CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase I/II, Double-Blind, Placebo-Controlled Study: Assessing Safety and Efficacy of Preoperative and Post-Transplant 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

Introduction

Over the past decade, improvements in immunosuppressive regimens, surgical techniques, and organ procurement have resulted in a significant increase in renal transplantation success (Oniscu et al, 2005). Currently, the worldwide rates for 1- and 5-year graft survival are 95% and 80%, respectively, with death with a functioning graft being the most common reason for renal graft loss after 1 year (Daly et al, 2005). Studies on renal transplantation outcomes have traditionally focused on patient and graft survival, with little to no consideration of graft function (Boom et al, 2000). Although graft loss is the worst type of graft dysfunction, grafts with an impaired function require the most intense follow-up, are economically most costly and require rigorous clinical management to preserve life-expectancy of the graft (Boom et al, 2000). For these reasons, parameters of graft function are being increasingly included as outcome measures in renal transplantation studies, including delayed graft function (DGF). Indeed, the new UNOS allocation policies (http://optn.transplant.hrsa.gov/policiesAndBylaws/policies.asp) scheduled for implementation in 2014 will tend to give higher risk kidneys to older diabetic recipients. This is likely to increase the risk significantly for DGF and poorer allograft function.

Despite a decline in the number of patients experiencing allograft rejection episodes over the past decade, the incidence of patients with DGF has remained steady and was reported in 2.6 percent of transplants from living donors, compared to 22, 28, and 41 percent of SCDs, ECDs, and donations after cardiac death patients respectively.

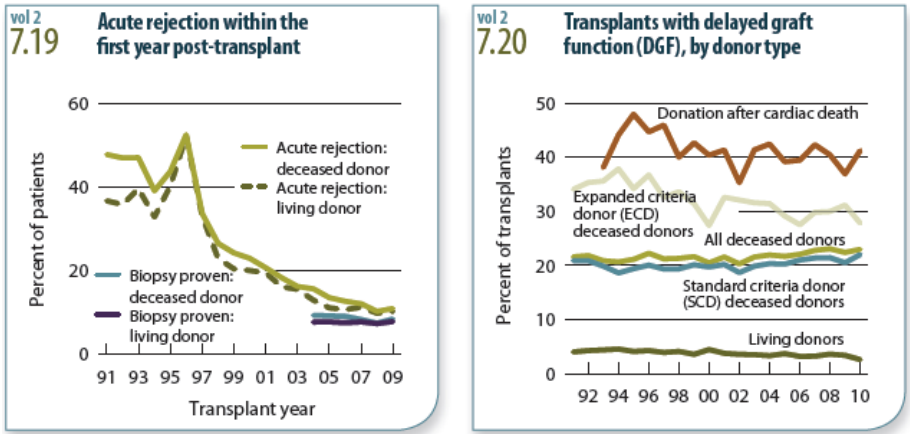

Figure 1: Data obtained from United States Renal Data Systems Report Transplantation 2012 Vol 2, pp 283-294.

Most deceased donor and some live donor organ transplants manifest a degree of early dysfunction (Halloran and Hunsicker, 2001). Delayed graft function (DGF) is a term used to describe the lack of acceptable function in a kidney after transplantation (Daly et al, 2005). DGF has been well described in association with an inferior functioning kidney at 1 and 2 years post-transplant (Halloran et al, 1988; Hariharan et al, 2003). Typical histological findings of DGF are dilatation of tubules, loss of proximal epithelial cell brush border, epithelial cell necrosis/apoptosis, and cellular casts (Smith et al, 2003). In the presence of DGF, kidneys are more likely to have adverse outcomes including decreased functional graft survival and 6-month patient survival, and increased acute rejection (Daly et al, 2005; Halloran and Hunsicker, 2000). It is interesting to note that analyses of the UNOS scientific renal transplant registry (United States) showed DGF was associated with increased probability of patient death in the first 6 months (Halloran and Hunsicker, 2000), whereas analyses in the Netherlands found DGF to be an independent risk factor for acute rejection and suboptimal renal function at 1 year, but not survival (Boom et al, 2000). The use of kidneys from extended criteria deceased donors (ECD) are also associated with higher rates of DGF and poorer long-term survival. These findings are especially important in view of recent publications which showed compromised outcomes in patients receiving kidneys from suboptimal donors. A recent analysis of outcomes from 9134 recipients of cardiac-death and brain-death donor kidneys, donor age ≥60 years was identified as a risk factor for graft failure and reduced long-term renal function. (Summers et al, 2010). These investigators found that graft survival and renal function decrease as the age of the donor increases, with recipients of these ECD kidneys having twice the risk of graft failure compared with recipients of younger donor kidneys. Another group performed a comprehensive systematic review of kidney transplants from ECDs and concluded that management protocols for this patient population need to be based on nephron-protecting strategies (Pascual et al, 2008). Thus strategies to reduce IRI and DGF are critical to increasing the number and long-term outcomes of marginal kidneys.

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 (Daly et al, 2005). More recently, efforts have been made to scientifically quantify DGF in a more stringent manner with various alternative definitions of DGF including; (1) the number of days to achieve a creatinine clearance of >10 mL/min, calculated by the Gault-Cockroft formula (Giral-Classe et al, 1998), (2) a serum creatinine level of >3 mg/dL on the fifth day post-transplant (Humar et al, 2000), (3) the need for dialysis within 72 hours after transplantation (Hetzel et al, 2002), (4) 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 (Boom et al, 2000), (5) 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 (Gonwa et al, 2002), (6) 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) (Halloran and Hunsicker, 2001), and (7) calculating the creatinine reduction ratio on day two following surgery (Salahudeen et al, 2004). 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.

The reported incidence of DGF varies widely depending on the source of the graft, with DGF estimated to occur in approximately 20-35% of all patients who receive a deceased donor graft (Koning et al, 1997; Halloran and Hunsicker, 2001), and rates varying up to 80% in association with extended criteria (ECD) donor grafts (SCJ personal data from CSMC). The risk factors for DGF are the same as those that influence graft survival and include donor tissue quality (age), brain death and other components of cadaver donation, preservation variables particularly cold ischemia time, immune variables, and recipient variables (Halloran and Hunsicker, 2001). The duration of cold ischemia time has been shown to have a direct effect on the presence of DGF and graft survival with durations longer than 28 hours associated with increased risk (Lechevallier et al, 1998; Jacobs et al, 1996; Peters et al, 1995; Kahan et al, 1987), and a 23% increase for every 6 hours of cold ischemia time (Ojo et al, 1997). Additionally, DGF is significantly associated with the use of kidneys from older donors, particularly donors of more than 50 years of age (Boom et al, 2000). In the United States, in the last decade, the proportion of deceased donors

older than 50 years of age has increased from 21% to 30% (Nathan et al, 2003; Ojo et al, 2001), however the kidney waiting list has increased by 260% and the number of deceased donor kidney transplants has increased by only 16% (Metzger et al, 2003; Port, 2001; Nathan et al, 2003). Due to the increasing disparity between organ supply and demand, the use of kidneys from "older" expanded criteria donors (ECDs) has become generally accepted and increasingly common (Metzger et al, 2003).

In the United States, the United Network for Organ Sharing (UNOS) (www.unos.org) which administers the national Organ Procurement and Transplantation Network (OPTN) (www.optn.org) defines two types of deceased donor kidneys, namely "standard criteria donors" (SCD) and "expanded criteria donors" (ECD). Using pre-transplant variables to identify increased risk of graft loss, an ECD donor kidney is defined as a kidney donated for transplantation from (1) a brain-dead donor over the age of 60 years, or (2) from a donor between the ages of 50-59 with at least two of the following: a history of hypertension, a terminal serum creatinine greater than or equal to 1.5 mg/dl (normal range 0.8-1.4 mg/dl), or death from a cerebral vascular accident (CVA) (stroke or aneurysm). In comparison, an SCD donor kidney is defined as a kidney donated for transplantation by a donor who has suffered brain death and does not fit the criteria for ECD. With the growing demand for first-time and repeat deceased donor renal transplants, ECD donor kidneys are being increasingly considered by transplant programs. As a consequence of the utilization of marginal kidneys, DGF is a major complication following transplantation with ECD donor kidneys.

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 1). 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_20 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 (Sacks et Zhou 2012. 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 (Sacks et Zhou 2012). 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 (Sacks et Zhou 2012) 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 (Naesens et al 2009). 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.

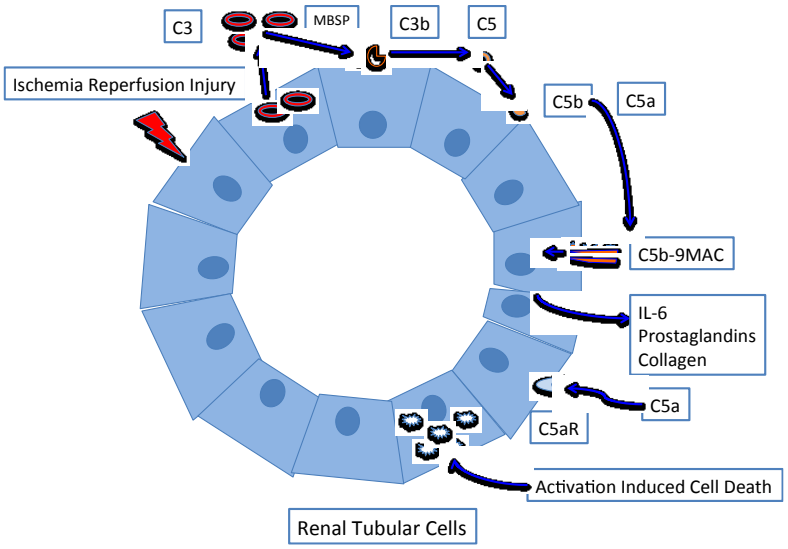

Figure 2 shows complement activation by I/R injury (from Sachs & Zhou 2012).

Evidence for Use of C1INH to Prevent IRI and DGF

Although limited, there are recent investigations which show dramatic results in prevention of IRI after C1INH treatment. (Dalle Lucca et al 2012) 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 (Castellano et al, 2010). 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.

2.0 Hypothesis

Since complement activation is detectable in animal models of IRI and in human kidneys after IRI and since 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, we hypothesize that the use of C1INH in patients receiving deceased donor (DD) kidney transplants with high risk for DGF will show significant reductions in DGF and improved outcomes post-transplant compared

with patients receiving DD transplants who do not receive C1INH treatment.

2.1 Study Objectives

In this study, we propose to investigate the application of pre-operative and post-transplant doses of C1INH (Berinert®)vs. placebo in adult subjects receiving a deceased donor renal allograft considered at high-risk for IRI and DGF. We hypothesize that C1INH treated patients will demonstrate improved function of the kidney allograft compared to placebo, with equivalence in safety. We will also evaluate biopsies at transplant in all entered patients.

The primary objectives of this study are: Using a double blinded, placebo controlled format, we will:

1. Evaluate and compare the safety of C1INH (50 U/kg, round to the nearest 500unit)administered pre-transplant and 24 hrs post-transplant in recipients of kidney allografts from high risk deceased donors. The secondary objectives are to:

1. On the basis of safety and efficacy, determine appropriate Berinert® study dose for Phase III investigation, and

2. Determine appropriate endpoint choice for Phase III investigation.

2.2 Study Synopsis

TITLE	A Phase I/II, Double-Blind, Placebo-Controlled Study: Assessing Safety and Efficacy of Intraoperative and Post-Transplant C1 Inhibitor(Human) (C1INH)vs. Placebo in Recipients of a Kidney Allograft from Deceased High Risk Donor and its impact on Risk for Delayed Graft Function (DGF)
INVESTIGATIONAL AGENT	C1INH (Berinert® [human][C1INH])
HYPOTHESIS	Pre-operative, infusion of C1INH before allograft reperfusion and 24 hour post-transplant will improve early graft function and reduce the rate of DGF 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 96,680 people are currently waiting for a kidney transplant in the United States (UNOS.org 3/22/13). Of the 15,092 kidney transplants performed in the US in 2011, ~11,000 (62%) were from deceased donors. Of these, approximately 17% were from expanded-criteria donors. The USRDS reports that more than 50% of patients on the waiting list are willing to accept a kidney from an expanded-criteria donor (ECD) or DCD donor.
NUMBER OF PATIENTS AND CENTERS	70 patients will be enrolled into the study (35 C1INH and 35 Placebo). The study will be initiated at Cedars-Sinai Medical Center and extended to collaborators with completion of contractual agreements.
INVESTIGATOR / CLINICAL TRIAL LOCATION	Stanley C. Jordan, M.D. Cedars-Sinai Medical Center

STUDY OBJECTIVES	• To evaluate and compare the safety of Berinert® 50U/kg in recipients of a kidney allograft from a high risk deceased donors receiving one IV dose of Berinert® 50U/kg (round to the nearest 500unit) or placebo pre-operatively and a repeat dose (Berinert® 50U/kg v. Placebo) 24 hrs. post-transplant. • To evaluate early kidney function in recipients of a kidney allograft from a high risk deceased donors following the administration of two IV doses of Berinert® pre-operatively and 24 hrs later as compared to placebo.
STUDY DESIGN	Patients who fulfill all I/E criteria will be enrolled into Study **I Study Group (70 patients):** *Treatment Arm* I - Patients will be administered one IV dose of 50U/kg of Berinert® (round to the nearest 500unit)on-call to OR for kidney transplant. *Control Arm* – Patients will be administered one IV dose of normal saline (NS) approximately on-call to the OR for kidney transplant in a volume identical to the volume of the IV dose of Berinert®. Berinert® (50U/kg) round to the nearest 500unit)or placebo will be administered to study subjects again at 24 hrs post-transplant.
STUDY POPULATION	**Inclusion Criteria:** • Adult men or women (18-70 years of age) who are on chronic dialysis therapy and acceptable candidates for receipt of a kidney transplant. • Recipients of kidney allograft from ECD donors • Recipients of kidney allograft from DCD donors

- Recipients of kidney allograft other than ECD and DCD who have risk index of 3-8 (minimum 3 and maximum 8) for DGF, based on the criteria in the risk index detailed in the table below
- Recipients who are ABO compatible with donor allograft
- Pre-transplant vaccination with Menactra® meningococcal vaccine
- Understand and sign a written inform consent prior to any study specific procedure

Women of childbearing potential must have a negative pregnancy test prior to randomization, and must be on an acceptable form of birth control.

Characteristic	**Risk Index**
Donor Age (years)	
<40	0
41-49	1
50-54	2
55-59	3
>60	6
Cold Ischemia time	
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
No diabetes	0
Donor Death due to CVA	
Donor age < 50 years	0
Donor age >50 years	3

Exclusion Criteria:

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

	• Patients with a history of thrombosis or hypercoagulable state, excluding access clotting. • Patients with a history of administration of C1INH containing products or recombinant C1INH within 15 days prior to study entry. • Patients with a known hypersensitivity to treatment with C1INH. • Patients with an abnormal coagulation function. (INR ≥2, PTT> 50, PLT<80,000) who are not on anti-coagulation. • Patients with known active presence of malignancies. • Patients who are PCR positive for Hep B, Hep C, or HIV. • Recipients of pre-emptive kidney transplantation. • Recipients of multi-organ transplants. (kidney and any other organ) • Recipients of kidney allograft from DD who: CIT < 18 hours, terminal serum creatinine ≤ 1mg/dl. • Recipients of kidney allograft that was on pump preservation for any period prior to transplantation. • Recipients of kidney allograft from a living donor. • 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 • Evaluation of blood chemistry, hematology, and coagulation parameters

	• Patient and graft survival at Day 90 • Rate of acute cellular rejection (ACR) and antibody mediated rejection at Day 90 **EFFICACY ASSESSMENTS:** **Primary Endpoints** ***For patients who do not require dialysis in the first 7 days:*** • Proportion of patients enrolled with serum creatinine >3mg/dL on postoperative day 5. • Proportion of patients with serum creatinine reduction ratio of < 30% from 24 to 48 hours post-transplant. ***For patients who require dialysis in the first 7 days:*** *(Excluding patients who get dialysis for hyperkalemia)* • The proportion of patients enrolled who require at least one session of dialysis in the first 7 days post transplant. • Number of dialysis sessions per patient in the first 7 days post transplant. **Secondary Endpoints** • Daily serum creatinine for seven days post transplant or until discharge. • Daily Calculated Creatinine Clearance for seven days post transplant or until discharge. • Serum creatinine at 14, 28, 60, and 90 days post transplant. • Total 24 hr urine output days 1-7 post-transplant. • Rate of dialysis use at 14, 28, 60, and 90 days post transplant.

	• Dialysis duration at 14, 28, 60, and 90 days post transplant. • Rate of acute cellular and antibody mediated rejection episodes by day 90. • Patient and graft survival by day 90. • Calculated creatinine clearance at 14, 28, 60, and 90 days post transplant. • Incidence of DGF as categorized by a DGF scale of increasing severity as follows: Grade 1 - immediate urine production and no need for dialysis with creatinine reduction ratio (CRR) between time 0 of transplantation and day 7 post-transplantation >70% Grade 2 - creatinine reduction ratio (CRR) between time 0 of transplantation and day 7 post-transplantation of >70% with need for dialysis Grade 3 - creatinine reduction ratio (CRR) between time 0 of transplantation and day 7 post-transplantation <70% with no need for dialysis Grade 4 - creatinine reduction ratio (CRR) between time 0 of transplantation and day 7 post-transplantation of <70% with need for dialysis. • Protocol biopsies will be performed at the time of implantation. Pathological analysis will be done to determine if there is an increase in interstitial

	fibrosis/tubular atrophy (IFTA), glomerulosclerosis, transplant glomerulopathy, and other markers of ischemic injury.
IMUNOSUPPRESSION REGIMEN	• Induction therapy using Thymoglobulin in divided doses for a total of 6mg/kg or Campath 1H 30mg SQ x 1. • Calcineurin inhibition (Tacrolimus or Cyclosporine) will be delayed for minimum 24 hours post transplant. • MMF will be started and used 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
DURATION OF STUDY	90 days

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 and/or institutions, 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 CSL Behring, 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 for DSMB charter and FDA Guidance for Clinical Trial Sponsors.

4. Investigational PlanStudy Design And Plan

This is a Phase I/II double-blind, randomized, placebo-controlled study assessing safety and limited efficacy of intraoperative C1INH (50U/kg) vs. Placebo administered prior to graft reperfusion in adult subjects receiving a deceased donor kidney allograft considered high-risk for development of DGF. Patients will also receive an additional dose 24 hrs. post-transplant (C1INH (50U/kg vs. placebo). 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.

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 at any one point in time, from time of admission up to the beginning of renal vein anastomosis **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. In addition, the patients will receive study treatments at 24 hrs. post-transplant. This will constitute the entirety of C1INH vs. placebo administration. The study format is shown below in figure 3.

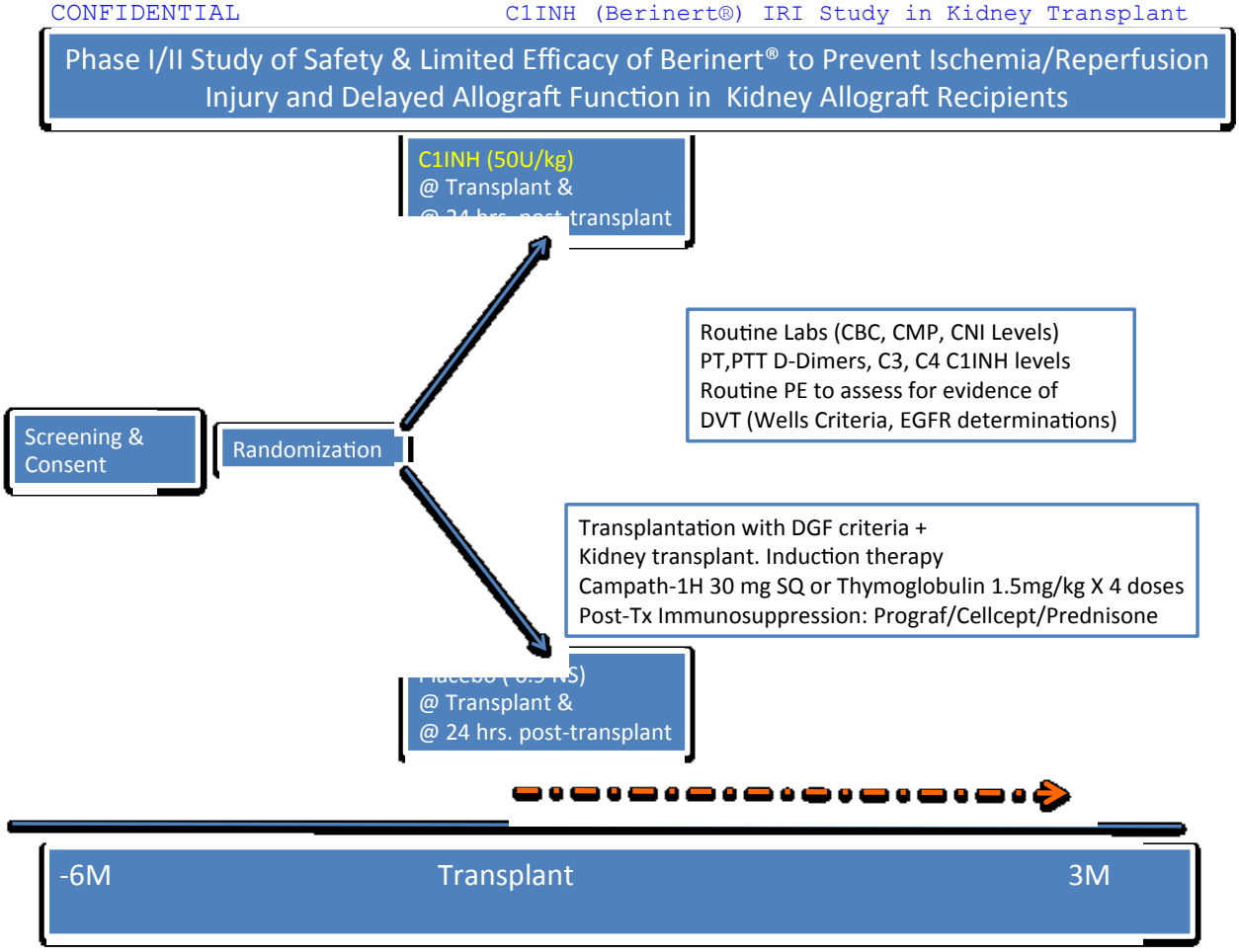

Figure 3: Study format to evaluate C1INH in DGF.

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 70 adult men and women (18-70 years of age) who are recipients of a kidney transplant and recipients of only a kidney allograft from a deceased donor who is high risk for DGF will be enrolled in the study.

4.2.1 Inclusion Criteria

Recipient Inclusion Criteria

1). Adult men or women (18-70 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.
4). Recipients of kidney allograft from ECD* donors.
5). Recipients of kidney allograft from DCD** donors.
6). Recipients of kidney allograft other than ECD and DCD who have risk index of 3-8 (minimum 3 and maximum 8) for DGF, based on the criteria in the risk index detailed in Table 1.
7). Women of childbearing potential must have a negative pregnancy test prior to randomization, and must be on an acceptable form of birth control.

Table 1: Risk factors for Delayed Graft Function

Characteristic	Risk Index
Donor Age (years)	
<40	0
41-49	1
50-54	2
55-59	3
>60	6
Cold Ischemia time	
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
No Diabetes	0
Donor cause of death due to CVA	
Donor age < 50 years	0
Donor age >50 years	3

*ECD Kidney: An ECD allograft is defined as a renal allograft donated for transplantation from a brain-dead donor over the age of 60 years or from a donor aged 50 to 60 years with two of the following: a history of hypertension, a pre-retrieval terminal serum creatinine greater than or equal to 1.5 mg/dl, or death from a cerebral vascular accident (stroke or aneurysm) (Cecka, 2004).

**DCD Kidney: Recovery of organs and or tissues from a donor whose heart has irreversibly stopped beating, previously referred to as non-heart-beating or asystolic donation (UNOS).

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 known hypersensitivity to treatment with C1INH or blood products.
4) Patients with an abnormal coagulation function. (INR $\geq$2, PTT> 50, PLT<80,000) who are not on anti-coagulation.
5) Patients with known active presence of malignancies.
6) Patients who are positive for Hep B, Hep C, or HIV PCR test.
7) All zero mismatch kidneys.
8) Recipients of multi-organ transplants. (kidney and any other organ)Recipients of kidney allograft from donors who: < 40 years of age, CIT < 18 hours, serum creatinine $\leq$ 1mg/dl.
9) Recipients of kidney allograft that was on pump preservation for any period prior to transplantation.
11) Recipients of kidney allograft from a living donor.
12) 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 patients 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, and the investigator/sponsor has the right to close a center, 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) must be returned to the sponsor. The investigator will retain all other documents until notification given by the sponsor for destruction.

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 35 patients in a treatment arm and 35 patients in a placebo arm.

This design is statistically powered to show significant differences if there is a 30-50% reduction in the treatment group and may trend towards positive treatment effect since extensive DGF (40-50%)is expected in ECD and DCD recipients. The dose of C1INH chosen is (50U/kg)(round to the nearest 500unit) X2 (high-dose treatment) which should increase serum C1INH levels significantly above physiologic levels. 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.

Patients who fulfill all I/E criteria will 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 CSL-Behring procedures, and a copy of the labels will be made available to the study site upon request.

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 at 50 units per kg body weight (round to the nearest 500units) and is administered by slow IV injection at a rate of approximately 4 mL per minute. Participation patients will receive 50U/kg C1 INH vs placebo (0.9% NS) on days 0 and day 1 post-transplant, (see Appendix A).

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 50U/kg (round to the nearest 500units) (maximum dose: 4000U) pre-operatively over a period of 10-20 minutes at any one point in time, from time of induction of anesthesia up to the beginning of renal vein anastomosis before graft reperfusion. For all dose reconstitution, 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. An additional dose of Berinert® (50U/kg,actual body weight, maximum dose 4000U) vs. placebo will be administered at 24 hours post-surgery.

4.5.4.2 Placebo Dosing

The placebo used in this study will be 0.9% normal saline administered as a single intravenous infusion intra-operatively over a period of 10-20 minutes pre-operatively at any one point in time, from time of induction of anesthesia up to the beginning of renal vein anastomosis before graft reperfusion. The total volume will be identical to that calculated for Berinert® infusions.

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.

4.5.3.1 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 held in this study for a minimum of 24 hours post transplant and will be initiated and monitored with trough levels using standard institutional treatment guidelines for use of these agents in this patient population.

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 use for a minimum of 6 months.

Ciprofloxacin will be administered at 250mg/daily X30 days for meningococcal prophylaxis.

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® 50U/kg, maximum dose 4000U) will be compared to a placebo control treatment arm, with a total of 35 adult subjects in each study group. A total of 70 adult subjects will be enrolled in the study and additional subjects will not be enrolled to replace dropouts. This design is statistically powered to show differences in DGF with a 30-50% reduction in DGF predicted for the Berinert® study group. Treatment effect will be investigated following intravenous treatment with two doses of Berinert® or an equivalent volume of placebo (0.9% normal saline) pre-operatively prior to graft reperfusion and repeated 24 hours post-transplantation.

4.5.8 Blinding

The 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 an IV syringe (total volume up to 70 ml Berinert® {4000U} for 80kg individual) and labeled with:

- Protocol Number
- Screening number
- Randomization number.

The blinded intravenous syringe of study treatment labeled as stated above will be transported to the surgical suite and matched with the matching patient chart.

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 Sponsor's Medical Monitor, 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 Sponsor 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 are only two application of the drug, which takes place approximately 60-120 minutes prior to graft reperfusion administered pre-operatively and 24 hours post-transplant.

4.6 Study Variables

4.6.1 Efficacy Variables

4.6.1.1 Primary Efficacy Endpoints

For patients who do not require dialysis in the first 7 days:

- Proportion of patients enrolled with serum creatinine >3mg/dL on postoperative day 5.
- Proportion of patients with serum creatinine reduction ratio of < 30% from 24 to 48 hours post-transplant.

For patients who require dialysis in the first 7 days:
(Excluding patients who get dialysis for hyperkalemia)

- The proportion of patients enrolled who require at least one session of dialysis in the first 7 days post transplant.
- Number of dialysis sessions per patient in the first 7 days post transplant.

4.6.1.2 Secondary Efficacy Endpoints

- Daily serum creatinine for seven days post transplant or until discharge.
- Daily Calculated Creatinine Clearance for seven days post transplant or until discharge.
- Serum creatinine at 14, 28, 60, and 90 days post transplant.
- Total urine output in hours 16-24, 40-48 post transplant.
- Rate of dialysis use at 14, 28, 60, and 90 days post transplant.
- Dialysis duration at 14, 28, 60, and 90 days post transplant.
- Calculated creatinine clearance at 14, 28, 60, and 90 days post transplant.

- Rate of acute cellular and antibody mediated rejection episodes by day 90.
- Patient and graft survival by day 90.

  - Protocol renal transplant biopsy at time of implantation.
  - Incidence of DGF as categorized by a DGF scale of increasing severity as follows:

  Grade 1 - immediate urine production and no need for dialysis with creatinine reduction ratio (CRR) between time 0 of transplantation and day 7 post-transplantation >70%

  Grade 2 - creatinine reduction ratio (CRR) between time 0 of transplantation and day 7 post-transplantation of >70% with need for dialysis

  Grade 3 - creatinine reduction ratio (CRR) between time 0 of transplantation and day 7 post-transplantation <70% with no need for dialysis

  Grade 4 - creatinine reduction ratio (CRR) between time 0 of transplantation and day 7 post-transplantation of <70% with need for dialysis

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® (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. To address the increased risk of TE, we will apply the Well's criteria for diagnosis of DVT (http://www.mdcalc.com/wells-criteria-for-dvt)(Wells, 2003,2006,2006). Patients will be assessed with each infusion for evidence of DVT or other TEs. Those receiving a high-risk score will have lower-extremity Doppler venous ultrasounds to rule-out the presence of DVTs. In addition, routine measurements of coagulation factors to evaluate DIC (D-Dimers, fibrinogen, PT, PTT) will be performed (See Appendix A).

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 Arzteblatt, 2000). 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 (50U/kg twice, Days 0 & 1), 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 (Cicardi 2010, 2010 and Zuraw 2010) 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. For that reason, the study will be randomized and patients will be monitored for DVT using the Wells Criteria. In addition, C1INH levels will be obtained at every visit and D-Dimers as well as PT/PTT will be monitored. 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 2012) suggests that thrombotic events do occur with C1INH therapy, but most cases are associated with the product (Cinryze®). Thus, continued surveillance will be part of this study.*

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 □g/ml) are produced without reported effects (Vinci,2002)(Appendix D). Other investigators have shown that ischemia-reperfusion injury is reduced in animals transgenic for C1INH expression (Vinci, 2002) (Appendix D). Data provided by CSL Berhing (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 CSL Behring, the DSMB and FDA prior to proceeding.

1.1.1.6 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.

4.6.2.1 Secondary Safety Endpoints

- Chemistry and coagulation parameters
- Patient survival at day 90.
- Graft survival at day 90.
- Rate of acute cellular and antibody mediated rejection episodes at day 90.

4.6.3 Assessment Periods

4.6.3.1 Screening Procedure – Day -30 to 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 (including DVT exam)
- 12-lead ECG (w/in 6 months)
- Chest X-ray (w/in 6 months)
- Hematology & chemistry profile
- PT, PTT, D-Dimer, Fibrinogen
- Review historical serologies for HIV, HBV, HCV, CMV and EBV
- Pregnancy test (for WOCP)
- Urine output measurement
- Urinalysis
- Concomitant medications
- Pneumococcal vaccine & Neisseria menigitides

4.6.3.2 Day 0 – Day of Transplantation

- Inclusion/Exclusion criteria (pre-transplant)
- Vital signs (pre- and post-transplant)
- Physical examination (pre- and post-transplant)
- Randomization (pre-transplant)
- Hematology & chemistry profile (pre- and post-transplant)
- PT, PTT and INR (pre- and post-transplant)
- Concomitant medications (pre- and post-transplant)
- ECG (pre-transplant)
- Chest x-ray (pre-transplant)

- Serum Creatinine (pre-and post-transplant, within 4-hours of surgery)
- Clinical Assessment (post-transplant)
- Berinert vs. Placebo infusion (on call to OR)
- C1 inhibitor, C3, C4 levels (prior to dose #1 of C1INH or placebo)
- Campath 1H or Thymoglobulin administration
-

4.6.3.3 Day 1-7 Assessments measured daily through day 7 or until discharge

- Berinert vs. Placebo infusion (24hrs post-transplant)
- C1 inhibitor, C3, C4 levels (prior to second dose of C1INH or placebo)

- Urine output between hours of 16-24, 40-48 post transplant
- Concomitant medications
- Serum creatinine measurements daily through Day 7 or until discharge.
- Dialysis assessment
- Vital Signs
- Clinical Assessment
- Calculated Creatinine / Calculated GFR
- Urine output measurement
- Adverse event assessment
- Hematology & chemistry profile
- PT, PTT and INR (day 1 and day 7 only)
-

4.6.3.4 Days 14 ± 2 days & 28 ± 2 days

- Concomitant medications
- Serum creatinine measurement
- Vital Signs

- Dialysis assessment
- Adverse Event Assessment
- Clinical Assessment
- Calculated Creatinine / Calculated GFR
- Hematology & chemistry profile

4.6.3.5 Days 60 ± 5 days & 90 ± 5 days

- Concomitant medications
- Serum creatinine measurement
- Dialysis assessment
- Vital Signs
- ACR assessment on Day 90
- Adverse Event Assessment
- Clinical Assessment
- Calculated Creatinine / Calculated GFR
- Hematology & chemistry profile

4.6.4 Observations And Measurements—see Appendix A.

4.6.4.1 Physical Examination

A complete physical examination will include; body weight and 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). In addition, Wells Criteria Assessment will be done for presence of DVTs.

4.6.4.2 Clinical Assessment

A clinical assessment will be preformed and will include a limited physical examination, the evaluation of the patient for clinical signs of infection, possible rejection, adverse events, and change in renal function. Any abnormalities will be recorded on the CRF.

4.6.4.3 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.

4.6.4.4 Serum Creatinine

Serum creatinine levels will be measured per institutional SOC.

4.6.4.5 Calculated Creatinine Clearance / Calculated GFR

Calculated creatinine clearance and GFR will be calculated using the MDRD or Cockroft & Gault formula.

4.6.4.6 Serum Creatinine Reduction Ratio

Serum creatinine reduction ratio will be calculated at 48 hours post transplant, using the formula described by Govani et al (2002).

4.6.4.7 Urine Output

Urine output will be collected and recorded for the first 5-7 days post-transplant.

4.6.4.8 PT, PTT and INR Tests

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

4.6.4.9 Hematology and Chemistry Profile

Hematology and Chemistry profile performed per institutional SOC and will include measurements of WBC, RBC, platelets, electrolytes, BUN, glucose, T Bili, Alb, Alk Phos, AST, ALT, BUN and Albumin.

4.6.4.10 ECG Testing

An ECG will be performed per institutional SOC.

4.6.4.11 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.

4.6.4.12 Rate and Duration of Dialysis

Duration of dialysis will be measured by the number of sessions of dialysis treatment needed in the first 7 days post transplant. As for rate of dialysis, one dialysis session will represent the need for dialysis treatment.

4.6.5 Drug Concentration Measurements

Complement levels (C3, C4, C1INH-Function, and C1INH % activity) will be measured during the first week of the study period.

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 Ethics Committee(s)/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 Ethics Committee approval

must be obtained and also forwarded to the sponsor. The Ethics Committees must supply to the sponsor, upon request, a list of the Ethics Committee members involved in the vote and a statement to confirm that the Ethics 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 EC/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 EC/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

A core information and Informed Consent Form will be provided. Prior to the beginning of the study, the investigator must have the EC/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 EC/IRB

together with the approved subject information/Informed Consent Forms 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.

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

The sample size calculations were based on a conservative assessment aimed to show ~50% reduction in DGF rates with C1INH application. Data from the Cedars-Sinai Medical Center Renal Transplant Program for DGF rates are shown below:

	Transplants 7/1/2011 until 7/1/2013
	N=237
	DGF Rate
ECD	27/36 (75%)
DCD	9/13 (69%)
Final Cr >/=1.5	28/37 (76%)
Non-ECD/DCD/Cr<1.5	33/100 (33%)

Briefly, the DGF rates at our center for the proposed study groups are >70% compared to 33% for SCD donors. Thus, a conservative proposal is explored below. The sample size calculations showing 35 subjects per group would sufficiently power the study (80%) to show 50% reduction when an anticipated DGF rate of 50% for the study group is anticipated.

The "proportion" below is the proportion with DGF.
A 2-sided test (to be more conservative) was performed.
We assumed a 50% DGF rate in the Placebo group.
Treated group DGF rate vary: 20%, 25%, and 30%.
sample size per group for 80% and 90% power are shown.

Two group continuity corrected χ^2 test of equal proportions (odds ratio = 1) (equal n's)

	1	2	3	4	5	6
Test significance level,	0.050	0.050	0.050	0.050	0.050	0.050
1 or 2 sided test?	2	2	2	2	2	2
Treated Group proportion, π_1	0.200	0.250	0.300	0.200	0.250	0.300
Placebo Group proportion, π_2	0.500	0.500	0.500	0.500	0.500	0.500
Odds ratio, $\psi = \pi_2 (1 - \pi_1) / [\pi_1 (1 - \pi_2)]$	4.000	3.000	2.333	4.000	3.000	2.333
Power (%)	80	80	80	90	90	90
n per group	45	66	103	58	85	134

A two group continuity corrected χ^2 test with a 0.05 two-sided significance level will have 80% power to detect the difference between a Treated Group proportion, π_1, of 0.20 and a Placebo Group proportion, π_2, of 0.50 (odds ratio of 4.00) when the sample size in each group is 45.

Note: The odds ratio (OR) is the OR for DGF. In Column 1, OR = 4, so the odds of DGF in the Placebo group is 4 times the odds of DGF in the Treated group.

One-sided tests:

Two group continuity corrected χ^2 test of equal proportions (odds ratio = 1) (equal n's)

	1	2	3	4	5	6
Test significance level, □	0.050	0.050	0.050	0.050	0.050	0.050
1 or 2 sided test?	1	1	1	1	1	1
Treated Group proportion, π_1	0.200	0.250	0.300	0.200	0.250	0.300
Placebo Group proportion, π_2	0.500	0.500	0.500	0.500	0.500	0.500
Odds ratio, $\psi = \pi_2 (1 - \pi_1) / [\pi_1 (1 - \pi_2)]$	4.000	3.000	2.333	4.000	3.000	2.333
Power (%)	80	80	80	90	90	90
n per group	37	54	83	48	71	111

Statistical Assumptions

- Since this study is a Phase I/II, we will primarily explore the safety of the proposed dose in the renal transplant population receiving high-risk ECD and DCD kidneys. Our previous experience in a population of highly-HLA sensitized renal allograft recipients showed that administration of 20U/kg (8 doses in 1 month) was safe and without AE or SAE when compared to placebo (*NCT01134510)*. Based on the calculations above, we propose a randomized, placebo controlled trial of C1INH vs. placebo entering 35 eligible patients into both arms of the study.

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, study sponsor 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 subjects 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 EC/IRB and Regulatory Authorities.

All AEs, SAEs, and SUSARs believed or possibly attributable to the investigational product must be reported to CSL-Behring in accord 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 CSL-Behring Inc. 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	Transplant Day 0 (Infusion #1 C1INH vs Placebo)	Day 1±6 hrs (Infusion #2 C1INH vs Placebo)	Day 2±6 hrs	Day 3±6 hrs	Day 4±6 hrs	Day 5±1 days	Day 6±2 days	Day 7 ±3 days *	Day 14 ±3 days
Informed Consent	X									
Inclusion/exclusion criteria review	X									
Medical History	X									
Complete Physical Exam (Including DVT Exam) (1)	X	X	X	X	X	X	X	X	X	
Vital signs/weight	X	X	X	X	X	X	X	X	X	X
12-lead ECG (w/in 6M)	X									
Chest X-ray (w/in 6M)	X									
Safety laboratory tests (CBC, CMP)	X	X	X	X	X	X	X	X	X	X
PT, PTT, D. Dimer, Fibrinogen	X	X	X						X	
Review Historical Serologies for HIV, HBV, HCV, CMV and EBV	X									
Pregnancy test (for WOCP)	X									
Urinalysis	X									X
Urine Output Measurement		X	X	X	X	X	X	X	X	
Estimated GFR (using MRDR or Cockroft & Gault equation)			X	X	X	X	X	X	X	X

Allograft biopsy		X								
Dialysis Assessment		X	X	X	X	X	X	X	x	X
Assessment for DVT (Using Wells Criteria Score) (2)		X	X						X	
Pneumococcal Vaccine & Neiserria Menigitides	X									
Berinert® vs Placebo Infusion		X	X							
C3, C4 Levels		X	X						X	
C1 Inhibitor Level (Prior to each infusion)		X	X						X	
Campath or Thymoglobulin administration		X								
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse Event Monitoring			X	X	X	X	X	X	X	X
Acute Rejection Assessment										

(1) DVT exam will be done on day 0 and day1 (days Berinert vs.Placebo are given)
(2) For scores indicating high risk for DVT, patient will have Doppler ultrasound.

*Day 4-7 assessments should be performed daily until the patient is discharged.

**If patient is discharged prior to day 7, day 7 lab assessments should be performed.