

## CLINICAL PROTOCOL

**TITLE:** Ciprofloxacin for Prevention of BK Infection in Renal Transplant Recipients

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**INVESTIGATOR SIGNATURE:**

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This clinical research protocol will be conducted in accordance with Good Clinical Practice and the guidelines of The Methodist Hospital Research Institute Institutional Review Board.

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## LIST OF ABBREVIATIONS

<b>Term</b>	<b>Definition</b>
AE	Adverse Event
CFR	Code of Federal Regulations
CMV	Cytomegalovirus
CRF	Case Report Form
CTCAE	Common Terminology Criteria of Adverse Event
CV%	Coefficient of Variance
DCD	Donors after Cardiac Death
ECD	Expanded Criteria Donor
eCRF	Electronic Case Report Form
eGFR	estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ITT	Intent-to-Treat
msec	Millisecond
mTOR	Mammalian Target of Rapamycin
NPO	Nothing by Mouth (Nil Per Os)
PCP	Pneumocystis Carinii Pneumonia
PCR	Polymerase Chain Reaction
POD	Post Operative Day
QTc	QT interval
R	Research
SAE	Serious Adverse Event
SCD	Standard Criteria Donor
SOC	Standard of Care
TMHRI	The Methodist Hospital Research Institute

## STUDY SYNOPSIS

<b>SPONSOR / PRINCIPAL INVESTIGATOR</b>	The Methodist Hospital Research Institute / A. Osama Gaber, MD
<b>TITLE:</b>	Ciprofloxacin for Prevention of BK Infection in Renal Transplant Recipients
<b>OBJECTIVES:</b>	<p>The primary objective of this study is</p> <ul style="list-style-type: none"> <li>• To evaluate the efficacy of routine ciprofloxacin administration post-transplantation for the reduction of the incidence of BK infection in renal transplant recipients</li> </ul> <p>Secondary objectives include:</p> <ul style="list-style-type: none"> <li>• To evaluate the safety and tolerability of routine ciprofloxacin administration in kidney transplantation</li> </ul>
<b>TRIAL DESIGN:</b>	The proposed study is a single-center, randomized, prospective, double-blind, placebo-controlled study
<b>TYPE AND NUMBER OF SUBJECTS:</b>	The study will be comprised of 180 kidney transplant subjects
<b>RANDOMIZATION</b>	2:1 study regimen to comparator group
<b>STUDY REGIMEN</b>	Ciprofloxacin 500 mg (dispensed as two-250 mg capsules) once daily for up to 90 days post-transplant
<b>COMPARATOR REGIMEN</b>	Placebo, dispensed as two-matching capsules, once daily for up to 90 days post-transplant
<b>Main Inclusion criteria</b>	<ol style="list-style-type: none"> <li>1. Male or female subjects over the age of 18 years</li> <li>2. Recipients of a primary or repeat renal allograft either alone (from a deceased or living donor) or as a dual-kidney transplant</li> <li>3. Signed informed consent form prior to any research assessment</li> </ol>
<b>Main Exclusion criteria</b>	<ol style="list-style-type: none"> <li>1. Patients with known severe allergy to ciprofloxacin</li> <li>2. History of tendon rupture or tendinitis</li> <li>3. Use of antiarrhythmic drugs known to prolong the QT interval such as class IA antiarrhythmic drugs (e.g. quinidine, procainamide, disopyramide), class III antiarrhythmic drugs (e.g. amiodarone, sotalol)</li> <li>4. Patients with history of previous non-renal transplantation</li> <li>5. Recipients administered rituximab within one year prior to transplantation, or recipients expected to receive rituximab as part of desensitization strategy or for the presence of historical donor specific antibodies</li> <li>6. Any condition present during the initial transplant hospitalization that in the investigator's judgment would increase the risk associated with participation in the study</li> <li>7. QTc interval of greater than 500 msec on admission or post-operative EKG</li> <li>8. BK nephropathy with previous transplant</li> <li>9. BK viremia on admission</li> </ol>
<b>TRIAL AND TREATMENT DURATION:</b>	<ul style="list-style-type: none"> <li>• 24 month enrollment + 12 month follow-up</li> <li>• 3 month treatment duration</li> </ul>

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## 1 Introduction

### 1.1 Background

BK virus is a member of the virus family polyomaviridae (“polyoma”). The virus, which can manifest as a viral nephritis, was first described in a renal transplant recipient in 1971, however it was not until the past decade that infection with BK virus became known as an important contributor to graft dysfunction and graft loss after renal transplantation. It has been widely accepted that emergence of BK virus correlates with the more potent immunosuppressive agents currently used to lower acute rejection rates ([1] Brennan et al. Am J Transpl 2005; 5(3):583-94). In contrast to other opportunistic infections after transplantation, for which routine prophylactic agents are administered, there is no effective agent for the prevention of BK infection, nor is there an effective agent for treating BK infection once it occurs.

Ciprofloxacin is a well known anti-infective agent in the fluoroquinolone class of antibiotics. It is most active against gram-negative enteric pathogens, and is commonly used for a variety of infectious indications.

Though classified as antibacterial agents, fluoroquinolones have been suggested to exhibit anti-BK viral effects by interfering with helicase activity of the BK virus large T antigen ([2] Ali et al. Antivir Ther 2007; 12:1-6). Ciprofloxacin has been shown in previous studies to reduce urine BK viral load ([3] Leung et al. Clin Infect Dis 2005; 40:528), and BK-associated hemorrhagic cystitis ([4] Miller et al. Biol Blood Marrow Transplant 2011) in the stem cell transplant population. Ciprofloxacin has also been associated with a lower incidence of BK viremia in one retrospective study in kidney transplant recipients ([5] Gabardi et al. Clin J Am Soc Nephrol 2010; 5: 1298). Based on these reports, we hope to find a reduction BK viremia and BK nephropathy using a prospective, randomized study design.

## 2 Purpose and objectives

### 2.1 Purpose

The purpose of this study is to evaluate the safety and efficacy of ciprofloxacin for the prevention of BK infection in renal transplant recipients.

### 2.2 Objectives

#### 2.2.1 Primary objective

To determine whether routine ciprofloxacin administration post-transplantation can lower the incidence of BK infection in renal transplant recipients

#### 2.2.2 Secondary objective

To evaluate the safety and tolerability of routine ciprofloxacin administration in kidney transplantation with respect to:

- Incidence of adverse events
- Incidence of urinary tract infections as defined by a midstream urine sample containing  $10^4$  or more colony-forming units per mL
- Incidence of quinolone-resistant urinary tract and bloodstream infections
- Incidence of *Clostridium difficile* infections
- Incidence and severity of BK nephropathy
- Time to onset of and quantitation of BK viremia
- Graft outcomes

### **3 Design Rationale**

The proposed study is a randomized, prospective, double-blind, placebo-controlled study. The rationale for a placebo-controlled arm is that there are no established preventative strategies for BK infection. Currently, there are no prospective studies evaluating preventative or treatment agents for BK infection.

### **4 Experimental Plan**

#### **4.1 Study Design**

This is a single-center, randomized, prospective, double-blind, placebo-controlled study. Eligible subjects who enroll in this study will be randomized prior to discharge from the initial transplant hospitalization in a 1:2 ratio standard of care (placebo), or 90 days of once-daily ciprofloxacin. Patients will be stratified based on the use of alemtuzumab (Campath) induction.

##### **4.1.1 Study Endpoints**

###### **4.1.1.1 Primary Endpoint**

The primary endpoint will be the proportion of patients developing BK infection at 6 months post-transplant. BK infection is defined as the presence of a detectable BK viral load in plasma by polymerase chain reaction (PCR), or the presence of BK viral inclusions on kidney biopsy specimens. All detectable PCRs must be confirmed by repeat PCR to be considered positive.

###### **4.1.1.2 Secondary Endpoint**

Secondary endpoints will include:

- Incidence of urinary tract infections. Incidence of urinary tract infections as defined by a midstream urine sample containing  $10^{14}$  or more colony-forming units per mL at 6 months
- Incidence of bloodstream infections at 6 months. Bloodstream infection is defined by a single positive blood culture that was not thought to be contaminated.
- Incidence of quinolone-resistant urinary tract and bloodstream infections at 6 months
- Incidence of clostridium difficile infection at 6 months
- Serious adverse events related to therapy
- Severe adverse events (CTC grade 3 or higher)
- Time to BK infection
- Proportion of patients developing BK infection at 1 year
- First and peak plasma viral loads
- Incidence of acute rejection at 1 year
- Incidence and severity of BK nephropathy, as defined by positive staining of histopathological specimen, at 1 year

###### **4.1.1.3 Additional Evaluations to be Tracked**

The following safety parameters will be assessed and measured during the study period:

- Dose discontinuation due to adverse event related to therapy
- Serum creatinine concentrations at 1, 3, 6, 9, and 12 months post-transplant
- Graft loss at 1 year
- Death at 1 year

#### **4.1.2 Number of Subjects**

A total of 180 kidney transplant recipients will be enrolled.

#### **4.1.3 Study Duration**

The study will begin at the time of transplant and subjects will be enrolled for 12 months post-transplant.

#### **4.1.4 Study Population**

Patients with end stage renal disease who are receiving a kidney transplant and who satisfy the following criteria will be considered for participation in this study.

##### **4.1.4.1 Inclusion Criteria**

1. Male or female subjects over the age of 18 years
2. Recipients of a primary or repeat renal allograft either alone (from a deceased or living donor) or as a dual-kidney transplant
3. Signed informed consent form prior to any research assessment

##### **4.1.4.2 Exclusion Criteria**

1. Patients with known severe allergy to ciprofloxacin
2. History of tendon rupture or tendinitis
3. Use of antiarrhythmic drugs known to prolong the QT interval such as class IA antiarrhythmic drugs (e.g. quinidine, procainamide, disopyramide), class III antiarrhythmic drugs (e.g. amiodarone, sotalol)
4. Patients with history of previous non-renal transplantation
5. Recipients administered rituximab within one year prior to transplantation, or recipients expected to receive rituximab as part of desensitization strategy or for the presence of historical donor specific antibodies
6. Any condition present during the initial transplant hospitalization that in the investigator's judgment would increase the risk associated with participation in the study
7. QTc interval of greater than 500 msec on admission or post-operative EKG
8. BK nephropathy with previous transplant
9. BK viremia on admission

## **5 Treatment Procedures**

### **5.1 Ciprofloxacin**

#### **5.1.1 Test Article and Administration**

The test article is defined as ciprofloxacin, and is supplied as 250 mg capsules by the sponsor. Matching placebo capsules will also be supplied by the sponsor.

In order to maintain blinding among subjects and investigators, study medication will be dispensed in pre-fill containers of 200 capsules each and labeled as "ciprofloxacin/placebo".

#### **5.1.2 Dosage and Administration**

The dosages of ciprofloxacin/placebo will be 500 mg daily, i.e. two of the 250 mg capsules once daily. This can be administered in the morning or in the evening. All study medication should be administered at least 1 hour prior to or 2 hours after administration of any antacid,

multivitamin, or other medications that contain divalent or trivalent cations (i.e. magnesium or calcium-containing supplements).

### **5.1.3 Dose Adjustments**

#### **5.1.3.1 Renal Dose Adjustments**

In patients with an estimated glomerular filtration rate of less than 30 ml/min/1.73m<sup>2</sup>, dosing of ciprofloxacin/placebo should be reduced to 1 capsule once daily.

### **5.1.4 Dose Interruptions**

#### **5.1.4.1 Dose Interruptions**

In situations where holding of the study drug is required (i.e. patient is NPO or patient requires treatment with fluoroquinolone antibiotic as described in section 5.1.4.2), study drug can be held for up to 14 days. After 14 days of being off study drug, the investigator may consider withdrawing the subject from the study.

#### **5.1.4.2 Concomitant Antibiotics**

All infectious complications or conditions requiring antibiotic administration will be managed per routine standards. In cases where ciprofloxacin or alternative quinolone can be administered as a treatment option, study drug should be held during administration for the appropriate duration. Upon completion of treatment the study drug can be resumed for remainder of study duration. If the study drug is held longer than 14 days the investigator may consider withdrawing the subject from study. In cases where an alternate class of medication is deemed necessary, the study drug should be continued throughout the duration of concomitant antibiotic use.

#### **5.1.4.3 Development of BK Viremia**

Subjects who develop BK viremia or BK nephropathy will be managed according to the center's routine protocol. Except in the case of an SAE, study drug should continue for the remainder of its specified course.

## **5.2 Concomitant Immune Suppression**

All patients are required to remain on concomitant maintenance immune suppression therapies, including at least 2 of the following agents: calcineurin inhibitors, antimetabolites, or mTOR inhibitors.

### **5.2.1 Calcineurin Inhibitors**

#### **5.2.1.1 Tacrolimus (Prograf)**

Tacrolimus (Prograf) dosages are administered every 12 hours and adjusted to target 12-hour trough concentrations of 5 – 15 ng/mL.

#### **5.2.1.2 Cyclosporine**

Cyclosporine modified dosages are administered every 12 hours and are adjusted to target 12-hour trough concentrations of 150 – 250 ng/mL.

## 5.2.2 mTOR Inhibitors

### 5.2.2.1 *Sirolimus (Rapamune)*

Sirolimus (Rapamune) dosages are administered once daily and adjusted to target 24-hour trough concentrations of 5 – 10 ng/mL.

When combined with tacrolimus, sirolimus and tacrolimus concentrations will be adjusted to maintain a total combined level of 8-12 ng/mL.

## 5.2.3 Antimetabolites

### 5.2.3.1 *Mycophenolate Mofetil (Cellcept)*

Mycophenolate mofetil (Cellcept) will be administered to target a cumulative dosage of 1000 to 2000 mg per day. Dosages may be reduced for common adverse effects such as gastrointestinal intolerance or leukopenia.

## 5.2.4 Induction agents

Induction therapy will be determined by the prescriber based on the centers standard of care protocol.

5.2.4.1 Patients will be stratified upon enrollment based on alemtuzumab induction.

## 5.2.5 Corticosteroids

All patients will receive intraoperative intravenous methylprednisolone, which will be tapered to an oral prednisone dosage at discharge. Long-term maintenance steroid use will be determined by the prescriber based on the centers standard of care protocol..

## 5.3 Study Drug Handling

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drugs to any persons except the subjects in this study.
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions, accessible only to those authorized by the investigator to dispense these test drugs.
- A study drug inventory will be maintained by the investigator/pharmacist. The inventory will include details of when they were dispensed and to which subject.
- At the conclusion or termination of this study, the investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the Drug Accountability Record.
- Used or unused study drug may be destroyed at the study center according to standard institutional procedures after drug accountability has been conducted. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the Sponsor or designee upon request. Unused study drug not destroyed at the site must be returned to the Sponsor or designee at the end of the study or upon expiration.

## **6 Study Procedures**

### **6.1 Consent Process**

After approval by The Methodist Hospital Research Institute's Institutional Review Board, the Principal Investigator, or a designated member of his study team, will approach potential subjects prior to transplantation regarding participation in the study. The study will be described by explaining the purpose of the study, the methods and objectives, and the potential risks associated with the study. An informed consent form (ICF) will be provided. Patients will be given time to read the ICF, and will be allowed to ask questions about the study. They will be informed that their participation is voluntary and that choosing not to be involved will not influence their care at The Methodist Hospital. They will be informed that they may choose to withdraw from the study at anytime for any reason. Subjects will be given an ICF to keep. The informed consent process will be documented in the patient's chart.

Any new information about the study medications that may be provided by the manufacturer or the Food and Drug Administration will be provided to the Institutional Review Board. Subjects will also be provided this information through a revised ICF and will be given the opportunity to decide whether or not to continue in the study.

### **6.2 Assessment of Eligibility**

At the time of transplant or, if possible, up to 14 days prior to transplant, the subject may be approached regarding potential interest in study involvement. Their medical history will be reviewed to assess for eligibility. Prior to performing any research-related procedures, informed consent will be obtained. Subjects must meet all inclusion criteria and none of the exclusion criteria or enrollment into the study will not be possible.

### **6.3 Enrollment**

Subjects who qualify for enrollment in this study after signing informed consent will be enrolled, and proceed into the study at the time of transplantation.

### **6.4 Procedures**

#### **6.4.1 Pre-treatment Data Collection**

BK PCR from plasma will be collected during the initial hospital visit prior to study drug administration (per standard of care). Study drug will be initiated upon discharge from initial hospitalization, and no later than day 7 post-transplant.

#### **6.4.2 Post-treatment Data Collection**

Patients will remain on study medication for 90 days post-transplant. All routine standard of care procedures/visits will apply. Patients are to have routine BK PCR drawn at 1, 2, 3, 6, 9, and 12 months post-transplant. Study visits will occur at baseline, 2 weeks, and 1, 2, 3, 6, 9, and 12 months post-transplant.

### **6.5 Standard Laboratory Tests**

At transplantation, prior to the transplant surgery, the following tests are routinely performed: Hematology and a Comprehensive metabolic panel (chemistry) (described below in Section 6.5.1). Daily hematology and chemistry are performed during hospitalization and upon discharge. A schedule of follow-up visits include basic hematology and chemistry assessments that will be recorded in the clinical record and in the study record. See Section 6.5.1 Sequence of events below for detail.

### 6.5.1 Sequence of Events

Time of Visit	Screening/Baseline -14 to 7 days post transplant	2 Weeks Post TXP	1 Month Post TXP	2 Months Post TXP	3 Months Post TXP	6 Months Post TXP	9 Months Post TXP	12 Months Post TXP
Visit Window	N/A	±7 Days	± 7 Days	± 7 Days	± 14 Days	±14 Days		
Visit Number	1	2	3	4	5	6	7	8
Inclusion/Exclusion criteria	X (R)							
Informed consent	X (R)							
Med History <sup>1</sup>	X (R)							
Concomitant Medications <sup>2</sup>	X (R)	X (R)	X (R)	X (R)	X (R)	X (R)	X (R)	X (R)
Transplant Data Collection <sup>3</sup>	X (R)							
Randomization <sup>4</sup>	X (R)							
Study Medication Dispensation or Return	X (R)	X (R)	X (R)		X (R)			
Study medication record	X (R)	X (R)	X (R)		X (R)			
BK PCR (serum)	X (SOC)		X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)
AE/SAE Assessment	X (R)	X (R)	X (R)	X (R)	X (R)			
Serum Creatinine	X (SOC)		X (SOC)		X (SOC)	X (SOC)	X (SOC)	X (SOC)
Urine Analysis and culture (if applicable) and blood cultures	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)		
Tacrolimus/Sirolimus levels	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)
Urine Protein to Creatinine Ratio			X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)	X (SOC)

### 6.5.2 Screening and Eligibility

Between day -14 and day 7 post-transplant after obtaining informed consent, subjects who fulfill all of the inclusion criteria and none of the exclusion criteria will be enrolled into the study. Documentation of the fulfillment of criteria will be included in the study files.

<sup>1</sup> Medical history includes history of age, diagnosis for renal failure, history of diabetes, duration and type of dialysis, cytomegalovirus (CMV) serology, and HLA typing.

<sup>2</sup> Immunosuppressant medications, including medications used to treat rejection, and concomitant anti-microbial use will be captured. At months 6,9 and 12 only immunosuppressant dosages are required.

<sup>3</sup>. Transplant information includes donor demographics (age, sex, race) and CMV serology, donor history (terminal serum creatinine, cause of death), type of transplant (ECD, DCD, or SCD), ischemia times, peak PRA and most recent PRA prior to transplant.

<sup>4</sup> Subject must meet all Inclusion and Exclusion Criteria prior to randomization.

### **6.5.3 Study Completion**

Subjects who attend the 12-month study visit and have completed all study-related evaluations described in Section 6.5.1 will be considered as having completed the study.

Subjects who elect to discontinue pre-maturely or are withdrawn from the study by the investigator, will be converted to standard of care treatment, will return any unused study drug, and will be asked to attend a final end-of-study safety evaluation visit. If it is not possible to complete the end-of-study visit, every attempt will be made to determine safety endpoints (adverse events, rejection, graft loss or death information) occurring since the previous visit. A phone visit may be utilized for this information if the subject is unable or unwilling to attend the end-of-study visit.

Subjects will be followed as standard of care after the study regimen has been completed or discontinued. Standard of care may include the continued monitoring of BK PCRs.

## **7 Blinding**

### **7.1 Blinding Method**

This is a double-blind, randomized, prospective study. Subjects will be assigned to a double-blind treatment arm in the order in which they meet the criteria for randomization. The pharmacist will be unblinded to treatment. All other study site staff and all members will remain blinded to treatment arm except as described below.

### **7.2 Retention of the Assignment Schedule and Procedure for Treatment Code Breaking**

The randomization schedule will be stored in the Site Pharmacy holding area. Study drug treatment may be revealed only for reasons relating to the subject's safety and when critical therapeutic decisions are contingent on knowing the assigned study drug. Withdrawal of a subject from the study is not a sufficient reason to break the study blind. If the blind is broken for a subject, the reason is to be documented as a written entry in the source document.

## **8 Statistical Analysis Plan**

### **8.1.1 Data Analysis**

A full analysis will be conducted based on the intent-to-treat (ITT) population. The ITT population will be defined as all randomized subjects who take at least one dose of the assigned therapy after randomization. A per-protocol analysis will be performed on all randomized patients completing 90 days of study drug. The primary endpoint of the difference in proportion of patients developing BK infection within 6 months will be determined using the chi-square test. All secondary and safety outcomes will be analyzed using chi-square or fisher exact testing for categorical variables, and analysis of variance or t-tests for continuous variables. Time to BK infection and graft survival will be estimated using Kaplan-Meier methodology. Univariate and multivariate proportional hazards Cox models will be developed to determine the risk factors of study outcomes.

## **9 Removal of Subject from Study**

### **9.1 Discontinuation of Study**

The Principal Investigator reserves the right to discontinue this study at any time. Should this occur, the appropriate authorities (eg, Institutional Review Board, FDA, and the funding agency) will be informed, and the reason for discontinuation will be indicated in the Case Report Form (CRF). A study termination CRF must be completed.

### **9.2 Withdrawal from Study**

#### **9.2.1 Discontinuation of Study Drug**

The Principal Investigator will discontinue dosing a subject if he believes it is in the subject's best interest. When a subject discontinues receiving study drug, the subject should be followed for 30 days from the last dose. The date that the subject discontinues receiving study drug will be recorded. Subjects experiencing adverse reactions that are believed to be related to the study drug should be followed until the reaction has resolved, stabilized, or are otherwise explained.

#### **9.2.2 Early Withdrawal/Study Termination**

Reasons why a subject may discontinue or be withdrawn from the study include, but are not limited to; intolerance to study drug, an adverse event, subject request, or investigator request.

## **10 Adverse event reporting**

### **10.1 Definition and Grading Intensity of Adverse Events (AE)**

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Study drug includes the investigational drug under evaluation and the comparator drug or placebo that is given during the study. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits, through physical examination, laboratory tests, or other assessments. Adverse events will be collected for up to 4 weeks after completion of study drug administration. All adverse events must be recorded on the Adverse Events eCRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug(s)
3. its duration (start and end dates or if continuing at final exam)
4. whether it constitutes a serious adverse event (SAE)

### **10.2 Criteria for Determining Relationship to Drug**

The clinical investigator will make a determination of the relationship of the AE to the study drug using a four category system (not related, possibly related, probably related, definitely related).

Not related: Any untoward AE that either was clearly pre-existent, or occurred at the time of test drug administration but sufficient information exists to indicate the etiology is unrelated to the clinical trial medication.

Possibly related: An AE that does not follow a reasonable temporal sequence from administration of the medication, does not follow a known or suspected response pattern, or could be explained by another etiology.

Probably related: An AE that follows a reasonable temporal sequence from administration of the medication, follows a known or suspected pattern of response to the medication, and cannot be reasonably explained by the known characteristics of the patient's clinical state.

Definitely related: An AE that follows a reasonable temporal sequence from administration of the drug and is characterized by either:

- A positive result in drug sensitivity tests, or
- A toxic level of the drug in the blood.

### **10.3 Serious Adverse Event**

A Serious Adverse Event (SAE) is any adverse event occurring for up to 4 weeks after completion of study drug administration that results in any of the following outcomes:

- Death
- Graft loss
- A life threatening event which may place the patient at an immediate risk of death
- Persistent or significant disability
- Hospitalization for administration of intravenous antibiotics due to presence of multidrug resistant infection
- Cardiac arrhythmia
- Tendon rupture

SAEs considered "definitely" related to the study drug must be submitted to IRB.

### **10.4 Potential Risks and Discomforts**

#### **10.4.1 Risks**

##### **10.4.1.1 Ciprofloxacin**

The most common adverse effects associated with ciprofloxacin in clinical trials were nausea (2.5%), diarrhea (1.6%), liver function test abnormalities (1.3%) vomiting (1%) and rash (1%).

Fluoroquinolone antibiotics, including ciprofloxacin, have been associated with an increased risk of tendinitis and tendon rupture. The risk may be increased in patients over the age of 60, and in kidney, heart, and lung transplant recipients. Patients should be advised to report signs of tendonitis or tendon pain, swelling, or inflammation immediately. Overall, musculoskeletal adverse effects occur in less than 1% of adults treated with ciprofloxacin.

Fluoroquinolone antibiotics, including ciprofloxacin, have the potential to cause QT prolongation and should be used cautiously in patients with known QT prolongation, and in those taking concomitant medications that are known to prolong the QT interval.

Fluoroquinolone antibiotics, including ciprofloxacin, should be used cautiously in patients with central nervous system disorders. Seizures have occurred in <1% although the risk can be increased in cases of overdosage.

All antibacterial agents alter the normal flora of the gastrointestinal tract and promote the growth of clostridia.

Other potential risks associated with fluoroquinolone antibiotics include sensitivity to the sun, sunburn like reactions, nerve pain, including tingling, burning, numbness, or weakness, tremors, hallucinations, depression and convulsions.

#### **10.4.1.2 Risks associated with Blood Draws**

The risk associated with multiple blood draws for PK assessments will be the increased potential for hematoma at the blood draw site.

#### **10.4.2 Potential Benefits**

This study will improve the knowledge of a potential prophylaxis strategy against BK virus in transplant recipients. Current data demonstrated increased graft loss among patients developing BK virus and BK nephropathy. Knowledge about possible preventative strategies may lead to reductions in BK-related adverse outcomes.

### **11 Ethics**

#### **11.1 Responsibilities of the Investigator**

The Principal Investigator will maintain complete study files (electronic and/or paper) to enable full documentation of the study procedures and data for purpose of verification and study analysis.

The Principal Investigator, or his designee, will explain the nature of the study to the subject, inform the subject that participation is voluntary, and that withdrawal at any time is allowed. The Principal Investigator will maintain documentation of written informed consent.

This study will be conducted using Good Clinical Practice as identified by

- International Conference on Harmonization (ICH) Tripartite Guidelines for Good Clinical Practice
- US Code of Federal Regulation (CFR) dealing with clinical studies (21 CFR parts 50, 54, 56 and 312)
- The principles stated in the Declaration of Helsinki concerning medical research in humans

#### **11.2 Institutional Review Board Approval**

This study will be reviewed and approved by The Methodist Hospital Research Institute Institutional Review Board (TMHRI IRB) prior to commencement of any subject-specific activities. A current letter of IRB approval will be maintained with the study files. No changes to the protocol or informed consent form will be made prior, to or without documented approval from TMHRI IRB.

All subjects will provide consent (indicated by their signature or their legally authorized representative's signature on the approved Informed Consent Form) prior to initiation of any study-related activities. Signed and dated ICFs will be maintained with the study archives.

## **12 Data Handling and Recordkeeping**

### **12.1 Confidentiality**

In order to maintain confidentiality, the subject will be identified only by his/her study screening number and/or randomization number.

### **12.2 Flow of Information and Records to be Kept**

Throughout the conduct of this study, all required data will be recorded in electronic CRFs that have been specifically designed to record all observations and other data pertinent to this clinical investigation. Data reported on eCRFs should be consistent with source documents when applicable, or the discrepancies should be explained. Any change or correction to a CRF will produce an audit trail within the eCRF system and will identify the user, date and time of the change.

The eCRFs should be completed in a timely fashion. The complete eCRFs will be maintained by the study site, as is required by institutional, local and government regulations.

The clinical investigator is responsible for maintaining adequate and accurate records as specified in Essential Documents for the Conduct of a Clinical Trail (section 8 of the ICH Guideline for Good Clinical Practice) to enable the conduct of the study to be fully documented, and the study data to be subsequently verified. The clinical investigator must notify the Sponsor prior to destroying any clinical study records.

Upon study termination, original documents will be maintained at TMHRI.

## **13 Financing**

Funding for this study will be provided by the Methodist Hospital Department of Surgery and the Methodist Hospital Department of Pharmacy.

## **14 Publication Policy**

The Principal Investigator holds final approving authority over whether or not any proposed publication (eg, abstract, manuscript) based on the data generated from this study can or should be submitted for publication to journals, scientific meetings, or any other medium.

## **15 References**

1. Brennan DC, Agha I, Bohl DL, et al. Incidence of BK with tacrolimus versus cyclosporine and impact of preemptive immunosuppression reduction
2. Ali SH, Chandraker A, DeCaprio JA, et al. Inhibition of Simian virus 40 large T antigen helicase activity by fluoroquinolones. *Antivir Ther.* 2007;12(1):1-6.
3. Leung AY, Chan MT, Yuen KY, et al. Ciprofloxacin decreased polyoma BK virus load in patients who underwent allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis.* 2005;40(4):528-37.
4. Miller AN, Glode A, Hogan KR, et al. Efficacy and safety of ciprofloxacin for prophylaxis of polyomavirus BK virus-associated hemorrhagic cystitis in allogeneic hematopoietic stem cell transplantation recipients. *Biol Blood Marrow Transplant.* 2011;17(8):1176-81.
5. Gabardi S, Waikar SS, Martin S, et al. Evaluation of fluoroquinolones for the prevention of BK viremia after renal transplantation. *Clin J Am Soc Nephrol.* 2010;5(7):1298-304.

## 16 Appendices

### 16.1 Appendix 1: Ciprofloxacin Package Insert

The package insert for ciprofloxacin can be found at the following URL:

<http://www.univgraph.com/bayer/inserts/ciprotab.pdf>

### 16.2 Appendix 2: Equation for Estimating Glomerular Filtration Rate

IDMS-traceable MDRD equation for estimating Glomerular Filtration Rate (eGFR).

$GFR \text{ (mL/min/1.73 m}^2\text{)} = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$  (conventional units)