PROTOCOL TITLE:

Randomized Controlled Trial Comparing the Tolerability and Efficacy of Maribavir vs. Valganciclovir for CMV Prophylaxis in High-Risk Kidney Transplant Recipients

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1.0 Objectives / Specific Aims

- Aim 1. Assess the incidence of leukopenia in those randomized to maribavir vs. valganciclovir prophylaxis in adult kidney transplant recipients at high-risk of CMV infection.
    - Hypothesis 1. The incidence of clinically meaningful leukopenia, defined as a WBC count of < 3,000 cells/mm^3 and a reduction in total mycophenolate dose below 1,500 mg/day or valganciclovir dose below 900mg per day (adjusted for renal function), will be significantly lower in the maribavir arm, as compared to the valganciclovir arm.
- Aim 2. Assess the efficacy of maribavir vs. valganciclovir prophylaxis in adult kidney transplant recipients at high-risk of CMV infection.
    - Hypothesis 2. The incidence of CMV infection and disease will be similar between the maribavir arm, as compared to the valganciclovir arm, at 3-, 6-, and 12-months post-transplant.
- Aim 3. Assess the impact of maribavir vs. valganciclovir prophylaxis on healthcare utilization and costs in adult kidney transplant recipients at high-risk of CMV infection.
    - Hypothesis 3. Healthcare utilization will be lower in the maribavir arm, as compared to the valganciclovir arm, at 6- and 12-months post-transplant, driven predominantly by reduced number of telephone calls, televisits, and laboratory monitoring encounters.
- Exploratory Aim 4. Assess the impact of maribavir vs. valganciclovir prophylaxis in adult kidney transplant recipients at high-risk of CMV infection on patient-reported outcomes for quality of life and satisfaction.
- Exploratory Aim 5. Assess any differences in leukopenia, efficacy, healthcare utilization and patient reported outcomes by race and sex in patients randomized to maribavir vs. valganciclovir prophylaxis in adult kidney transplant recipients at high-risk of CMV infection.

2.0 Background

Despite substantial advances in screening, monitoring, therapeutics and management, CMV infection remains a significant problem in kidney transplantation and CMV is still considered by clinicians to be the most important post-transplant infection.[1-4] Although universal prophylaxis with potent antiviral therapy has significantly reduced the risk of early CMV infection and disease (≤6 months), late onset CMV (> 6 months post-transplant) is still quite common and can be difficult to clinically manage, particularly in high-risk patients, including those receiving rabbit antithymocyte globulin (rATG) induction and those that are sero mismatched (D+/R-). A recent systematic review demonstrated that with antiviral prophylaxis, early CMV infection occurred in only 6% (95% CI 1 to 31%) of kidney transplant recipients, while late infection occurred in more than one in six patients (17%, 95% CI 2 to 29%).[4] The results of the IMPACT study, a randomized controlled trial comparing 100-days to 200-days of oral valganciclovir therapy in D+/R- patients highlights the continued issue of late CMV infection. Although patients randomized to the 200-days of therapy had a significant reduction in CMV disease, rates were still quite high. The 12-month incidence of CMV disease was 16.1% in these patients, despite receiving more than 6-months of valganciclovir prophylaxis.[5]

Valganciclovir antiviral prophylaxis is highly effective at preventing CMV infection, but it has numerous limitations. Of particular concern is the high rates of cytopenias; most notably, leukopenia and neutropenia. This often leads to a clinical conundrum, whereby it is unclear if the low WBC count is due to valganciclovir therapy itself, a breakthrough CMV infection, or mycophenolate therapy. Oftentimes, this clinical dilemma causes multiple additional laboratory interrogations, reductions in full dose valganciclovir and/or mycophenolate therapies, and in severe cases, the administration of filgrastim (Neupogen®, G-CSF).[6-10] In studies using valganciclovir for CMV prevention, the reported the incidence of post-kidney transplant leukopenia is 20 to 40% and neutropenia is upwards of 10% at 30%.[6-12]

Maribavir has been evaluated for the prevention of CMV infection in phase II and phase III trials within allogeneic stem cell transplant recipients. At 6-months post-transplant, the rates of CMV infection using PCR were not different between treatment and placebo arms, although the rates of pp65 antigenemia were lower in the maribavir group. However, these studies used a low dose of 100mg PO BID. In subsequent studies within solid organ transplantation, maribavir dosed at 400 to 1200mg PO BID was equally efficacious to valganciclovir for the treatment of CMV infection. Of note and importance to this proposal, the rates of neutropenia were 4-5% in the maribavir treated patients vs. 15-18% in valganciclovir patients. Thus, at an appropriate dose, maribavir appears to have similar efficacy to valganciclovir in treating CMV infection with a significantly reduced incidence of neutropenia. Currently, there is a lack of randomized controlled trials assessing the safety and efficacy of adequately dosed (≥400mg PO BID) maribavir for the prevention of CMV infection in solid organ transplant recipients.[13-19]

3.0 Intervention

Patients will be randomized to receive either maribavir 400mg PO BID or valganciclovir 900mg daily (standard of care dose, adjusted for renal function) for CMV prophylaxis for 3 to 6 months post-transplant. Those that are CMV serostatus D+/R- will receive 6 months of antiviral therapy; all others will receive 3-months of therapy. The current gold-standard therapy is valganciclovir for 3- to 6-months of therapy. Those randomized to maribavir will also receive 1-month of acyclovir 400mg PO BID for HSV prophylaxis (standard of care dose). Beyond these interventions, all follow-up care and laboratory monitoring will be conducted as per usual care protocols. All immunosuppression will be given and dosed as per usual care protocols. There will be no additional visits or laboratory measurements as part of this study.

4.0 Study Endpoints

Safety Measures

1. Leukopenia with an accompanying dose reduction (Primary Outcome) – Defined as a total WBC count of < 3,000 cells/mm^3 with a reduction in the total daily dose of mycophenolate below 1500mg per day or valganciclovir below 900mg daily (adjusted for renal function). This will be assessed as a dichotomous outcome (yes/no) per patient as well as a rate (number of unique leukopenia events per patient-year). Events will be considered unique once the WBC count recovers to normal range on two consecutive measures. The length of time a patient has leukopenia, and the severity of leukopenia (nadir WBC) will also be assessed. This endpoint will be measured at 3-, 6-, and 12-months post-transplant.

2. Neutropenia (Secondary Outcome) – Defined as an absolute neutrophil count of <1,000 cells/mm^3. This will be assessed as a dichotomous outcome (yes/no) per patient as well as a rate (number of unique neutropenic events per patient-year). Events will be considered unique once the neutrophil count recovers to normal range on two consecutive measures while not receiving G-CSF therapy. The length of time a patient has neutropenia, and the severity of leukopenia (nadir WBC) will also be assessed. This endpoint will be measures at 3-, 6-, and 12-months post-transplant.

3. Mycophenolate mofetil dose reduction (Secondary Outcome) – Defined as a reduction in dose of <1,500 mg per day (<750 mg PO BID). This will be assessed as a dichotomous outcome (yes/no) per patient as well as a rate (number of unique mycophenolate dose reduction events per patient-year). Events will be considered unique once the mycophenolate dose is returned to full dose for at least one week. The length of time a patient has their mycophenolate dose <1,500 mg per day and the severity of mycophenolate dose reduction (nadir dose) will also be assessed. This endpoint will be measures at 3-, 6-, and 12-months post-transplant.

4. Valganciclovir dose reduction (Secondary Outcome) – Defined as a reduction in dose of <900mg per day (adjusted for renal function. This will be assessed as a dichotomous outcome (yes/no) per patient as well as a rate (number of unique valganciclovir dose reduction events per patient-year). Events will be considered unique once the valganciclovir dose is returned to full dose for at least one week. The length of time a patient has their valganciclovir dose reduced and the severity of dose reduction (nadir dose) will also be assessed. This endpoint will be measures at 3-, 6-, and 12-months post-transplant.

5. CMV prophylaxis drug dose adjustment or discontinuation (Secondary Outcome) – Defined as a reduction in dose, holding or discontinuation of the maribavir or valganciclovir therapy. This will be assessed as a dichotomous outcome (yes/no) per patient as well as a rate (number of unique dose adjustment events per patient-year). Events will be considered unique once the CMV prophylaxis drug dose is returned to full dose for at least one week. The length of time a patient has their CMV prophylaxis drug dose reduced or held and the severity of dose reduction (nadir dose) will also be assessed. This endpoint will be measures at 3- and 6-months post-transplant.

6. Acute Rejection (Secondary Outcome) - defined as a renal allograft biopsy demonstrating at least grade 1A rejection by Banff criteria. We will also record and assess all borderline acute rejections and antibody mediated rejections using the most current Banff classification system. All patients will be required to have biopsy confirmation of rejection episodes, as per usual care and the MUSC clinical protocol. It is standard care that all kidney allograft biopsies performed for transplant recipients occur at the transplant center (study institution). Biopsies will be read by the local pathologist, as usual care. The study coordinator capturing clinical event data will review the medical record to determine the timing, severity, treatment regimen and reversibility of each acute rejection episode for all patients in the study.

7. Hospitalizations (Secondary Outcome) – Defined as any admission to a hospital with at least one overnight stay. All-cause hospitalization will be assessed for this study. Hospitalizations due to CMV and other infections will be sub-analyzed as well.

8. ED Visits (Secondary Outcome) – Defined as any visit to the emergency room for any cause during the post-transplant period. We will collect the cause and date of the ED visit as well. ED visits due to CMV and other infections will be sub-analyzed as well.

9. Graft function, Graft Failure and Death (Exploratory Outcome) – graft function will be defined using the 4-variable MDRD equation to estimate GFR. This equation has been validated as an accurate reflection of true GFR within kidney transplant recipients. Routine serum creatinine concentrations, which are measured as part of usual care, will be utilized to estimate GFR and aggregated at 3-, 6- and 12-months post-transplant. Graft failure will be defined as return to chronic dialysis, nephrectomy, retransplantation or death.[20,21] The study coordinator capturing clinical event data will review the medical record at regular intervals to determine if a study patient has developed graft failure. The timing and cause of each graft loss will be recorded for comparative analysis. Patient death will also be captured in a similar fashion, with timing and cause recorded as well.

Efficacy Measures

10. CMV Infection (Secondary Outcome) – defined as detectable CMV in the patient's plasma. Currently, MUSC uses CMV DNA PCR (plasma IU/mL) to assess for infection with nucleic acid amplification techniques that are calibrated to the WHO international standard for human CMV. The lower level of detection is 50 IU/mL. Per the MUSC CMV protocol and usual care (see Appendix), any level >1,000 IU/mL will be considered CMV infection for the purposes of this study. All cases of CMV infection, regardless of the presence or absence of symptoms, will be classified as infection. CMV DNA PCR is measured at MUSC per our protocol using event-driven criteria, which includes either leukopenia or symptoms consistent with CMV infection (N/V/D, anorexia, fever, chills, and/or malaise). For the purposes of this study, the reason for measuring CMV DNA PCR will be captured and analyzed as well. Further, MUSC usual care CMV protocol suggests measuring CMV DNA PCR in those that are D+/R- after prophylaxis is discontinued (post-transplant month 7, 9 and 12). The protocol also recommends measuring CMV DNA PCR at month 4, 7, and 12 after discontinuation of antiviral prophylaxis in moderate risk patients (R+, see Appendix). CMV symptoms and treatment will also be recorded. Late CMV infection will be defined based on occurrence of first CMV infection after completion of CMV prophylaxis (3- or 6-months post-transplant). These endpoints will be assessed at 3-, 6-, and 12-months post-transplant. Breakthrough cases of CMV infection, defined as the presence of CMV DNA while on anti-CMV prophylaxis, will also be assessed.[22]

11. CMV Disease (Secondary Outcome) – defined as the presence of organ dysfunction in the setting of CMV infection with biopsy proven presence of CMV in the affected organ, done at MUSC using DNA hybridization. This will be sub-classified by organ type; most common in kidney transplant recipients will be CMV gastrointestinal disease, CMV pneumonia, or CMV nephritis. Less common include CMV hepatitis, CMV retinitis, CMV encephalitis, CMV cystitis, CMV myocarditis, and CMV pancreatitis.[22] Late CMV disease will be defined based on occurrence of first CMV infection after completion of CMV prophylaxis (3- or 6-months post-transplant). This endpoint will be assessed at 3-, 6-, and 12-months post-transplant. Breakthrough cases of CMV disease will also be assessed.

12. Probable or Likely Refractory CMV Infection (Exploratory Outcome) – defined as a persistent viral load (CMV viral load at the same level or higher than the peak viral load within 1 week but <1 log 10 increase in CMV DNA titers done in the same laboratory and with the same assay) after at least 2 weeks of appropriately dosed anti-viral therapy.[23]

13. CMV Antiviral Drug Resistance (Exploratory Outcome) – defined as a viral genetic alteration that decreases susceptibility to one or more antiviral drugs. This is a send out laboratory assessment at MUSC. All send our reports for patients in this study will be reviewed for possibility of resistance.[23,24] We will capture and report the type of resistance in terms of the specific mutations and which agents are likely to incur resistance based on these gene variants.[23]

Additional Measures

14. BK Infection (Exploratory Outcome) – defined as BK viremia of at least 2,000 copies/mL. Severe BK infection will be defined at BK viremia of at least 10,000 copies/mL. BK nephropathy will be defined based on the pathology report from the kidney allograft biopsy. The severity and duration of BK infection will be recorded for all patients.[24]

15. Non-CMV, Non-BK Infections (Exploratory Outcome) – defined as any diagnosed and treated infection that leads to hospitalization, and will be sub-classified as bacterial, viral, or fungal etiologies. Opportunistic infections will also be sub-classified for this study as viral, bacterial, or fungal and defined as infections not seen in immunocompetent individuals. The study coordinator capturing clinical event data will review the medical record to determine the timing, severity, treatment regimen and cure time of each infection episode.

16. Healthcare Utilization (Secondary Outcome) – each encounter will be captured during the 12-month study and classified as hospitalizations, ED visits, ambulatory care visits, ambulatory care procedures, radiology encounters, televisits, telephone calls, and laboratory encounters. Only MUSC encounters will be captured. Data will be analyzed based on utilization type and provider type (Transplant vs. Other). Healthcare charges will be captured from MUSC hospital accounting. Charges will be converted to estimated costs using the Medicare Cost-to-Charge Ratio (CCR) for MUSC.[25] This endpoint will be assessed at 3-, 6-, and 12-months post-transplant.

17. Health-Related Quality of Life (Exploratory Outcome) – the PROMIS QOL will be used to assess health-related quality of life. This questionnaire will be administered to patients at 3-, 6-, and 12-months post-transplant. Results will be compared between study arms.

18. Patient Satisfaction (Exploratory Outcome) – a validated survey provided by will be used to assess patient experience and satisfaction. This instrument will be administered at 3-, 6-, and 12-months post-transplant.

5.0 Inclusion and Exclusion Criteria/ Study Population

Inclusion Criteria

1. Kidney transplant recipient at study institution
2. ≤7 days of transplant
3. Received at least one dose of rATG induction or patient is D+/R- CMV serostatus
4. Persons with impaired decision making

Exclusion Criteria

1. Age <18 years at time of transplant
2. Recipient of pancreas, liver, heart, lung transplant

3. Recipient of investigational, non-FDA approved medication

6.0 Number of Subjects

70 patients will be randomized 1:1 (35 in each arm) in blocks of 10. Once a patient is randomized and receives at least one dose of CMV prophylaxis medication they will be included in the study in an intent-to-treat manner. Those that are lost to follow-up, withdraw, or are taken off study drug will not be replaced.

7.0 Setting

There will be one study site, the Medical University of South Carolina Kidney Transplant Center. The MUSC IRB will review and approve the study and protocol. Patients will be screened, approached, consented, and randomized prior to discharge from the hospital for their kidney transplant event on 6E or during a routine clinic appointment (9^{th} floor RT) as long as it is within 7 days of transplant.

8.0 Recruitment Methods

Each weekday, the study coordinator will review the kidney transplant roster to determine new patients that received a transplant within the past 24 to 72 hours. The coordinator will screen each patient to determine if they meet inclusion and exclusion criteria and review with the study team prior to approaching for consent.

9.0 Consent Process

Patients that are screened and meet criteria will be approached by study personnel for informed consent within 7 days of kidney transplantation. This may occur during the index hospitalization for the transplant or during a routine clinic follow-up in the ambulatory care setting. The MUSC IRB approved consent form will be reviewed with each patient. The study rationale and all study-related interventions and procedures will be reviewed with the potential participant. All questions will be answered, and patients will be given adequate time to review the information, including the consent documentation. Participation is completely voluntary, and patients will be informed of the usual process should they not care to be involved in this study.

Persons that have impaired decision making may be included in this study. These patients will be provided with the same information provided all patients, but this information will be discussed in detail with both the patient and their legal representative that has the authority to make medical decisions for the patient.

10.0 Study Design / Methods

This will be a 12-month, single-center, open-label, randomized controlled clinical trial enrolling 70 total patients (35 in each arm). Given the limited sample size and single center design, this is a small, exploratory trial with limited power to detect significant differences between treatment arms for rates of CMV infection and other clinical endpoints (acute rejection, graft loss, death). The study is powered to detect clinically meaningful and statistically significant differences in the incidence of leukopenia accompanied by a reduce in total mycophenolate dose or valganciclovir dose (see power/sample size section). Patients will be randomly assigned to receive valganciclovir

900mg PO daily (this is considered standard usual care, adjusted for renal function) for 3-6 months post-transplant (based on CMV D/R serostatus as detailed below) or maribavir 400mg PO BID for 3-6 months post-transplant (based on CMV D/R serostatus as detailed below) + acyclovir 400mg PO BID for 1-month post-transplant (investigation arm, the addition of acyclovir to maribavir is considered standard usual care for HSV prophylaxis). Patients that are D+/R- will receive 6 months of prophylaxis, while all other CMV serostatuses will receive 3 months of prophylactic therapy (per MUSC usual care CMV protocol). All other medications, including immunosuppression and additional anti-infective prophylaxis, will be per standard usual care. All follow-up laboratory assessments and clinic visits will occur as per usual care as well. The only additional procedure specific to this study is that patients will be self-administered two surveys at 3, 6, and 12-months post-transplant, which can be completed online during a routine clinic visit or at home. There will be no visits conducted solely for this research study.

Data collection will be as follows: Baseline data will include sociodemographics, comorbidities, serologies, donor information and transplant characteristics. Follow-up data will include induction therapy, immunosuppression type, dosing and levels, laboratory data, biopsy pathology reports, infection type and severity, hospitalizations and cause, ED visits and cause, allograft function, graft loss and death. All data will be gathered in a comprehensive manner using both electronic and manual chart abstraction. There are no study-specific procedures that will be conducted. All follow-up data that is accessible in the MUSC electronic medical record (EMR) will be gathered, curated, aggregated, and analyzed. Both MUSC and external non-MUSC labs are entered into the EMR. All acute rejections are confirmed by biopsy and pathology reports available in the EMR. All graft loss and death events are also documented in the EMR. Clinically significant infections, particularly CMV, are also well-documented in the MUSC EMR. Hospitalizations and ED visit within MUSC will be captured; however, non-MUSC outside hospitalizations and ED visits will not be accessible for this study. Below is a table outlining key follow-up time periods and data elements collected during these times.

Assessments		**Pre-transplant**	**Day Post-transplant**							**Week Post-Txp**		**Month Post-transplant**		
Time Frame			1	2	3	4	5	6	7	2	4	3	6	12
RANDOMIZATION			X											
History and Physical[1]		X							X		X	X	X	X
Vital Signs		X	X			X			X	X	X	X	X	X
Serologies[2]		X												
Laboratory Assessment	CBC and BMP	X	X			X			X	X	X	X	X	X
	Tacrolimus levels				X				X	X	X	X	X	X
CMV Infection Assessment									X		X	X	X	X
Clinical assessment[3]									X	X	X	X	X	X
HRQOL PROMIS Survey												X	X	X
QualityMetric Patient Satisfaction Survey												X	X	X

Foot notes:
1. Within 48 hours of transplant
2. Includes testing for CMV, Epstein-Barr, hepatitis B & C and HIV for donor and recipients
3. Includes assessments of adverse events, antiviral drug doses, allograft rejection, infection, need for dialysis, hospitalization, ED visits, graft loss, and all immunosuppressant medications and doses

Statistical Methods

The analyses to assess for study Aims will be conducted using standard and widely accepted statistical methods. Data will be reported using percentages for nominal variables and univariate comparisons using Fisher's exact test or Pearson's chi-squared test as appropriate. This includes baseline demographics and transplant characteristics, as well as the non-time to event outcome

variables. For continuous variables with normal distribution, results will be reported using means and standard deviations with univariate statistical comparison using Student's t-test for two independent samples. For non-normally distributed variables, data will be reported using medians and interquartile ranges, with univariate statistical comparison conducted using the Mann Whitney U test. Normal distribution of continuous variables will be assessed using normality plots and the Shapiro-Wilk test. Normal variance will be assessed using Levene's test for equality of variances. Chi square or Fisher's exact test will be used for univariate assessments of key outcomes, including the incidence of leukopenia, neutropenia, CMV antiviral prophylaxis dosing interruption, CMV infection, acute rejection, graft loss and death.

If necessary, multivariable analysis assessments for Aims 1 and 2 will be conducted using Cox regression time to event models. The primary variable of interest in these models will be treatment (maribavir vs. valganciclovir). If necessary and appropriate given event rates, Cox regression analysis will also be used for survival analyses involving all time to event outcomes, including time to acute rejection, time to graft loss and time to death. Models will be adjusted for key variables known to influence outcomes, including CMV serostatus and rATG induction. To prevent overfitting, no more than one covariate for every 5 events will be included in these models. Given the small sample size and expected event rates, Cox models will likely be overfit if including >2 covariates plus the primary treatment variable. Thus, multivariable modeling will be limited to only include key baseline variables that are known to influence the risk of CMV infection and that significantly differ by treatment arm based on preliminary univariate analyses; this will most likely only include CMV D+/R- serostatus and/or rATG induction. Prior to conducting Cox regression, modeling assumptions will be assessed, including proportionality of hazards across treatment arms and assessing the optimal functional forms of non-dichotomous covariates.

For Aim 3, total hospital charges and healthcare utilization will be modeled using a validated method we have used in previous studies. This will be a two-part statistical models for zero-heavy continuous data. The general format of the suggested model in which we fit a logistic model for the probability of non-zero response and a conditional generalized linear model (GLM) for the mean response given that it is non-zero. We will consider several distributions for the GLM part (eg, log-normal, gamma and Weibull, zero-inflated negative binomial [ZINB]) and the best fitting model will be selected using Bayesian information criterion (BIC). Parameter estimates of percent change in total hospital charge per unit increase in the values of each covariate in the model and their 95% CI will be computed using SAS Proc FMM.[25]

For Aim 4, survey results will be aggregated using validated methods for each survey. The mean scores will be compared between treatment arms, as well as the mean change across the three measurement timepoints. Comparisons will be made using standard statistical tests based on the distribution of the results (Student's t-test for normal variance or the Mann-Whitney test for non-normally distributed data). Mean change will be assessed using general linear modeling (GLM) for repeated measures data with the appropriate link based on the distribution of the measures.

For Aim 5, interaction terms will be added to multivariable models (Cox regression or GLM) to assess if there are differences by race (race*treatment) or sex (sex*treatment). A p-value of <0.1 will be considered sufficient evidence of likely effect modification and the analysis will then be stratified by the appropriate variable (either race or sex) for a given outcome if there is in fact a significant interaction. Given the limited sample size, there is likely low power to detect statistically significant differences for this Aim; thus Aim 5 is considered exploratory in nature.

We will also assess for any impact of maribavir on tacrolimus dosing or trough concentrations. Steady-state stable doses of tacrolimus (mg/day) and whole blood trough concentrations will be assessed and compared in patients during maribavir therapy versus after completion of therapy. Changes will be compared between the treatment arms using difference in difference methodology to assess for drug-drug interactions. The level-normalized dose (dose needed to achieve a level of 8 ng/mL using linear proportions) will also be compared using difference-in-difference analysis. Finally, the proportion of patients in the maribavir arm that have more than a 10% change in level-normalized dose after discontinuing maribavir therapy will be collected and reported. These analyses are considered exploratory.

Power/Sample Size

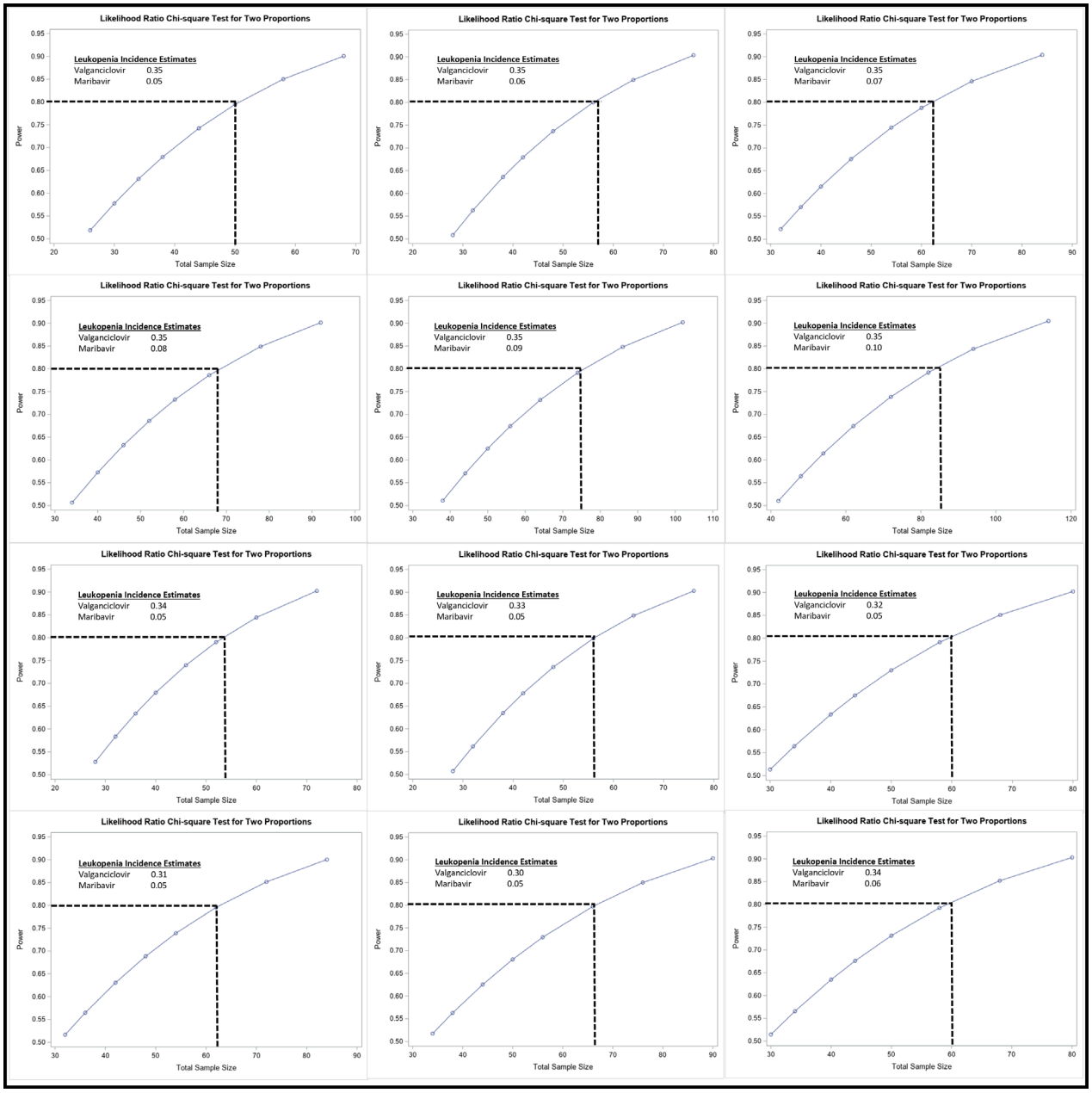
This study is adequately powered to detect a clinically meaningful and statistically significant difference in the incidence of clinically significant leukopenia in those randomized to maribavir vs. valganciclovir under most incident rate scenarios. For this study, clinically significant leukopenia is defined as a WBC count of <3,000 AND a reduction in the dose of mycophenolate or valganciclovir dose. Based on a retrospective analysis of internal data, the expected incidence of clinically significant leukopenia in the valganciclovir arm is between 33 and 35%. To support this incident rate, we conducted a retrospective analysis of our internal data to fully assess the incidence of clinically significant leukopenia. In this analysis, we included 446 adult kidney transplant recipients transplanted at MUSC between 2007 and 2015. We chose this time period as we had comprehensive data on induction, WBC counts, and MMF dosing to allow for assessment of the incidence of clinically significant leukopenia. Of these patients, 127 (28%) received rATG induction. The incidence of WBC <3K with and without MMF dose reduction is detailed in the table below, which was assessed within 1 year of transplant. This data matches our expected incidence of leukopenia in the VGC arm of 35%. This is because patients in the proposed study will be receiving rATG or be CMV D+/R- and receive 6-months of VCG/maribavir and be at higher risk of leukopenia.

Induction Agent	N	WBC <3K	WBC <3K and MMF Dose Reduction
Basiliximab	319	36.7%	21.3%
rATG	127	56.7%	34.6%

The incidence of clinically significant leukopenia (WBC <3K AND dose reduction in MMF) is difficult to assess in the maribavir arm, as this specific issue is not reported in the published data. However, there are several studies that can be used to estimate this incidence for power/sample size purposes. In a study conducted in liver transplant patients, known to be at higher risk for cytopenias than kidney recipients, the incidence of neutropenia was 6% in the maribavir arm (Winston DJ et al Am J Transplant 2012;12:3021-30.). In a phase III prophylaxis study in allogeneic stem-cell transplants, who are very high risk for cytopenias, the incidence of neutropenia was similar between the maribavir, and placebo arms and the average WBC count was 4.2K in the placebo arm and 4.4K in the maribavir arm (Papanicolaou GA et al. Clin Inf Diseases 2019;68:1255-64.). Thus, maribavir does not appear to induce or worsen leukopenia and a 5% incidence is a reasonable expectation in the maribavir treatment arm for estimating sample size and power.

To meet at least 80% power, given an incident rate of 33 to 35% in the valganciclovir arm and 5 to 6% in the maribavir arm, 32 patients in each arm is required, assuming two independent samples, a two sided α=0.05, and using the chi square test. This sample-size will be inflated to 35 patients per arm to address an expected dropout/lost to follow-up rate of 3-5% in each arm. Thus, 70 total patients, 35 in each arm, will provide adequate power to assess the primary aim of this study. SAS 9.4 (SAS Institute, Cary, NC) was utilized to conduct sample-size estimations (Proc Power).
For comprehensiveness, we conducted 17 different power/sample size analyses to assess different incident rates of clinically significant leukopenia in both the valganciclovir arm and maribavir arm. These ranged from 30-35% in the valganciclovir arm and 5-10% in the maribavir arm. The results are summarized in the table below. With a sample size of 70 patients, 35 in each arm, we have adequate power to determine statistically significant differences between arms in 71% of these incident rate scenarios. The figure below this table displays the varying power estimates from 0.5 to 0.95 based on the 12 most likely incident rate scenarios for leukopenia with valganciclovir and maribavir and the estimated required sample sizes needed for these power calculations. Based on these incident rate estimates, adequate power is achieved for sample sizes between 50 and 75 patients in these scenarios. Required sample sizes beyond 70 patients are not common and appear to depend more on higher rates of leukopenia in the maribavir arm (increasing above 7%) vs. lower rates of leukopenia in the valganciclovir arm (decreasing below 32%).

Incidence of Leukopenia in the Valganciclovir Group	Incidence of Leukopenia in the Maribavir Group	N Total	Actual Power	N Total with 5% Inflation Due to Dropouts	N Total with 3% Inflation Due to Dropouts
0.35	0.05	52	0.81	**55**	**54**
0.35	0.06	58	0.813	**61**	**60**
0.35	0.07	62	0.801	**66**	**64**
0.35	0.08	70	0.809	**74**	**73**
0.35	0.09	76	0.802	80	79
0.35	0.10	84	0.802	89	87
0.34	0.05	54	0.805	**57**	**56**
0.33	0.05	58	0.812	**61**	**60**
0.32	0.05	60	0.805	**63**	**62**
0.31	0.05	61	0.808	**65**	**63**
0.30	0.05	68	0.809	**72**	**71**
0.34	0.06	60	0.806	**63**	**62**
0.33	0.07	70	0.803	**74**	**73**
0.32	0.08	84	0.807	89	87
0.31	0.09	100	0.803	105	103
0.30	0.10	122	0.803	129	126
0.33	0.06	64	0.809	**68**	**66**



11.0 Specimen Collection and Banking (if applicable)

No specimens will be collected, banked, or analyzed specifically for this study. All clinical data, including laboratory results and biopsies, will be collected as part of usual care.

12.0 Data Management

Data capture will be accomplished using an electronic extraction and a study coordinator for manual chart abstraction. Data will be collected in a comprehensive longitudinal manner by review of the patient's electronic and paper medical records. Data collection will include all baseline donor/recipient demographics and transplant characteristics as well as longitudinal collection of medications, laboratory data and clinical events during

the post-transplant timeframe. The Research Electronic Data Capture (REDCap) system will be used for data management. REDCap is a secure, web-based application designed exclusively to support data capture for research studies. REDCap provides: 1) an intuitive interface for data entry (with data validation); 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages (SPSS, SAS, Stata, R); 4) procedures for importing data from external sources; and 5) advanced features, such as branching logic and calculated fields. The REDCap project (http://project-redcap.org/) was initiated at Vanderbilt University and includes more than 70 active institutional partners from CTSA, GCRC, RCMI funded institutions, including MUSC, and others through a collaborative international consortium.

13.0 Provisions to Monitor the Data to Ensure the Safety of Subjects

The terms adverse event (AE), serious adverse event (SAE), and adverse drug reaction (ADR), fatal, life threatening, disability, congenital anomaly, hospitalization, medically important, association with the use of drug, and unexpected adverse drug experience shall have the meaning as defined in 21CFR312.32, as detailed below.

Serious adverse event or serious suspected adverse reaction. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or unexpected suspected adverse reaction. An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the

pharmacological properties of the drug but are not specifically mentioned as occurring with the particular drug under investigation.

A Product Quality Issue (PQI) is defined as any defects related to the safety, identity, strength, quality, or purity of a medicinal product or with the physical characteristics, packaging, labeling, or design of a medicinal product.

Special Situation Report (SSR) is defined as any of the following events:

- Pregnancy: Any case in which a pregnant patient is exposed to a medicinal product or in which a female patient or female partner of a male patient becomes pregnant following treatment with a medicinal product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: Including any accidental or intentional overdose
- Drug abuse, misuse or medication error (potential or actual)
- Suspected (in the sense of confirmed or potential) transmission of an infectious agent: by a medicinal product.
- Lack of efficacy of a medicinal product
- Accidental exposure
- Use outside the terms of the marketing authorization, also known as “off-label” use
- Use of falsified medicinal product
- Unintended benefit

An SSR should be reported even if there is no associated AE.

Reporting Responsibilities:

As the sponsor of the Study, MUSC and/or the PI shall be solely responsible for reporting any and all serious and unexpected adverse drug experiences or other safety information associated with the use of the Study Drug to the applicable Regulatory Authorities, the IRB or IECs and any Other Investigators, as required by applicable laws and regulations, including 21CFR312.32 within the timelines required, and whether or not the Study is being performed under an IND.

a) MUSC and/or the PI must notify TAKEDA or its designee within one (1) working day of becoming aware of a fatal or life-threatening SAE, within four (4) calendar days for other SAEs, and within seven (7) calendar days for all other events/issues listed above. This is achieved by submitting an AE Report Form to TAKEDA’s Pharmacovigilance Department to PVSafetyAmericas@takeda.com.

b) MUSC and/or the PI may be contacted by TAKEDA or its designee to obtain additional information on an adverse event or for data clarification. MUSC and/or the PI shall use its best efforts to obtain the requested additional information and will notify TAKEDA or its designee within one (1) working day of obtaining the additional information for a fatal or

life-threatening SAE, within four (4) calendar days for other SAEs, and within seven (7) calendar days for all other events/issues listed above.

c) MUSC and/or the PI agrees to update the Protocol and the informed consent at the request of TAKEDA for safety-related reasons.

14.0 Withdrawal of Subjects

Participation in this study is completely voluntary. Patients may withdraw at any time during the study. Treating physicians or providers may also request patients are withdrawn from the study if there are any safety concerns with participation. Patients that withdraw will be asked if they are willing to allow the data already collected on them to be included in analyses. Inclusion in the data analysis is also completely voluntary. If patients are agreeable, patient data will be censored at the time of withdrawal and these patients will be included in the intent-to-treat analyses.

15.0 Risks to Subjects

As both maribavir and valganciclovir are FDA approved for the treatment of CMV infection, comparison of these therapies to prevent CMV infection (prophylaxis) in solid organ transplant recipients is not expected to induce undue harm or risk. There is the potential that either maribavir or valganciclovir prophylactic therapy may lead to reduced or improved safety and/or efficacy in preventing CMV infection; however, this has yet to be proven in the context of CMV prophylaxis in kidney transplant recipients. Thus, there is sufficient equipoise to conduct this clinical trial. Patients and outcomes will be closely monitored in both treatment arms during the conduct of this study. Given the small sample size, interim analyses will not be conducted unless requested by Takeda Pharmaceuticals or the MUSC IRB.

16.0 Potential Benefits to Subjects or Others

Given previous data, there is a strong possibility that those randomized to the maribavir arm will have similar efficacy with regards to preventing CMV infection, as compared to valganciclovir while also having lower rates of leukopenia that leads to reductions in mycophenolate dosing and/or valganciclovir therapy.

17.0 Sharing of Results with Subjects

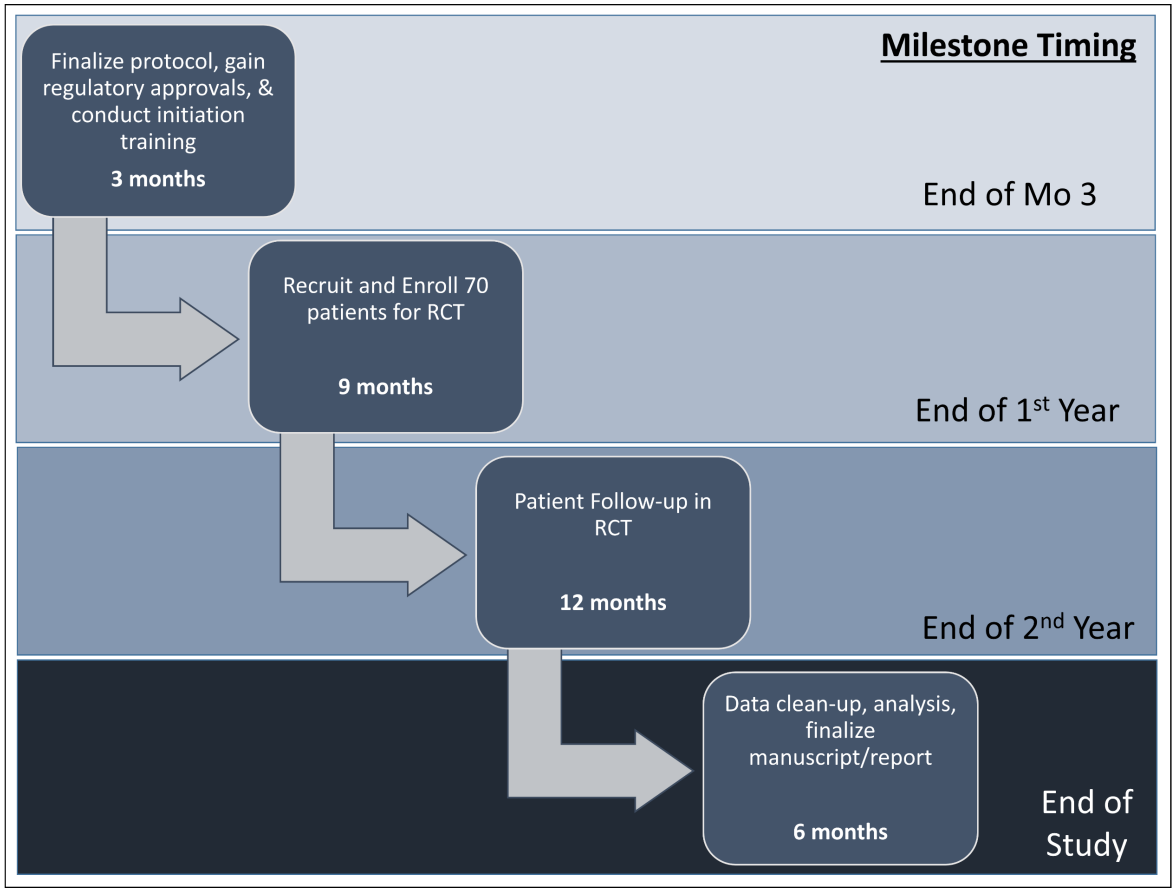
Results will be shared with participants after the study is complete. We will share results by updating the clinicaltrials.gov website with outcomes data and sharing the site with patients enrolled in the study. We will also share results to healthcare providers through presentation at transplant conferences and publication in peer reviewed journals.

18.0 Drugs or Devices

Valganciclovir is considered current gold-standard therapy to prevent CMV infection in transplant recipients. Those randomized to valganciclovir will receive it through usual care processes. The prescription will be filled by the Rutledge Tower Pharmacy or a pharmacy of the patient's choice and it will be billed to the patient's insurance. The patient will be responsible for any copays related to valganciclovir prophylactic therapy. Those randomized to the maribavir arm will receive both the maribavir and acyclovir through the study, dispensed by the MUSC Investigational Drug Services (IDS) at no charge to the patient. The research study coordinator will ensure the patient receives these medications, either by hand delivery to the patient or through mailing the medications to the patient.

19.0 Study Timeline

We propose to complete the entire proposal within 30-months of signing the contract, which includes completing the final study protocol and consent form, gaining FDA IND exempt status, gaining MUSC IRB approval, conducting personnel training and site initiation, opening the study, enrolling 70 patients, completing the 12-month follow-up for all 70 patients, completing data collection and completing data clean-up, data analysis and final study report. An outline of the specific milestones and timing of each is detailed in the figure below.



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