 2009

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Article

Three-Year Outcomes of a Randomized, Double-Blind, Placebo-Controlled Study Assessing Safety and Efficacy of C1 Esterase Inhibitor for Prevention of Delayed Graft Function in Deceased Donor Kidney Transplant Recipients

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Abstract

Background and objectives Delayed graft function is related to ischemia-reperfusion injury and may be complement dependent. We previously reported from a randomized, placebo-controlled trial that treatment with C1 esterase inhibitor was associated with a shorter duration of delayed graft function and higher eGFR at 1 year. Here, we report longer-term outcomes from this trial.

Design, setting, participants, & measurements This is a *post hoc* analysis of a phase 1/2, randomized, controlled trial enrolling 70 recipients of deceased donor kidney transplants at risk for delayed graft function (NCT02134314). Subjects were randomized to receive C1 esterase inhibitor 50 U/kg (n=35) or placebo (n=35) intraoperatively and at 24 hours. The cumulative incidence functions method was used to compare graft failure and death over 3.5 years. eGFR slopes were compared using a linear mixed effects model.

Results Three deaths occurred among C1 esterase inhibitor–treated patients compared with none receiving placebo. Seven graft failures developed in the placebo group compared with one among C1 esterase inhibitor–treated recipients; the cumulative incidence of graft failure was lower over 3.5 years among C1 esterase inhibitor–treated recipients compared with placebo (P=0.03). Although no difference in eGFR slopes was observed between groups (P for group-time interaction =0.12), eGFR declined in placebo-treated recipients (−4 ml/min per 1.73 m² per year; 95% confidence interval, −8 to −0.1) but was stable in C1 esterase inhibitor–treated patients (eGFR slope: 0.5 ml/min per 1.73 m² per year; 95% confidence interval, −4 to 5). At 3.5 years, eGFR was 56 ml/min per 1.73 m² (95% confidence interval, 42 to 70) in the C1 esterase inhibitor group versus 35 ml/min per 1.73 m² (95% confidence interval, 21 to 48) in the placebo group, with an estimated mean eGFR difference of 21 ml/min per 1.73 m² (95% confidence interval, 2 to 41 ml/min per 1.73 m²).

Conclusions Treatment of patients at risk for ischemia-reperfusion injury and delayed graft function with C1 esterase inhibitor was associated with a lower incidence of graft failure.

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Introduction

Delayed graft function (DGF), defined as the need for dialysis in the first week after kidney transplant, is estimated to occur in >20% of deceased donor kidney transplants (1). Its development is associated with an increased risk of rejection, poorer long-term kidney allograft function, and lower patient and graft survival (2,3). This association is modified by the severity of DGF as indicated by the duration of dialysis dependence after transplant, where longer periods of dialysis dependence are associated with progressively higher hazards of rejection and graft failure (4). Not surprisingly, kidneys at higher risk for DGF are more likely to be discarded in the United States, despite the well-documented shortage in donor organ supply (5,6).

The predominant mechanism of DGF is ischemia-reperfusion injury. This is marked by an alloantigen-independent inflammatory response characterized by an influx of proinflammatory cells early after ischemic injury (7). Additionally, the complement cascade can be activated in response to ischemia-induced membrane changes (8). Although the alternative pathway has historically been thought to play the major role in ischemia-reperfusion injury, evidence suggests that the classical and mannose binding lectin (MBL) pathways are also important (9,10). Damage-associated molecular patterns, polysaccharides, and intracellular antigens

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ORIGINAL ARTICLE

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A phase I/II, double-blind, placebo-controlled study assessing safety and efficacy of C1 esterase inhibitor for prevention of delayed graft function in deceased donor kidney transplant recipients

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Delayed graft function (DGF) is defined as need for dialysis early posttransplant. DGF is related to ischemia–reperfusion injury (IRI) that diminishes allograft function and may be complement dependent. Here, we investigate the ability of C1 esterase inhibitor (C1INH) to prevent IRI/DGF in kidney transplant recipients. Seventy patients receiving deceased donor kidney transplants at risk for DGF were randomized to receive C1INH 50 U/kg (#35) or placebo (#35) intraoperatively and at 24 hours. The primary end point was need for hemodialysis during the first week posttransplant. Assessments of glomerular filtration rate and dialysis dependence were accomplished. Complications and safety of therapy were recorded. Similar characteristics with no significant differences in cold-ischemia time or risk factors for DGF were seen. C1INH did not result in reduction of dialysis sessions at 1 week posttransplant, but significantly fewer dialysis sessions ($P = .0232$) were required 2 to 4 weeks posttransplant. Patients at highest risk for DGF (Kidney Donor Profile Index ≥85) benefited most from C1INH therapy. Significantly better renal function was seen at 1 year in C1INH patients ($P = .006$). No significant adverse events were noted with C1INH. Although the primary end point was not met, significant reductions in need for dialysis and improvements in long-term allograft function were seen with C1INH treatment.

KEYWORDS
clinical research/practice, delayed graft function (DGF), donors and donation: donation after circulatory death (DCD), donors and donation: extended criteria, glomerular filtration rate (GFR), ischemia reperfusion injury (IRI), kidney transplantation/nephrology, translational research/science

Abbreviations: AE, adverse event; C1INH, C1 esterase inhibitor; DAMP, damage-associated molecular pattern; DCD, donor after cardiac death; DGF, delayed graft function; ECD, extended-criteria deceased donor; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; FDA, US Food and Drug Administration; IRI, ischemia–reperfusion injury; KAS, kidney allocation system; KDPI, Kidney Donor Profile Index; MAC, membrane attack complex; RF, random forest; rhC1INH, recombinant human C1 esterase inhibitor; SAE, serious adverse event; SDC, supplementary digital content; SD, standard deviation; UNOS, United Network for Organ Sharing.

Stanley C. Jordan and Jua Choi contributed equally as first authors.

Appendix C


Berinert Thrombosis.pdf

Appendix D


ThromboticC1INHFDA.pdf


Berinert & Cinryze FOI Summary.pdf


Berinert Rat Study Report Part I of II.pd


Berinert Rat Study Report Part II of II.p


Transgenic mice.pdf

Appendix E


FDA Guidance for Clinical Trial Sponsors

9.1 Calculation of GFR from age, gender, race, urea, creatinine and albumin (MDRD equation) (Levey et al, 1999; Tattersall, 2003)

Albumin in g/dL, age in years. GFR in mL/min/1.73 m^2.

Multiply by 1.18 if patient is black. Multiply by 0.762 if patient is female.

SI units (Creatinine in µmol/L, Urea in mmol/L)

$$GFR = 170 \times (Creat \times 0.0113)^{-0.999} \times age^{-0.176} \times (Urea \times 2.8)^{-0.17} \times Alb^{0.318}$$

US units (Creatinine in mg/dL, BUN in mg/dL)

$$GFR = 170 \times Creat^{-0.999} \times age^{-0.176} \times BUN^{-0.17} \times Alb^{0.318}$$