An open-label pilot protocol to evaluate the efficacy of letermovir for the prevention of human cytomegalovirus (CMV) infection and disease in adult lung transplant recipients with idiopathic pulmonary fibrosis

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1. Background
    a. General Information

Cytomegalovirus (CMV) is a significant opportunistic pathogen and a major cause of morbidity and mortality in solid organ transplant recipients. Lung transplant recipients (LTRs) are disproportionally affected by CMV as compared to other organ recipients, and the incidence of CMV infection in LTRs is close to 30% despite prophylaxis [1]. CMV infection in LTRs is associated with an increased risk of bronchiolitis obliterans syndrome and decreased survival [2-4].

Idiopathic pulmonary fibrosis (IPF) is currently the leading indication for lung transplantation, corresponding to about a third of all lung transplants performed [5]. IPF has been linked to genetic defects in telomerase and telomere length. In a previous study, we showed that 71% of IPF LTRs have significantly short telomeres. We also demonstrated that IPF LTRs have an increased incidence of CMV viremia and other CMV complications compared to age-matched non-IPF LTRs. The highest risk of CMV complications was seen in the subset of IPF LTRs who had short telomeres. Short telomeres were associated with significantly impaired CMV-specific proliferative responses, T-cell effector function, and induction of the major type-1 transcription factor T-bet (T-box 21;*TBX21*) [6].

Short telomere syndrome is associated with an increased risk of bone marrow complications in the form of cytopenias. Valganciclovir and ganciclovir, which are utilized for CMV prophylaxis in LTRs, are associated with bone marrow suppression. This combination leads to a disproportionate amount of bone marrow complications in IPF LTRs, which often leads to frequent start and stops of (val)ganciclovir or dose reductions, which may cause breakthrough CMV viremia or, even worse, development of ganciclovir-resistance, which is associated with worse outcomes [7].

The use of letermovir (LET), an anti-CMV agent without bone marrow toxicity, in IPF LTRs may lead to decreased CMV burden and be bone marrow sparing.

LET is currently approved for CMV prevention in allogeneic stem cell transplantation. A clinical trial is ongoing to evaluate its efficacy in the prevention of CMV in CMV donor positive/recipient negative (D+/R-) kidney transplant recipients. Data on prophylaxis in other organ transplant recipients is lacking. An abstract at the American Transplant Congress this year described the experience

with LET in 46 thoracic transplant recipients, including 39 LTRs. Patients who received LET for primary prophylaxis were transitioned from valganciclovir at a median of 510 days post-transplant, primarily due to myelosuppression. No patient received LET prophylaxis as first-line therapy. There was no virologic failure with LET when used for prophylaxis [8].

We currently measure telomere length, and telomerase and telomere gene variance on all IPF patients listed for lung transplantation. After the completion of this protocol we will be able to characterize these patients extremely well. We will have their telomere data, CMV immune responses, bone marrow function, renal and liver function, and CMV data. We believe we will have enough data to show that in IPF LTRs LET reduces the burden of CMV and is bone marrow sparing, therefore creating the foundation for a larger study with valganciclovir as the comparator arm.

2. Hypothesis and Objective
    a. Hypothesis

Our hypotheses are:

1) LET is effective for the prevention of CMV infection and disease following lung transplantation for IPF in patients who are CMV D+/R- and in patients who are CMV recipient positive (CMV R+)
2) Impaired CMV immunity correlates with an increased risk of CMV DNAemia and disease after discontinuation of prophylaxis
3) LET is well tolerated, and bone marrow sparing in LTRs with IPF

    b. Potential Risks and Benefits
        i. End points – Efficacy

1) Proportion of LTRs with IPF with CMV infection or disease during LET prophylaxis. This will be compared to the proportion of CMV infection or disease in historical LTRs with IPF who received valganciclovir prophylaxis
2) Proportion of LTRs with IPF with CMV infection or disease in the 3 months following completion of prophylaxis with LET. This will be compared to the proportion of CMV infection or disease in the 3 months following in historical LTRs with IPF who received valganciclovir prophylaxis.

a. Definition of CMV infection: evidence of CMV replication without symptoms, defined as detection of CMV DNA in plasma or whole blood[9].
b. Definition of CMV disease: evidence of CMV infection with attributable symptoms. It can be further characterized as CMV viral syndrome or tissue invasive disease. Tissue invasive disease will be characterized by the specific type of tissue invasive disease (eg. hepatitis, pneumonitis, colitis, etc) and as proven or probable CMV tissue invasive disease[9].

i. End points – Safety

1) Tolerability of LET:

a. Discontinuation events: This will be compared to discontinuation of valganciclovir in historical controls.
b. Proportion of participants who develop any of the following while receiving LET: total WBC count ≤ 3,500 cells/mL or absolute neutrophil count ≤ 1,000 cells/mL. This will be compared to the rate of total WBC count ≤ 3,500 cells/mL or absolute neutrophil count ≤ 1,000 cells/mL in historical controls while receiving valganciclovir prophylaxis.

b. Number of Subjects to be enrolled

Approximately 30 patients with IPF listed for lung transplantation will be enrolled and 15 are expected to undergo lung transplantation during the study period and receive the intervention.

c. Criteria for Recruitment

The lung transplant program at UPMC currently performs about 30 transplants a year in patients with IPF. We intend to enroll patients with IPF who are active on the lung transplant list and within the first 72 hours post-transplant. Our goal is to recruit 30 participants and, from those, 15 will undergo lung transplantation during the study period and meet inclusion/exclusion criteria at the time of transplant. We estimate that it will take 6 to 9 months to transplant 15 patients who will be CMV D+/R- or R+ and who meet inclusion/exclusion criteria.

d. Inclusion Criteria

1) Age ≥18 years on day of signing informed consent
2) Listed for lung transplantation (single or double) due to a diagnosis of IPF or receipt of a lung transplant (single or double) for IPF in the 72 hours prior to enrollment
3) Have a documented positive serostatus for CMV (CMV IgG seropositive, R+)
4) Have a documented negative serostatus for CMV (CMV IgG seronegative, R-) and anticipate receiving or having received a lung allograft from a CMV IgG positive donor, D+). Only participants who are R+ or who are CMV D+/R- will receive intervention. Participants who are CMV D-/R- will be considered screen failures
5) Able to travel to UPMC for routine post-transplant visits for a minimum of 15 months after transplantation
6) Able to provide informed consent
7) Be willing to use a contraceptive method while receiving LET and for at least 90 days following last dose of LET

e. Exclusion Criteria

1) Receipt of a previous solid organ transplant or hematopoietic stem cell transplant
2) Multi-organ transplant recipient, i.e., heart-lung or lung-liver
3) HIV seropositive
4) HCV antibody or HCV RNA positive
5) Donor HCV NAT positive
6) Anticipated need for use of ganciclovir, valganciclovir, foscarnet, or cidofovir at the time of transplant
7) Known or suspected hypersensitivity to LET or acyclovir
8) CrCl < 10 ml/min or dialysis on day of transplant
9) Child-Pugh Class C severe hepatic insufficiency
10) Pregnancy or expected to conceive while on LET and through at least 90 days following cessation of LET

f. Withdrawal Criteria

A participant must be withdrawn from the study if the participant or participant's legally authorized representative withdraws consent from the study. If a

participant withdraws from the study, they will no longer receive study treatment or be followed at scheduled protocol visits.

g. Subject Replacement

A participant who discontinues from the study will not be replaced.

3) Trial Schedule

a. Study Design

This is an interventional, open-label, single center, pilot study with historical controls to test the efficacy of LET for the prevention of CMV infection and disease in adult LTRs with IPF.

Approximately 30 patients with IPF listed for lung transplantation will be enrolled and 15 are expected to undergo lung transplantation during the study period and receive the intervention. Historical controls will be LTRs for IPF from 2010-2019 who are CMV R+ or CMV D+/R-. CMV prophylaxis in the historical controls was with valganciclovir for 6 months for CMV R+ and for 12 months for CMV D+/R-. Patients will be matched for CMV serostatus, induction immunosuppression, age, and telomere length.

Participants who are CMV R+ will receive LET prophylaxis for 6 months, and participants who are CMV D+/R- will receive LET prophylaxis for 12 months. The duration of prophylaxis is per current standard of care. LET will be administered at a dose of 480 mg IV or oral once daily. IV administration will occur only for those patients unable to swallow tablets. If LET is co-administered with cyclosporine A (CsA), the dosage of LET should be decreased to 240 mg once daily. All patients will be followed for 12 weeks after completion of LET for the occurrence of CMV infection or disease after prophylaxis.

Induction and maintenance immunosuppression, and antifungal and *Pneumocystis* prophylaxis will follow institution's protocol. Induction therapy is with alemtuzumab for CMV R+, and with basiliximab for CMV D+/R- and those with a previous history of malignancy. Standard immunosuppression consists of tacrolimus, mycophenolate mofetil and prednisone. Participants on this protocol will receive acyclovir 400 mg orally BID for the duration of LET therapy for herpes simplex virus and varicella zoster virus prophylaxis.

CMV immune response will be assessed at baseline immediately after transplant, half-way through LET administration, at the end of LET administration, when the patient develops CMV infection or disease, and at the end of study. The following assays will be performed at each of the specified time points.

- CMV T-cell effector response assays: will evaluate peripheral blood mononuclear cell responses to *in vitro* stimulation with pooled overlapping peptides of phosphoprotein 65 (pp65) and immediate early Ag-1 (IE1) and CMV lysate in addition to unstimulated cells and Staph Enterotoxin B (SEB); positive control . Will measure pp-65 specific IFN-g, TNF-a, the cytotoxic degranulation marker CD107a, and loading of the cytotoxic molecule Granzyme B (GrzB) in $CD8^+$ T cells in an ex vivo 6-hour assay. Will also evaluate CMV-specific CD4+ effector responses to these antigens.
- CMV T cell phenotyping: Using a pool a 10 CMV HLA class I dextramers that span the HLA of 85% of patients (Hoji et al), we will perform T cell phenotyping to key markers such as KLRG1, CD57, PD1, CD27, CD28, CD45 RA/RO and other markers to assess CMV T cell phenotypes.
- CMV-specific T cell proliferation: We will assess 6-day CMV proliferative responses in response to pp65 and IE1[6, 10].

4) Methods and Assessment
    a. Study Visits and Procedures

CMV PCR will be measured following the schedule of our lung transplant program standard of care protocol: at least monthly while on prophylaxis and at least biweekly x 12 weeks once prophylaxis is discontinued. CMV PCR will be performed at CLIA-certified laboratories and reported in IU/ml.

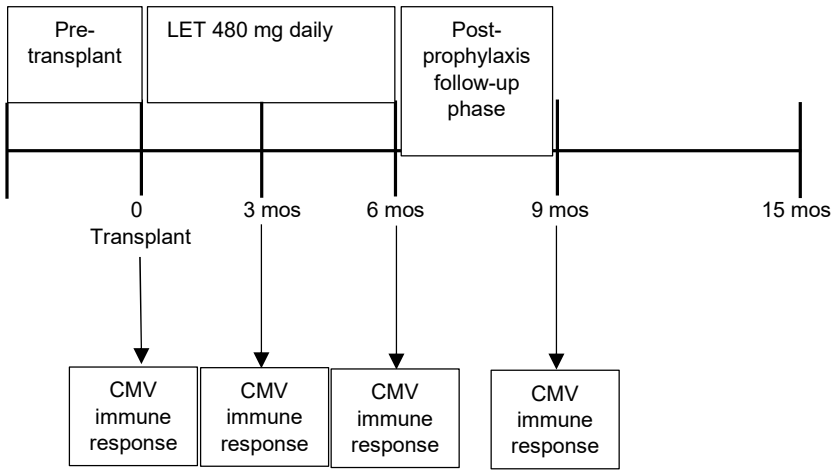
CMV immune response will also be assessed if patient develops CMV infection/disease.

Complete blood count and comprehensive metabolic panel are performed at least monthly.

All laboratory tests will be performed at CLIA-certified laboratories. These tests will be done as part of routine clinical care and the choice of laboratory will be

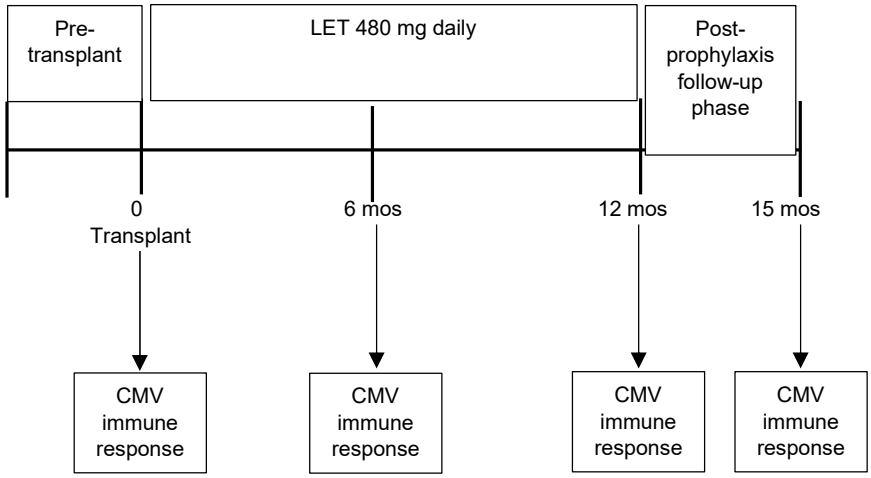
according to patient's preference. CMV immune response assays will be performed at Dr. John McDyer's research laboratory at the University of Pittsburgh.

CMV R+ LTRs:



CMV immune response will also be assessed if patient develops CMV infection/disease.

CMV D+/R- LTRs:



CMV immune response will also be assessed if patient develops CMV infection/disease.

Screening visit – anytime from transplant listing at UPMC until 72h post-transplant:

The study procedures in the screening period will include:

- Informed consent
- Inclusion/exclusion criteria
- Medical history
- Current medications, therapies, and procedures
- Review of CMV serology of donor and recipient (clinical test)
- Creatinine and liver enzymes (clinical test obtained within 3 months prior to informed consent is acceptable)
- Participants will be instructed that they are required to use birth control, starting from the time of consent through 90 days after the last dose of LET

Prior to first dose administration of LET:

The study procedures prior to the first dose administration of LET will include:

- Current medications, therapies, and procedures
- Review of donor and recipient serology
- Complete blood count, creatinine and liver enzymes
- Pregnancy test (urine or serum) for all females of childbearing potential

Patients will receive the first dose of LET within 72h of lung transplantation. Valganciclovir/ganciclovir, if initiated by the clinical team, will be discontinued prior to first dose of LET.

The screening and prior to first dose administration of LET visits can occur at the same time.

CMV prophylaxis phase – LET administration:

The study procedures during the LET administration phase will include:

- Liver enzymes every other week for the first 12 weeks, then monthly
- Complete blood count weekly for the first 8 weeks, then monthly

- Creatinine weekly for the first 8 weeks, then monthly
- CMV PCR per standard protocol at UPMC, no more than weekly and at least monthly, and during any symptomatic or clinically indicated time
- CMV immune response assays within 72 h of first dose of LET, halfway through LET prophylaxis. CMV immune assays will be performed as detailed above and previously described [6, 10]
- Adverse event assessment on weeks 1 and 2, then monthly
- Medications, therapies, and procedures monthly
- Confirmation that participant and his/her partner are using acceptable methods of contraception monthly
- Assessment of graft function monthly
- Assessment of patient survival monthly

LET administration will be for 6 months for patients who are R+ and 12 months for CMV D+/R-, as per current standard of care protocol at UPMC's lung transplant program. Patients will receive acyclovir 400 mg PO BID while on LET for HSV/VZV prophylaxis.

Patients with CMV DNA detection ≥ 1,000 IU/ml while receiving LET will undergo detection of UL56 mutation. Sample will be sent to Viracor.

End of prophylaxis with LET:

The study procedures at the end of LET administration phase will include:

- Liver enzymes
- Complete blood count
- Creatinine
- CMV PCR
- CMV immune response assays
- Adverse event assessment
- Medications, therapies, and procedures
- Confirmation that participant and his/her partner are using acceptable methods of contraception
- Assessment of graft function
- Assessment of survival

Post-LET follow-up phase:

The study procedures in the post-prophylaxis follow-up phase will include:

- CMV PCR no more than weekly and at least biweekly, and during any symptomatic or clinically indicated time
- Complete blood count, creatinine, and liver enzymes monthly
- CMV immune response assay
- Adverse event assessment monthly
- Medications, therapies, and procedures monthly
- Confirmation that participant and his/her partner are using acceptable methods of contraception monthly
- Assessment of graft function monthly
- Assessment of patient survival monthly

The following medications will be prohibited during LET administration: valganciclovir, ganciclovir, foscarnet, and cidofovir, except for cidofovir for treatment of severe adenovirus disease.

The concomitant use of LET with certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions or reduced therapeutic effect of LET or the concomitant drug. If oral or intravenous LET is co-administered with CsA, the dosage of LET will be decreased to 240 mg once daily. Concomitant medications will be reviewed by one of the investigators and steps to prevent or manage possible or known significant drug interactions will be followed as suggested in the Prevymis™ Package Insert[11] and summarized in appendix A. Participants will be monitored for adverse reactions associated with LET and concomitant medications.

5) Trial Material
    a. Trial Product

Letermovir (Prevymis) 240 mg and 480 mg tablets, injection 20 mg/ml

    b. Storage and Drug Accountability

Trial product will be stored and dispensed by the Investigational Drug Service (IDS). IDS can develop protocol specific accountability logs or it can use the sponsor's accountability logs. If the sponsor accountability logs do not have a running total, IDS will u lize a secondary log for running totals of study drug.

6) Treatment

a. Rationale for Selection of Dose

Selected dose follows the recommendations of the package insert.

b. Study Drug Formulations

240 mg and 480 mg tablets, injection 20 mg/ml

c. Study Drug Administration

LET will be administered at a dose of 480 mg orally or intravenously (IV) once daily. LET will be used IV only in patients unable to take oral therapy. Patients will be switched to oral LET as soon as they are able to take oral medications. It is anticipated that administration in the first 24-72h post-transplant will be IV, until extubation and clearance for oral intake. If oral or IV LET is co-administered with CsA, the dosage of LET will be decreased to 240 mg once daily. If CsA is initiated after starting LET, the next dose of LET will be decreased to 240 mg once daily. If CsA is discontinued after starting LET, the next dose of LET will be increased to 480 mg once daily. If CsA dosing is interrupted due to high CsA levels, no dose adjustment of LET will be needed.

7) Safety Measurements

a. Definitions

The patient population under study is complex. For this study, AEs will be reported only if study related or unexpected. For this study, a reportable adverse event is defined as:

- Any clinically important untoward medical occurrence in a subject receiving study drug that is different from what is expected in the clinical course of a patient with a lung transplant (see appendix B for events considered to be part of the expected course of lung transplant) OR

- Any clinically important, untoward medical occurrence that is thought to be related to the study drug, regardless of the "expectedness" of the event for the course of a patient with a lung transplant. Expected events for lung transplant are untoward clinical occurrences that are deemed by the investigator to occur with reasonable frequency in the day-to-day care of patients with a lung transplant (see appendix B for events considered to be part of the expected course of lung transplantation)

b. Collection, Recording and Reporting of Serious Adverse Event (SAE/Safety/Suspected Unexpected Serious Adverse Reaction (SUSAR)

All reportable AEs will be captured in the case report form. The following information will be collected: event description, time of onset, clinician's assessment of severity, and time of resolution/stabilization of the event. Reportable AEs occurring while on study will be documented appropriately and will be followed to resolution or stabilization. The determination of seriousness and severity of an AE will be made by an investigator who is qualified (licensed) to diagnose AE information, provide a medical evaluation of AEs, and classify AEs based upon medical judgment. This is a small study in a critically ill population, therefore relationship of AEs to study product will not be assigned.

Lung transplant recipients represent a critically ill population in whom a high rate of untoward medical events is commonly seen during the routine post-transplant course as part of their underlying medical condition, transplant surgery or postoperative state. In an effort to document only clinically-relevant untoward medical events that have a greater likelihood of being study-related, rather than the normal course of lung transplantation, study endpoints and certain pre-specified expected events commonly seen in this population (see appendix B for list of expected events for lung transplant recipients) will not be reported as serious adverse events (SAEs) even if they meet serious event criteria. Reportable SAEs for this study will be adverse events that are serious and unexpected, i.e., not expected to occur with a reasonable frequency in the typical course of a patient following lung transplant (appendix B). Death will be recorded in the CRF

although it will not be a reportable SAE unless it meets the study's reportable criteria of related and/or unexpected (see appendix B for list of expected events for lung transplant recipients). Reportable SAEs will be recorded on appropriate CRF, followed through resolution by a study clinician, reviewed and evaluated by a study clinician.

c. Pregnancy and Exposure During Breastfeeding

No adequate human data are available to establish whether letermovir poses a risk to pregnancy outcomes. In animal reproduction studies, embryo-fetal developmental toxicity (including fetal malformations) was observed in rats during the period of organogenesis at letermovir exposures (AUC) 11 times higher than human exposure at the recommended human dose. In rabbits, no embryo-fetal developmental toxicity was noted at exposures that were not maternally toxic (up to letermovir exposures 2 times higher than human exposure at the recommended human dose). In a rat pre/post-natal development study, total litter loss was observed at maternal letermovir exposures approximately 2 times higher than human exposure at the recommended human dose.

The background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively[11].

Although pregnancy and infant exposure during breastfeeding are not considered adverse events, any pregnancy or infant exposure during breastfeeding in a participant while receiving LET or within 90 days of receipt of the last dose of LET, including the pregnancy of a male participant's female partner, will be captured in the case report form. All reported pregnancies will be followed to the completion or termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, fetal death, intrauterine death, miscarriage, and stillbirth will be reported as serious events. If the pregnancy continues to term, the outcome will be captured.

d. Safety Monitoring Plan

The principal investigator will have oversight of the DSMP. The principal investigator, co-investigators, and primary research coordinator will meet monthly.

Attendance by an investigator with expertise in Transplant Infectious Diseases will be mandatory. The following elements will be reviewed at the meetings:

- Overall study progress, including recruitment and retention
- Adverse events, unanticipated problems, and subject withdrawals. An assessment of any change to the anticipated benefit-to-risk ratio of study participation will be made and, based on that, it will be determined if the study should continue as originally designed, should be changed, or should be terminated.
- Assessment of new pertinent scientific literature or therapeutic developments that may have an impact on the safety of study participants or the ethics of this research protocol
- Breaches of confidentiality and procedures to protect the privacy of research subjects and confidentiality of research data

Any unanticipated events or reportable adverse events will be reported to the University of Pittsburgh IRB as per its current policies. A summary of the DSMP meetings and its findings will be provided to the IRB yearly, at the time of study renewal.

e. Complaint Handling

Any concerns raised by participants will be answered by the investigators and, if not resolved, will be referred to the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh.

8) Sample Size and Statistical Methods

a. Determination of Sample Size

The incidence of CMV infection and disease in LTRs is approximately 30%. It is higher in IPF LTRs, particularly in those with short telomeres. Seventy percent of our IPF LTRs have short telomeres. This pilot, single arm, exploratory study will use a convenience sample to estimate the frequency of CMV infection and disease in the target population. A sample size of 10 to 30 is usually suggested for pilot studies and it is estimated that the UPMC transplant numbers will provide a sufficient sample size of n=15.

Approximately 85 lung transplants are performed per year at UPMC. Thirty patients will be consented, of which we estimate 15 will undergo lung transplantation and receive LET prophylaxis.

The results of this study will generate foundational data to examine the efficacy of LET in future studies with a larger sample size and more comprehensive protocols.

b. Statistical and Analytical Plans

This is an exploratory pilot study to generate preliminary data on the efficacy of LET prophylaxis in lung transplant recipients and support future hypothesis testing studies based on those data. As such, descriptive non-parametric statistics will be used to characterize the study population and outcomes, including means and medians for continuous measures, frequencies for count data, standard deviations, and interquartile ranges for variance. This analysis will be applied to both the LET prophylaxis and post-prophylaxis periods. Regression analysis will be used to find predictors of outcomes. Differences in proportions in the group receiving LET and historical controls will be compared with Fisher's exact test.

9) Ethical Considerations

a. Informed Consent

The process of obtaining informed consent will be documented in the medical records, clinic chart, and/or research chart. The consent form must be signed and dated by the study participant or legal guardian before participation in the study. A copy of the signed consent form must be provided to the study participant or legal guardian. Signed consent forms must remain in each study participants study file and must be available for verification at any time. Informed consent will be obtained by a physician.

b. IRB Review

This protocol will be reviewed by the University of Pittsburgh Institutional Review Board.

10) Schedule of study procedures:

Schedule of study procedures: R+ LTR

	Screening	Prior to 1st dose of LET																												
Study week/month/year	**Any time prior to transplant until 72h post-transplant**	**0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24 (EOT)**	**Wk 25**	**Wk 26**	**Wk 27**	**Wk 28**	**Wk 29**	**Wk 30**	**Wk 31**	**Wk 32**	**Wk 33**	**Wk 34**	**Wk 35**	**Wk 36**
Informed consent	X																													
Inclusion/exclusion criteria	X																													
Medical history	X																													
Current medications, therapies and procedures	X	X																												
Review of CMV serology of donor and recipient	X	X																												
Complete blood count		X	X	X	X	X	X	X	X	X				X	X	X	X				X				X				X
Creatinine	X	X	X	X	X	X	X	X	X	X				X	X	X	X				X				X				X
Liver enzymes	X	X	X		X		X		X		X		X		X	X	X				X				X				X
Pregnancy test		X																												

CMV PCR			X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
UL56 mutation detection			**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**	**X[a]**													
CMV immune response assays			**X**											**X**			**X**												**X**
Adverse event assessment			X	X		X				X				X			X				X				X				X
Medications, therapies, and procedures						X				X				X	X	X	X				X				X				X
Assessment of graft function						X				X				X	X	X	X				X				X				X
Assessment of survival						X				X				X	X	X	X				X				X				X

a: only obtained once and if CMV PCR ≥ 1,000 IU/ml
Bold: performed for study purposes only

Schedule of study procedures: D+/R- LTR

	Screening	Prior to 1st dose of LET																																		
Study week/month/year	**Any time prior to transplant until 72h post-transplant**	**0**	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Wk 8**	**Wk 9**	**Wk 10**	**Wk 11**	**Wk 12**	**Wk 16**	**Wk 20**	**Wk 24**	**Mo 7**	**Mo 8**	**Mo 9**	**Mo 10**	**Mo 11**	**Mo 12 (EOT)**	**Wk 53**	**Wk 54**	**Wk 55**	**Wk 56**	**Wk 57**	**Wk 58**	**Wk 59**	**Wk 60**	**Wk 61**	**Wk 62**	**Wk 63**	**Wk 64 (15 mo)**
Informed consent	X																																			
Inclusion/ exclusion criteria	X																																			
Medical history	X																																			
Current medications, therapies and procedures	X	X																																		
Review of CMV serology of donor and recipient	X	X																																		

Complete blood count		X	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X				X				X				X
Creatinine	X	X	X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X				X				X				X
Liver enzymes	X	X	X		X		X		X		X		X		X	X	X	X	X	X	X	X	X				X				X				X
Pregnancy test		X																																		
CMV PCR			X	X	X	X	X	X	X	X				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
UL56 mutation detection			**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]	**X**[a]													
CMV immune response assays			**X**														**X**						**X**													**X**
Adverse event assessment			X	X		X				X				X			X	X	X	X	X	X	X				X				X				X
Medications, therapies, and procedures						X				X				X	X	X	X	X	X	X	X	X	X				X				X				X
Assessment of graft function						X				X				X	X	X	X	X	X	X	X	X	X				X				X				X
Assessment of survival						X				X				X	X	X	X	X	X	X	X	X	X				X				X				X

a: only obtained once and if CMV PCR ≥ 1,000 IU/ml
Bold: performed for study purposes only

11) Publications

1. Avery RK, Silveira FP, Benedict K, et al. Cytomegalovirus infections in lung and hematopoietic cell transplant recipients in the Organ Transplant Infection Prevention and Detection Study: A multi-year, multicenter prospective cohort study. Transpl Infect Dis **2018**; 20(3): e12877.
2. Kerschner H, Jaksch P, Karigl G, Popow-Kraupp T, Klepetko W, Puchhammer-Stockl E. Cytomegalovirus DNA load patterns developing after lung transplantation are significantly correlated with long-term patient survival. Transplantation **2009**; 87(11): 1720-6.
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APPENDIX A: POTENTIALLY SIGNIFICANT DRUG INTERACTIONS WITH CO-ADMINISTRATION WITH LETERMOVIR AND RECOMMENDED MONITORING AS INDICATED IN THE PREVYMIS™ PRESCRIBING INFORMATION

Concomitant Drug	Effect on Concentration	Comments
Anti-arrhythmic agents		
Amiodarone	↑ amiodarone	Close clinical monitoring for adverse events related to amiodarone is recommended during co-administration. Frequently monitor amiodarone concentrations when amiodarone is co-administered with LET
Antibiotics		
Nafcillin	↓ letermovir	Co-administration of LET and nafcillin is not recommended due to potential for loss of efficacy of LET
Anticoagulants		
Warfarin	↓ warfarin	When LET is co-administered with warfarin, frequently monitor International Normalized Ratio (INR)
Anticonvulsants		
Carbamazepine	↓ letermovir	Co-administration of LET and carbamazepine is not recommended due to potential for loss of efficacy of LET
Phenobarbital	↓ letermovir	Co-administration of LET and phenobarbital is not recommended due to potential for loss of efficacy of LET
Phenytoin	↓ letermovir ↓ phenytoin	Co-administration of LET and phenytoin is not recommended due to potential for loss of efficacy of LET
Antidiabetic agents		
Glyburide, repaglinide, rosiglitazone	↑ glyburide ↑ replaglinide ↑ rosiglitazone	When LET is co-administered with glyburide, repaglinide, or rosiglitazone, frequently monitor glucose concentrations. When LET is co-administered with CsA, use of repaglinide is not recommended.
Antifungals		

Voriconazole	↓ voriconazole	If concomitant administration of voriconazole is necessary, closely monitor for reduced effectiveness of voriconazole.
Antimycobacterials		
Ribabutin	↓ letermovir	Co-administration of LET and rifabutin is not recommended due to potential for loss of efficacy of LET
Rifampin	↓ letermovir	Co-administration of LET and rifampin is not recommended due to potential for loss of efficacy of LET
Antipsychotics		
Pimozide	↑ pimozide	Co-administration is contraindicated due to risk of QT prolongation and torsades de pointes.
Thioridazine	↓ letermovir	Co-administration of LET and thioridazine is not recommended due to potential for loss of efficacy of LET
Endothelin antagonists		
Bosentan	↓ letermovir	Co-administration of LET and bosentan is not recommended due to potential for loss of efficacy of LET
Ergot alkaloids		
Ergotamine, dihydroergotamine	↑ ergotamine, dihydroergotamine	Co-administration is contraindicated due to risk of ergotism
Herbal products		
St. John's wort	↓ letermovir	Co-administration of LET and St. John's wort is not recommended due to potential for loss of efficacy of LET
HIV medications		
Efavirenz	↓ letermovir	Co-administration of LET and efavirenz is not recommended due to potential for loss of efficacy of LET

Etravirine	↓ letermovir	Co-administration of LET and etravirine is not recommended due to potential for loss of efficacy of LET
Nevirapine	↓ letermovir	Co-administration of LET and nevirapine is not recommended due to potential for loss of efficacy of LET
HMG-CoA reductase inhibitors		
Atorvastatin	↑ atorvastatin	When LET is co-administered with atorvastatin, do not exceed an atorvastatin dosage of 20 mg daily. Closely monitor patients for myopathy and rhabdomyolysis. When LET is co-administered with CsA, use of atorvastatin is not recommended.
Pitavastatin, simvastatin	↑ HMG-CoA reductase inhibitors	Co-administration of LET and pitavastatin or simvastatin is not recommended. When LET is co-administered with CsA, use of either pitavastatin or simvastatin is contraindicated due to significantly increased pitavastatin or simvastatin concentrations and risk of myopathy or rhabdomyolysis.
Fluvastatin, lovastatin, pravastatin, rosuvastatin	↑ HMG-CoA reductase inhibitors	When LET is co-administered with these statins, a statin dosage reduction may be necessary. Closely monitor patients for myopathy and rhabdomyolysis. When LET is co-administered with CsA, use of lovastatin is not recommended. When LET is co-administered with CsA, refer to the statin prescribing information for specific statin dosing recommendations.
Immunosuppressants		
Cyclosporine	↑ cyclosporine ↑ letermovir	Decrease the dosage of LET to 240 mg once daily. Frequently monitor CsA whole blood concentrations during treatment and after discontinuation of LET and adjust the dose of CsA accordingly.
Sirolimus	↑ sirolimus	When LET is co-administered with sirolimus, frequently monitor sirolimus whole blood concentrations during treatment and after discontinuation of LET and adjust the dose of sirolimus accordingly. When LET is co-administered with CsA and sirolimus, refer to the sirolimus prescribing information for specific sirolimus dosing recommendations.
Tacrolimus	↑ tacrolimus	Frequently monitor tacrolimus whole blood concentrations during treatment and after discontinuation of LET and adjust the dose of tacrolimus accordingly.

Proton pump inhibitors		
Omeprazole	↓ omeprazole	Clinical monitoring and dose adjustment may be needed
Pantoprazole	↓ pantoprazole	Clinical monitoring and dose adjustment may be needed
Wakefulness-promoting agents		
Modafinil	↓ letermovir	Co-administration of LET and modafinil is not recommended due to potential for loss of efficacy of LET
CYP3A substrates		
Alfentanil, fentanyl, midazolam, and quinidine	↑ CYP3A substrate	When LET is co-administered with a CYP3A substrate, refer to the prescribing information for dosing of the CYP3A substrate with a moderate CYP3A inhibitor. When LET is co-administered with CsA, the combined effect on CYP3A substrates may be similar to a strong CYP3A inhibitor. Refer to the prescribing information for dosing of the CYP3A substrate with a strong CYP3A inhibitor. CYP3A substrates pimozide and ergot alkaloids are contraindicated.

APPENDIX B: EXPECTED EVENTS FOR LUNG TRANSPLANT RECIPIENTS

The following events are expected to occur with a reasonable frequency in the typical/expected clinical course of a patient following lung transplant:

- Pulmonary: acute lung injury, respiratory distress syndrome, aspiration, atelectasis, mucus plugging, respiratory failure, dyspnea, hypoxia, pneumonia, pleural effusion, pneumothorax, pulmonary edema, sinusitis, need for mechanical ventilation, intubation or reintubation, chest tube insertion, tracheostomy insertion, embolism, pulmonary hypertension, graft rejection, primary graft dysfunction, diffuse alveolar hemorrhage, need for ECMO
- Surgical: anastomotic dehiscence, return to the operating room for surgery, subcutaneous emphysema, wound dehiscence, retransplantation, wound infection, fluid collection, seroma, hematoma
- Gastrointestinal: vomiting, diarrhea, dyspepsia, abdominal distention or bloating, abdominal pain, anorexia, perforation, ischemic bowel, reflux gastritis, ascites, ileus, bowel obstruction, GI bleed
- Neurologic: tremors, seizures, confusion, dizziness, hallucinations, delusion, psychosis, insomnia, somnolence, lethargy, depressed level of consciousness, agitation, amnesia, anxiety, emotional lability, vertigo, abnormal dreams, encephalopathy, posterior reversible encephalopathy syndrome, tacrolimus toxicity, neuropathy
- Neuromuscular and skeletal: incoordination, leg cramps, nerve compression
- Constitutional/systemic: fever, asthenia, failure to thrive, weight loss or weight gain, anasarca, embolism, multiorgan failure, malnutrition
- Infection: fever, hypothermia, rigors, chills, systemic inflammatory response syndrome, infection (documented or suspected), sepsis, multisystem organ failure
- Electrolyte and metabolic: acidosis or alkalosis, low albumin, dehydration, gout, increase or decrease in the levels of sodium, potassium, blood urea nitrogen, creatinine, glucose, calcium, magnesium, phosphate, uric acid, cholesterol, lipids, iron
- Hematologic: anemia, blood loss, prolonged PT or PTT, abnormalities in coagulation, hematoma, hemorrhage, bleeding, venous thrombosis, thrombocytopenia/thrombocytosis, leukopenia/leukocytosis, thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, pancytopenia

- Cardiac: arrhythmias (will capture atrial fibrillation and use of amiodarone), prolonged QT interval, QRS or ST segment abnormal, tachycardia, bradycardia, torsade de pointes, hypertension, hypotension, pulmonary hypertension, myocardial ischemia or infarction, syncope, postural hypotension, phlebitis, thrombosis
- Renal: acute renal failure, albuminuria, nephropathy, hematuria, proteinuria, acute tubular necrosis, interstitial nephritis, hemorraghic cystitis
- Genitourinary: bladder spasm, dysuria, nocturia, incontinence, urinary frequency, urinary retention
- Malignancies: lymphoproliferative disorder, skin neoplasm
- Dermatologic: edema at any body site, rash, ecchymosis, bruising, flushing, cellulitis, dermatitis, decubitus ulcer, photosensitivity, skin ulcer, impaired wound healing