PROTOCOL	
TITLE:	Letermovir for cytomegalovirus prophylaxis in patients with hematological malignancies treated with alemtuzumab
STUDY NUMBER:	OSU-19289
IND NUMBER:	147864
TEST PRODUCTS:	NA
COMMERICAL PRODUCTS:	Letermovir
INDICATION:	Hematologic malignancies treated with alemtuzumab
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SUPPORT PROVIDED BY:	The Ohio State University Merck

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TRIAL SUMMARY

TITLE	Letermovir for cytomegalovirus prophylaxis in patients with hematological malignancies treated with alemtuzumab
PHASE	II
OBJECTIVES	Primary Objective 1. To estimate the rate of CMV reactivation in patients treated with letermovir at 3 months after completion of alemtuzumab therapy. Secondary Objectives 1. To evaluate the tolerability of letermovir in combination with alemtuzumab. 2. To evaluate the efficacy of letermovir for the prevention of clinically significant CMV disease. 4. To estimate the overall survival of patients in the study population
STUDY DESIGN	Single center, single arm, non-randomized
KEY ELIGIBILITY CRITERIA	Inclusion Criteria 1. Confirmed diagnosis of any lymphoid malignancy including, but not limited to, T- or B-PLL, CLL, PTCL, CTCL, Sézary syndrome, or LGLL. 2. Intent to treat with alemtuzumab (monotherapy or in combination with chemotherapy). 3. Confirmed seropositivity for CMV IgG 4. Confirmed lack of active CMV infection as evidenced by CMV DNA PCR ≤ 200 IU/mL and no clinical evidence of CMV disease within 14 days of first letermovir dose. 5. Age ≥18 years old 6. Able to provide informed consent 7. Life expectancy >4 months 8. ECOG performance status ≤3 9. Highly unlikely to become pregnant or impregnate a partner (post-menopausal, sterile, abstinence, or adequate contraceptive method) Exclusion Criteria 1. History of confirmed CMV disease within 1 year of study entry. 2. History of prior allogeneic hematopoietic stem cell transplant within 6 months of enrollment. Allogeneic transplant more than 6 months prior to enrollment is allowed as long as the subject is off immunosuppression without active GVHD. 3. End stage renal disease with creatinine clearance < 10 mL/min 4. Severe hepatic impairment defined as Child-Pugh class C OR AST or ALT > 5 x ULN OR serum total bilirubin > 2.5 x ULN. 5. Both moderate hepatic insufficiency AND moderate renal insufficiency defined as Child Pugh Class B AND creatinine clearance less than 50 mL/min 6. Cytopenias are NOT an exclusion criteria 7. Received antiviral medications with activity against CMV or contraindicated medication within specified windows (see Section 3.2 for details) 8. Received cidofovir, CMV hyper-immune globulin, or an investigational anti CMV agent within 30 days.

	9. Infection or underlying disease necessitating ongoing use of prohibited medications (Section 4.4). 10. Suspected or known hypersensitivity to active or inactive ingredients of letermovir formulations 11. Active HIV, hepatitis B, or hepatitis C infection (see section 3.2 for exceptions) 12. Pregnant, breastfeeding, or expecting to conceive. 13. Expecting to donate eggs or sperm 14. Current or recent participation in a study with an unapproved investigational compound. 15. Previous participation in a study using letermovir. 16. Any condition which might interfere with subjects participation as judged by investigator.
STATISTICS	The primary objective of this single center, single arm phase II study is to determine the efficacy of letermovir prophylaxis in PLL, CLL, PTCL or CTCL patients treated with alemtuzumab. The efficacy will be measured through the CMV reactivation rate during letermovir prophylaxis (3 months after completion of alemtuzumab therapy). All eligible patients who receive any letermovir will be included in the tolerability analysis, and all patients who receive ≥90% of planned letermovir doses are evaluable for the efficacy analysis. Fleming's two-stage design will be used with the following parameters: • Null hypothesis: CMV reactivation rate of 30% or higher is not acceptable (70% safety rate) • Alternative hypothesis: CMV reactivation rate of 10% or less is acceptable (90% safety rate) With a one-sided type I error rate of 5% and 85% power, Fleming's two-stage design allows a first-stage analysis after the first 14 patients are enrolled and evaluated: • If ≥4 CMV reactivations, trial will terminate due to futility • If 0 CMV reactivations, trial will terminate due to efficacy • If 1-3 CMV reactivations, trial will accrue an additional 14 patients. o If at least 24 of 28 enrolled patients are CMV free, we will conclude the regimen effective To account for the possibility that some patients will not be evaluable, we will allow a 5% over-accrual for a total target enrollment of 30.
TOTAL NUMBER OF SUBJECTS	14 to 30 depending upon results of interim analysis.
ESTIMATED ENROLLMENT PERIOD	Stage 1: 10 months from first patient enrolled Stage 2: 20 months from first patient enrolled
ESTIMATED STUDY DURATION	Stage 1: 17 months from first patient enrolled Stage 2: 27 months from first patient enrolled

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1 BACKGROUND AND RATIONALE

1.1 Mature T-cell Lymphomas

Approximately 10-15% of non-Hodgkin lymphomas (NHL) are derived from mature (i.e. post-thymic) T lymphocytes [1]. The heterogeneity of these lymphomas and poor understanding of their pathogenesis continue to impede their classification and the development of novel therapeutic strategies.

1.1.1 Peripheral T-cell Lymphoma

The most common subtype of peripheral T-cell lymphoma (PTCL) lacks any distinguishing characteristics and is designated by the World Health Organization as “PTCL, not otherwise specified (PTCL, NOS)” [1, 2]. While the development of combination immunochemotherapy (e.g. “R-CHOP”) has led to significant survival benefits in B-cell NHL, the PTCLs are associated with inferior responses to therapy and overall survival [3]. In fact, the vast majority of PTCL patients will ultimately succumb to their disease, most within a few years of diagnosis [1, 2, 4]. Novel therapeutic strategies are needed if improved outcomes are to be achieved. The observation that PTCL incidence rates are increasing faster than almost any other subgroup of NHL further heightens this sense of urgency [5, 6].

1.1.2 Cutaneous T-cell Lymphoma

Primary cutaneous T-cell lymphoma (CTCL), of which the two most common forms are mycosis fungoides (MF) and Sézary syndrome (SS), predominantly involves the skin. Most CTCL patients present with limited-stage disease that is confined to the skin (i.e. patches or plaques) and are managed with topical therapies. In contrast, patients with advanced-stage disease with significant blood, nodal or visceral organ involvement are managed with systemic therapies [7]. A variety of single agent or combination chemotherapy regimens are utilized, as there is no standard of care for these patients. Therefore, the National Comprehensive Cancer Network (NCCN) guidelines endorse these agents or participation in a clinical trial as first-line therapy in these patients. Median overall survival for patients with stage IV disease ranges from 1.4-3.8 years, depending upon the extent of blood, nodal or visceral organ involvement [8]. Five FDA approved agents are currently available for CTCL patients failing at least one prior therapy, including bexarotene, vorinostat, romidepsin, brentuximab vedotin (for CD30 positive disease), and mogamulizumab. These agents are associated with overall response rates of 28-56% [9-15] with generally short duration of response. Despite the use of these novel agents, the long term outlook for most CTCL patients remains grim.

1.1.3 T-cell Prolymphocytic Leukemia

T-cell prolymphocytic leukemia (T-PLL) is a rare T-cell malignancy most often presenting in adult males[16]. While most presentations of this disease are acute, a minority of patients will not require treatment immediately. There is a limited response to conventional chemotherapy with alkylating agents or anthracyclines, with a median overall survival (OS) of 7 months in historical series [16, 17]. In the absence of a clinical trials, patients should be offered alemtuzumab as front line therapy. Alemtuzumab has a high overall response rate >80% in the front line setting [18] and 51-76% in the relapsed setting [19-22]. Even with high response rates, relapse is common in the absence of consolidative therapy. Allogeneic hematopoietic stem cell

transplantation is frequently recommended as consolidation therapy with resulted prolongation of overall survival and cure in a minority of cases [23-26]

1.2 Alemtuzumab

Alemtuzumab is a humanized IgG1 kappa monoclonal antibody directed against the CD52 antigen, which is mostly expressed by B- and T-lymphocytes. Clinical activity of alemtuzumab has been evaluated in multiple lymphoid malignancies including peripheral T cell lymphoma (PTCL), mycosis fungoides (MF), Sézary syndrome (SS), T-cell prolymphocytic leukemia (T-PLL), and chronic lymphocytic leukemia (CLL)[27].

In the relapsed setting, alemtuzumab monotherapy results in 36% overall response rate (ORR) with 21% complete response rate (CRR) in PTCL [28]. Patients with MF/SS have an ORR ranging from 55% to 100% with an average ORR of 65% [29]. Patients with erythrodermic MF or SS have significantly better responses (ORR 85-100%) even with lower doses of alemtuzumab therapy[30, 31]. Alemtuzumab is considered standard front line therapy for symptomatic T-PLL (NCCN guidelines) with ORR of 51-76% and CRR of 40-60% [21, 22]. Alemtuzumab has also been used in combination with various chemotherapeutic agents in the front line and relapsed setting in these diseases including CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin), and pentostatin [32-34]. Efficacy is improved with these combinations, but also results in cumulative toxicities.

In general, therapy with alemtuzumab is well tolerated, but cytomegalovirus (CMV) reactivation and other infectious complications remain a significant barrier to more widespread clinical use. In clinical trials where data is available, reported rates of CMV reactivation average 30% (see Table 1).

1.3 Cytomegalovirus

Infection with human cytomegalovirus (CMV) is relatively frequent in the human population with a seroprevalence ranging from 45-100% [35]. Following initial exposure, the virus establishes a lifelong latent infection that can periodically reactivate with shedding of infectious virus, although this rarely results in a clinically significant infection in healthy individuals. In contrast, reactivation is responsible for significant mortality and morbidity in immunocompromised patients [35]. CMV replication involves the cleaving of concatameric genomic viral DNA and the packaging of each genome into preformed viral capsids. This process is mediated by the CMV-terminase complex (UL51, UL56, and UL89) [36].

Risk factors associated with CMV reactivation include seropositivity of the recipient while undergoing therapy immunosuppressive therapy with autologous or allogeneic transplant or drugs like high dose steroids or alemtuzumab. Clinical manifestations include interstitial pneumonitis, encephalitis, retinitis, fevers, hepatitis, hemorrhagic cystitis and diarrhea [37]. Current management focuses on reduction in immunosuppression and initiation of antiviral therapies including ganciclovir, cidofovir, foscarnet, and valganciclovir [37, 38]. Use of these agents, while necessary, carries significant side effect profiles including marrow suppression and nephrotoxicity. Furthermore, the development of antiviral resistance via mutations to CMV UL97 or UL54 genes limits the available agents effective against CMV [38]. Antiviral drug resistance should be suspected in patients who fail to improve (i.e., >1 $\log_{10}$ increase in CMV

DNA levels in blood or serum) after 2 weeks of appropriately dosed antiviral therapy [38]. Although the incidence of drug resistant CMV remains low (0-8%)[39, 40], it can still pose significant challenges to treatment when it occurs. Therefore, novel therapies to reduce the risk of CMV reactivation are needed in order to avoid serious side effects of antiviral therapies and to avoid drug resistance to these agents.

A review of published studies using alemtuzumab in the target patient population for this trial is summarized in Table 1. This shows that the CMV reactivation rate in this patient population is ~30%.

Table 1: Reported rates of CMV reactivation with alemtuzumab in target patient population

Ref	Population	CMV Reactivation (n)	Total Patients (n)	Reactivation Rate	CMV Prophy*	Chemo Combination	Front Line Therapy	Relapsed Therapy
[34]	PTCL, T-PLL, T-LGL, T-ALL, MF	9	24	38%	Y	Y	Y	Y
[41]	HTLV+ ATLL	29	29	100%	Y	N	Y	Y
[42]	PTCL	5	20	25%	N	Y	Y	N
[43]	PTCL	5	41	12%	N	Y	Y	N
[32]	PTCL	7	20	35%	N	Y	Y	N
[44]	PTCL	12	38	32%	N	Y	Y	Y
[33]	PTCL	16	31	52%	N	Y	Y	N
[45]	T-PLL	13	21	62%	N	Y	Y	N
[46]	PTCL, T-ALL	6	13	46%	N	Y	Y	Y
[47]	PTCL	8	15	53%	N	Y	Y	N
[48]	PTCL	8	24	33%	N	Y	N	Y
[49]	SS	3	5	60%	N	Y	N	Y
[30]	SS	3	14	21%	N	N	Y	Y
[50]	CTCL	10	39	26%	N	N	Y	Y
[51]	T-LGL	6	13	46%	N	N	Y	Y
[20]	CLL, PLL, CTCL, PTCL, T-LGL, MCL, HCL	15	78	19%	N	N	Y	Y
[52]	SS	2	5	40%	N	N	Y	Y
[21]	T-PLL	3	76	4%	N	N	Y	Y
[28]	PTCL	6	14	43%	N	N	N	Y
[53]	CLL, PLL	5	34	15%	N	N	N	Y
[54]	MF, SS	0	10	0%	N	N	N	Y
[55]	PTCL, CTCL	1	10	10%	N	N	N	Y
[56]	MF, SS	1	8	13%	N	N	N	Y
[57]	MF, SS	4	22	18%	N	N	N	Y
[58]	MF, SS	0	18	0%	N	N	N	Y

Ref	Population	CMV Reactivation (n)	Total Patients (n)	Reactivation Rate	CMV Prophy*	Chemo Combination	Front Line Therapy	Relapsed Therapy
[59]	SS	3	6	50%	N	N	N	Y
[60]	PTCL	10	20	50%	NR	Y	Y	N
[61]	PTCL	5	16	31%	NR	Y	N	Y
[62]	PTCL	1	10	10%	NR	Y	N	Y
[18]	T-PLL	2	9	22%	NR	N	Y	N
[22]	T-PLL	1	39	3%	NR	N	Y	Y
[19]	T-PLL	1	15	7%	NR	N	N	Y
[63]	SS	6	13	46%	NR	N	N	Y
[64]	SS	1	1	100%	NR	N	N	Y
[65]	SS	3	6	50%	NR	N	NR	NR
[66]	NHL, PTCL, AML, ALL, MDS, AA	66	180	37%	Variable	Y	Y	Y
	TOTAL	**276**	**937**	**29%**				

*CMV prophylaxis defined as planned routine use of: ganciclovir (any dose), valganciclovir (any dose), foscarnet (any dose), acyclovir (>3200 mg by mouth per day or >25 mg/kg IV per day), valacyclovir (>3000 mg by mouth per day), or famciclovir (>1500 mg by mouth daily).

Abbreviations: AA = aplastic anemia, ALL = T-cell acute lymphoblastic leukemia, AML = acute myeloid leukemia, ATLL = adult T-cell leukemia/lymphoma, CLL = chronic lymphocytic leukemia, CMV = cytomegalovirus, CTCL = cutaneous T-cell lymphoma, HCL = hairy cell leukemia, HTLV = human T-lymphotropic virus, MCL = mantle cell lymphoma, MDS = myelodysplastic syndrome, MF = mycosis fungoides, N = no, NHL = non-Hodgkin lymphoma, NR = not reported, PLL = prolymphocytic leukemia, Prophy = prophylaxis, PTCL = peripheral T cell lymphoma, SS = Sézary syndrome, T-LGL = T-cell large granular lymphocytic leukemia, Y = yes

1.4 Letermovir

Letermovir is a highly potent anti-CMV agent recently FDA approved for anti-CMV prophylaxis post-transplant based on the results of a recent randomized phase 3 trial [67]. Letermovir inhibits CMV replication by binding components of the terminase complex resulting in impaired cleavage and packaging of viral DNA into capsids [68, 69].

In the trial leading to FDA approval, 565 CMV seropositive patients without detectable CMV DNA at baseline undergoing allogeneic hematopoietic stem cell transplantation were randomized to receive letermovir prophylaxis or placebo through week 14 after transplantation. Patients treated with letermovir experienced a statistically significant decrease in clinically significant CMV infection compared to placebo (37.5% vs 60.6%, P<0.001). Additionally, the frequency and severity of adverse events were statistically similar between the two groups overall. Patients in the letermovir group may have experienced slightly higher rates of nausea and vomiting, peripheral edema, and atrial fibrillation. Importantly, the use of letermovir prophylaxis was associated with a trend toward lower all-cause mortality compared to placebo in this trial and this was confirmed in a post hoc analysis of survival [70].

Based on these data and the high rate of CMV reactivation following alemtuzumab therapy, we propose the following phase 2 clinical trial of letermovir prophylaxis in patients with hematologic malignancies receiving alemtuzumab.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

1. To estimate the rate of CMV reactivation in patients treated with letermovir at 3 months after completion of alemtuzumab therapy.

2.1.2 Secondary Objectives

1. To evaluate the tolerability of letermovir in combination with alemtuzumab
2. To evaluate the efficacy of letermovir for the prevention of clinically significant CMV disease
3. To estimate the overall survival of patients in the study population

2.1.3 Exploratory Objectives

1. To evaluate mechanisms of antiviral resistance in letermovir prophylaxis failures.

2.2 Endpoints

2.2.1 Primary Endpoint

1. CMV reactivation as defined in section 10.2.

2.2.2 Secondary Endpoints

1. Adverse events (AEs) using NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.
2. Development of CMV disease per the Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum [71] (Appendix 12.1)
3. Overall survival as defined in section 10.3

2.2.3 Exploratory Endpoints

1. Genotyping to evaluate mutations in CMV terminase complex genes (UL51, UL56, UL89) [72-79]

3 PATIENTS AND METHODS

3.1 Inclusion Criteria

1. Confirmed diagnosis of any lymphoid malignancy including, but not limited to, T-cell or B-cell prolymphocytic leukemia, chronic lymphocytic leukemia, peripheral T-cell lymphoma, cutaneous T-cell lymphoma, Sézary syndrome, or large granular lymphocytic leukemia.

2. Intent to treat with alemtuzumab. Monotherapy or combination with chemotherapy is allowed.
3. Confirmed seropositivity for CMV IgG (≥0.7 U/mL) within 1 year of first letermovir dose.
4. Confirmed lack of active CMV infection as evidenced by CMV DNA PCR ≤ 200 IU/mL and no clinical evidence of CMV disease within 14 days of first letermovir dose.
5. Age ≥18 years old
6. Able to provide informed consent.
7. Life expectancy >4 months
8. Eastern Cooperative Oncology Group (ECOG) performance status ≤3 (Appendix 12.2)
9. Highly unlikely to become pregnant or impregnate a partner by meeting at least one of the following:
    a. A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subject who is not of reproductive potential is defined as one who:
        i. has reached natural menopause (defined as 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone [FSH] levels in the postmenopausal range as determined by the local laboratory, or 12 months of spontaneous amenorrhea)

        OR

        ii. is 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy

        OR

        iii. has undergone bilateral tubal ligation. Spontaneous amenorrhea does not include cases for which there is an underlying disease that causes amenorrhea (e.g., anorexia nervosa).
    b. A male subject who is not of reproductive potential is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as one whom has undergone a successful defined as:
        i. microscopic documentation of azoospermia

        OR

        ii. a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post-vasectomy
    c. A male or female subject who is of reproductive potential agrees to true abstinence or to use (or have their partner use) an acceptable method of birth control starting from the time of consent through 90 days after the last dose of study therapy. True abstinence is defined as abstinence in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., abstinence only on certain calendar days, abstinence only during ovulation period, use of symptothermal method, use of post-ovulation methods) and withdrawal are not acceptable methods of contraception. Acceptable methods of birth control are:
        i. intrauterine device (IUD), diaphragm with spermicide, contraceptive sponge, condom, and vasectomy OR use of appropriate double barrier

contraception. Hormonal contraceptives (e.g., birth control pills, transdermal patch, or injectables) are also acceptable.

3.2 Exclusion Criteria

1. History of confirmed CMV disease within 1 year of study entry.
2. History of prior allogeneic hematopoietic stem cell transplant within 6 months of trial enrollment. Subjects who have undergone allogeneic transplant more than 6 months prior to enrollment are eligible as long as the subject is off immunosuppression without active GVHD.
3. End stage renal disease with creatinine clearance < 10 mL/min as defined by Cockcroft-Gault equation using serum creatinine within 7 days of enrollment
    a. Creatinine clearance (males) = $\frac{(\text{Weight in kg})(140-\text{age})}{(72)(\text{creatinine in mg/dL})}$
    b. Creatinine clearance (females) = $\frac{(\text{Weight in kg})(140-\text{age})}{(72)(\text{creatinine in mg/dL})} * 0.85$
4. Severe hepatic impairment defined as:
    a. Child-Pugh class C (see appendix 12.2) within 7 days of enrollment
    b. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN) or serum total bilirubin > 2.5 x ULN.

    Note: Subjects who meet this exclusion criterion may, at the discretion of the investigator, have one repeat testing done. If the repeat value does not meet this criterion, they may continue in the screening process. Only the specific out of range value should be repeated (not the entire panel).
5. Both moderate hepatic insufficiency AND moderate renal insufficiency:
    a. Moderate hepatic insufficiency is defined as Child Pugh Class B (see Appendix 12.2)
    b. Moderate renal insufficiency is defined as a creatinine clearance less than 50 mL/min, as calculated by the Cockcroft-Gault equation (as above)
6. Cytopenias are NOT an exclusion criteria in this trial as cytopenias are common in this patient population and letermovir has no known adverse effects on blood counts. Patients will be treated per institutional standard of care with as needed transfusions and growth factor support.
7. Received any of the following drugs within 7 days of enrollment or plans to receive any of the following during the study:
    a. ganciclovir
    b. valganciclovir
    c. foscarnet
    d. acyclovir (at doses > 3200 mg PO per day or > 25 mg/kg IV per day)
    e. valacyclovir (at doses > 3000 mg PO per day)
    f. famciclovir (at doses > 1500 mg PO per day)
    g. Cyclosporine A

h. Pimozide
i. Ergot alkaloids (ergotamine and dihydroergotamine)
j. Atorvastatin at doses greater than 20 mg daily (see Table 5)

8. Received any of the following within 30 days prior to enrollment
    a. cidofovir
    b. CMV hyper-immune globulin
    c. Any investigational CMV antiviral agent/biologic therapy
9. Infection or underlying disease necessitating ongoing use of prohibited medications (Section 4.3).
10. Suspected or known hypersensitivity to active or inactive ingredients of letermovir formulations
11. Positive at the time of screening for:
    a. HIV with CD4 count <350. If HIV positive, must remain on antiretroviral therapy that is not anticipated to interact with letermovir throughout study.
    b. Hepatitis B surface antigen or core antibody positivity associated with detectable viral load. For any patient with serologic evidence of prior infection but undetectable viral load, viral load and surface antigen will be monitored every 2 weeks. Those with evidence of reactivation (detectable viral load) will be treated with entecavir or lamivudine. Upon resolution of detectable viral load, the patient will be allowed to continue on trial assuming adequate liver function as defined above. Alternatively, patients may be put on prophylactic entecavir or lamivudine to prevent hepatitis B reactivation at the investigators discretion.
    c. Hepatitis C if no prior or current curative antiviral therapy. For those currently on curative antiviral therapy, they will be allowed on trial if HCV quantitation is below the limit of detection and adequate liver function as above.
12. Pregnant or expecting to conceive, is breastfeeding, or plans to breastfeed from the time of consent through 90 days after the last dose of study therapy.
13. Expecting to donate eggs or sperm starting from the time of consent through 90 days after the last dose of study therapy.
14. Currently participating or has participated in a study with an unapproved investigational compound or device within 28 days, or 5X half-life of the investigational compound (excluding monoclonal antibodies), whichever is longer, of initial dosing on this study. Subjects previously treated with a monoclonal antibody will be eligible to participate after a 28-day washout period.
15. Previous participation in a study using letermovir.
16. Has a history or current evidence of any condition, therapy, lab abnormality, or other circumstance that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or would be put at undue risk as judged by the investigator, such that it is not in the best interest of the subject to participate in this study

3.3 Screening Procedures

Patients may be screened for study entry when the determination has been made by the treating physician that they need therapy with alemtuzumab. Application to receive alemtuzumab for compassionate use would be started by the treating physician team, as per standard of care, while patient is being screened for trial. Application for compassionate use of alemtuzumab can be accessed here: https://www.campathproviderportal.com.

4 TREATMENT PLAN

4.1 Premedication Administration

No premedication is necessary for letermovir.

4.2 Agent Administration

Letermovir will be administered at 480 mg by mouth daily starting up to two weeks after the first administration of alemtuzumab. Treatment will continue for 3 months after the last dose of alemtuzumab is given.

If for any reason, the subject is unable to take the oral formulation of letermovir for an extended period of time, the intravenous (IV) formulation of letermovir may be use. Simultaneous use of IV and oral study therapy is not allowed. The IV formulation should be switched to oral study therapy (i.e., at the next planned dose) as soon as such subjects are able to swallow and/or the condition necessitating the use of the IV formulation resolve.

Study therapy with letermovir may begin as early as the first day of alemtuzumab infusion to no later than 14 days after the first alemtuzumab infusion, once the subject is determined to be negative for active CMV infection as outlined in the inclusion criteria. Letermovir should continue through 90 days after the final planned alemtuzumab infusion.

Study therapy should be administered at the same time each day. Tablets are to be swallowed whole (i.e., no crushing or chewing the tablet is allowed). Study therapy may be administered with or without food.

If a subject misses a dose, the missed dose should be given as soon as possible during the same day. If more than 18 hours have gone by after the regular dosing time, then the missed dose should be skipped and the normal dosing schedule should be resumed. The next dose should not be doubled in order to “make up” what has been missed.

Study therapy can be administered with or without food. Subjects must avoid consumption of grapefruit, Seville oranges or their respective juices, and other quinine-containing drinks or food during the trial from 2 weeks prior to study drug administration until 72 hours after the final administration of study drug.

4.3 Rationale for Dose Selection

Please refer to the letermovir package insert for further details of preclinical data and study results in humans.

Letermovir belongs to a new class of anti-CMV agents which have a different mechanism of action compared to currently available drugs for the treatment of CMV infection. By inhibiting the viral terminase complex, the drug plays a key role in cleavage and packaging of genomic virus DNA into provirions.

Letermovir is anticipated to be efficacious based on both the *in vitro* potency of letermovir as well as its *in vivo* efficacy for CMV prophylaxis in a Phase III trial in allogeneic hematopoietic stem cell transplantation (HSCT) recipients [67]. In this trial, 565 CMV seropositive patients without detectable CMV DNA at baseline undergoing allogeneic HSCT were randomized to receive letermovir prophylaxis (480 mg daily or 240 mg daily or patients concomitantly receiving CsA) or placebo through week 14 after transplantation. Patients treated with letermovir experienced a statistically significant decrease in clinically significant CMV infection compared to placebo (37.5% vs 60.6%, P<0.001). Additionally, the frequency and severity of adverse events were statistically similar between the two groups overall. Patients in the letermovir group may have experienced slightly higher rates of nausea and vomiting, peripheral edema, and atrial fibrillation.

Based on all available safety data, letermovir efficacy in the Phase II and III studies, and the exposure-response data, this study will use a dose of 480 mg daily. Patients who have had allogeneic transplant within 6 months prior to trial enrollment and patients receiving cyclosporine A (CsA) are excluded; phase I studies have demonstrated that co-administration of letermovir with CsA increases letermovir exposure ~3 fold. Patients who have undergone allogeneic transplant more than 6 months prior to enrollment are eligible as long as the subject is off immunosuppression without active GVHD.

4.4 Concomitant Medications and Supportive Care

Allowed Medications/Therapies

The following medications/therapies are **allowed** in this study:

- Standard antimicrobial prophylaxis (e.g., levofloxacin for bacteria, fluconazole/ voriconazole/posaconazole for fungi)
- Acyclovir, valacyclovir, or famciclovir for prophylaxis of herpes simplex virus (HSV) or varicella zoster virus (VZV) infections at doses no greater than prohibited doses of these medications (see below)

Prohibited Medications/Therapies

The following medications/therapies are **prohibited** in this study:

Antiviral drugs or therapies for prevention/treatment of CMV, including but not limited to:

- ganciclovir
- valganciclovir
- foscarnet
- cidofovir
- acyclovir (at doses > 3200 mg PO per day or > 25 mg/kg IV per day)

- valacyclovir (at doses > 3000 mg PO per day)
- famciclovir (at doses > 1500 mg PO per day)
- CMV hyper-immune globulin
- any investigational CMV antiviral agent/biologic therapy
- CMV vaccine

Investigational Agents

Investigational agents are not permitted with the following exceptions: (1) Investigational chemotherapy regimens involving approved agents and (2) investigational antimicrobial regimens involving approved antibacterial/antifungal/antiviral agents.

Other Agents:

- Cyclosporine A
- Pimozide
- Ergot alkaloids (ergotamine and dihydroergotamine)
- Atorvastatin at doses greater than 20 mg daily (see Table 5)

Medications/Therapies to be Administered with Caution

Preclinical studies suggest MK-8228 acts as a weak to moderate inhibitor of cytochrome (CYP)3A4, CYP2C8, CYP2B6 and the transporters OATP1B1 and OATP1B3. It is therefore possible that MK-8228 may increase the exposure of co-administered drugs whose primary route of clearance involves these enzymes or transporters. Please see Table 5 (section 8.3) for a list of potentially clinically significant drug interactions.

5 TOXICITIES, DOSE DELAYS, AND DOSE MODIFICATIONS

The NCI Common Terminology Criteria for Adverse Events (CTCAE) v5 will be used to grade adverse events.

Subjects enrolled in this study will be evaluated clinically and with standard laboratory tests before and at regular intervals during their participation in this study as specified in Study Calendar & Evaluations.

Subjects will be evaluated for adverse events (all grades), serious adverse events, and adverse events requiring study drug interruption or discontinuation as specified in Study Calendar & Evaluations (section 6).

5.1 Dose Delays and Modifications

Dose modifications are not allowed on trial.

5.2 Protocol Therapy Discontinuation

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be

withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

A subject must be discontinued from the trial for any of the following reasons:

- CMV reactivation as defined in section 10.2 at any time during the study period, study therapy will be discontinued and the subject may be treated according to the local standard of care (outside the context of the study). In this setting, any of the prohibited anti-CMV medications (outlined in section 4.4) may be used.
- The subject becomes pregnant during the study
- The subject's investigator feels it is in the best interest of the subject to discontinue.

A subject may be discontinued from therapy for any of the following reasons:

- Any AE/SAE assessed by the physician investigator as possibly or probably related to study therapy. Investigator may continue the subject in the trial if it is deemed to be in the best interest of the subject to stay on study therapy.
- Failure to comply with the dosing, evaluations, or other requirements of the trial.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.

6 STUDY EVALUATIONS

6.1 Calendar of Events

Cycle = **28 days**	Screen (-28 days)	On Treatment[1]	At CMV reactivation[2]	AE follow up[3]
REQUIRED ASSESSMENTS				
Review of eligibility criteria, informed consent	X			
Medical history	X			
ECOG PS[4]	X			
Physical exam, vital signs[5]	X	X	X	X
AEs, concomitant medications	X	X	X	X
Drug diary		X	X	
Assessment of contraception method[6]	X			
CMV disease assessment[7]			X	X
LABORATORY ASSESSMENTS				
Complete blood cell count with differential (CBC)	X	X	X	X
Comprehensive metabolic profile (CMP)[8]	X	X	X	X
Prothrombin time (INR)	X			
Urine pregnancy test in WOCBP	X	X	X	X
HIV, hepatitis B, and hepatitis C screen[9]	X			

CMV IgG[10]	X			
CMV viral load[11] (at least every other week, weekly preferred)	X	X	X	X
CORRELATIVE STUDIES (SPECIMEN COLLECTION)				
CMV Genotyping			X	

1. On study visits will occur every 28 days (+/- 7 days). Treatment with letermovir should be continued for 90 after the last dose of alemtuzumab.
2. CMV reactivation defined as CMV DNA by real time polymerase chain reaction >500 IU/mL
3. AE follow up to occur 30 days (+/- 7 days) from last dose of letermovir therapy. If patients have any ongoing toxicity related to letermovir, investigator should continue to monitor and provide appropriate supportive care. If patient has active CMV infection or reactivation, investigator should continue to monitor and provide appropriate treatment including antiviral therapy.
4. See Appendix 12.2
5. Vital signs include height, weight, blood pressure, heart rate, respiratory rate, temperature
6. See section 3.1 for acceptable methods of contraception
7. CMV disease assessment is a focused history and physical exam guided by known manifestations of CMV disease (see Appendix 12.1). CMV disease assessment is to be performed if reactivation occurs as defined in Section 10.2.
8. CMP should include at least the following: sodium, potassium, chloride, creatinine, glucose, calcium, phosphorus, total bilirubin, AST, ALT, alkaline phosphatase, albumin.
9. Screening to be completed with: HIV antibody, hepatitis B surface antibody, hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody. If hepatitis B surface antigen or core antibody is positive, hepatitis B viral load quantification with PCR should be ordered; if hepatitis C antibody is positive, viral load quantification by PCR should be ordered.
10. CMV IgG seropositivity may be confirmed up to 1 year prior to starting letermovir.
11. CMV viral load testing by PCR will be completed **at least every other week** while on therapy with letermovir. Weekly monitoring is preferred but can be reduced to every 2 weeks at the investigator's discretion. Window for screening is within 2 weeks of first dose of letermovir.

6.2 Biospecimen Studies and Procedures

The correlative studies will include genotyping to evaluate mutations in CMV terminase complex genes (UL51, UL56, UL89) through Viracor.

6.3 Source and Timing of Biospecimen Collections

Peripheral blood of approximately 10 ml in EDTA (lavender top) tube will be inverted to mix anti-coagulant and then kept at room temperature until transport to the OSU Leukemia Tissue Bank (LTB). Plasma and PBMCs will be separated and cryopreserved by standard methods. Samples will be labeled with the study time point, collection date and protocol number as well as study participant number. Frozen plasma samples would be batch analyzed after the completion of the study for CMV genotyping studies.

6.4 Storage of Biospecimens

Samples will be stored in OSU LTB.

7 CRITERIA FOR DISEASE EVALUATION

CMV reactivation is defined in section 10.2. CMV disease will be defined as in Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum [71] (Appendix 12.1).

8 LETERMOVIR INFORMATION

8.1 Letermovir Description and Mechanism of Action

Letermovir inhibits the CMV DNA terminase complex (pUL51, pUL56, and pUL89) which is required for viral DNA processing and packaging. Biochemical characterization and electron

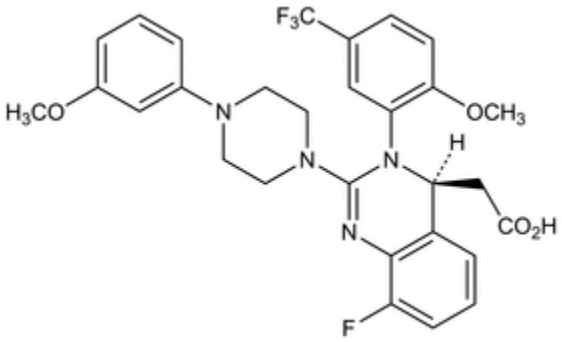
microscopy demonstrated that letermovir affects the production of proper unit length genomes and interferes with virion maturation. Genotypic characterization of virus resistant to letermovir confirmed that letermovir targets the terminase complex.

The median EC50 value of letermovir against a collection of clinical CMV isolates in a cell-culture model of infection was 2.1 nM (range = 0.7 nM to 6.1 nM, n = 74). There was no significant difference in EC50 value by CMV gB genotype (gB1=29; gB2=27; gB3=11; and gB4=3). No antagonism of the antiviral activity was seen when letermovir was combined with CMV DNA polymerase inhibitors (cidofovir, foscarnet, or ganciclovir).

8.2 Clinical Pharmacology

Letermovir has a molecular formula of C29H28F4N4O4 and a molecular weight of 572.55. The chemical name for letermovir is (4S)-2-[8-Fluoro-2-[4-(3-methoxyphenyl)piperazin-1-yl]-3-[2-methoxy-5(trifluoromethyl)phenyl]-3,4-dihydroquinazolin-4-yl] acetic acid. Letermovir is very slightly soluble in water.

The chemical structure of letermovir is:



8.3 Pharmacokinetics and Drug Metabolism

The pharmacokinetic properties of letermovir are displayed in Table 2.

Table 2: Absorption, Distribution, Metabolism, Elimination (ADME), and Pharmacokinetic Properties of letermovir

Pharmacokinetics in HSCT Recipients	
Treatment Regimen	Steady-state median (90% prediction interval) AUC (ng•hr/mL) of letermovir
480 mg oral once daily, no cyclosporine	34,400 (16,900, 73,700)
480 mg IV once daily, no cyclosporine	100,000 (65,300, 148,000)
240 mg oral once daily, with cyclosporine	60,800 (28,700, 122,000)
240 mg IV once daily, with cyclosporine	70,300 (46,200, 106,000)
Pharmacokinetics in Healthy Subjects	

Treatment Regimen 480 mg oral once daily	Steady-state geometric mean AUC and Cmax of letermovir Cmax: 13,000 ng/mL AUC: 71,500 ng•hr/mL
Dose proportionality	Greater than proportional following single and multiple oral or IV doses of letermovir 240 mg and 480 mg
Accumulation ratio†	Cmax: 1.03 AUC: 1.22
Time to steady-state	9-10 days
Absorption	
Bioavailability	Healthy subjects administered letermovir without cyclosporine: 94% at an oral dose range of 240 mg to 480 mg HSCT recipients administered letermovir without cyclosporine: 35% with 480 mg oral once daily HSCT recipients administered letermovir with cyclosporine: 85% with 240 mg oral once daily
Median Tmax (hr)	45 min to 2.25 hr
Effect of food (relative to fasting) ‡	AUC: 99.63% [84.27% - 117.80%] Cmax: 129.82% [104.35% -161.50%]
Distribution	
Mean steady-state volume of distribution	45.5 L following IV administration in HSCT recipients
% *In vitro* bound to human plasma proteins	99% across the concentration range of 0.2 to 50 mg/L
In vitro blood-to plasma ratio	0.56 across the concentration range of 0.1 to 10 mg/L
Metabolism	
In vitro metabolism	UGT1A1/1A3 (minor)
Drug-related component in plasma	97% unchanged parent No major metabolites detected in plasma
Elimination	
Route of elimination	Hepatic uptake (OATP1B1/3)
Mean terminal $t_{1/2}$ (hr)	12 hrs after dosing of letermovir 480 mg IV once daily
% of dose excreted in feces§	93%

% of dose excreted in urine§	<2%
% of unchanged drug excreted in feces§	70%

* Values were obtained in studies of healthy subjects unless otherwise indicated.

† Based on geometric mean data.

‡ Values refer to geometric mean ratio [fed/fasted] percentage and 90% confidence interval back transformed from linear mixed-effects model performed on natural log-transformed values. The meal administered was a standard high fat and high calorie meal (33 grams protein, 65 grams carbohydrates, 58 grams fat; 920 total calories).

§ Single oral administration of radiolabeled letermovir in mass balance study.

517

518 Specific Populations

519 *Pediatric Population*

520 The pharmacokinetics of letermovir in patients less than 18 years of age have not been
521 evaluated.

522 *Age, Gender, Race, and Weight*

523 Age (18 to 78 years), gender, race (White vs. non-White), and body weight (up to 100 kg) did
524 not have a clinically significant effect on the pharmacokinetics of letermovir.

525 *Renal Impairment*

526 Letermovir AUC was approximately 1.9-and 1.4-fold higher in subjects with moderate (eGFR
527 greater than or equal to 30 to 59 mL/min/1.73m2) and severe (eGFR less than 30
528 mL/min/1.73m2) renal impairment, respectively, compared to healthy subjects.

529 Hydroxypropyl betadex present in the intravenous letermovir formulation is mainly eliminated by
530 glomerular filtration. Decreased elimination of hydroxypropyl betadex has been reported in the
531 literature in patients with severe renal impairment.

532 *Hepatic Impairment*

533 Letermovir AUC was approximately 1.6-and 3.8-fold higher in subjects with moderate (Child-
534 Pugh Class B [CP-B], score of 7-9) and severe (Child-Pugh Class C [CP-C], score of 10-15)
535 hepatic impairment, respectively, compared to healthy subjects.

536 *Drug Interaction Studies*

537 Drug interaction studies were performed in healthy subjects with letermovir and drugs likely to
538 be co-administered or drugs commonly used as probes for pharmacokinetic interactions (see

539 Table **3** and

Table **4**).

In vitro results indicate that letermovir is a substrate of drug metabolizing enzymes CYP3A, CYP2D6, UGT1A1, and UGT1A3, and transporters OATP1B1/3 and P-gp. Oxidative metabolism is considered to be a minor elimination pathway based on *in vivo* human data. Inhibitors of OATP1B1/3 may result in increases in letermovir plasma concentrations. Changes in letermovir plasma concentrations due to inhibition of P-gp or UGTs are not anticipated to be clinically relevant.

Based on *in vitro* studies, the metabolism of letermovir is not mediated by CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18, CYP2C19, CYP2E1, CYP4A11, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15, or UGT2B17. The transport of letermovir is not mediated by OATP2B1, OCT1, OAT1, BCRP, or MRP2 *in vitro*.

Letermovir is a time-dependent inhibitor and inducer of CYP3A *in vitro*. Co-administration of letermovir with midazolam resulted in increased exposure of midazolam, indicating that the net effect of letermovir on CYP3A is moderate inhibition (see

554 Table **4**). Based on these results, co-administration of letermovir with CYP3A substrates may
555 increase the plasma concentrations of the CYP3A substrates (see

Table **4**). Letermovir is a reversible inhibitor of CYP2C8 *in vitro*. When co-administered with letermovir, plasma concentrations of CYP2C8 substrates are predicted to be increased (see

Table **4**). Co-administration of letermovir reduced the exposure of voriconazole, most likely due to the induction of voriconazole elimination pathways, CYP2C9 and CYP2C19. Co-administration of letermovir with CYP2C9 and CYP2C19 substrates may decrease the plasma concentrations of the CYP2C9 and CYP2C19 substrates (see Table 5). Letermovir is an inducer of CYP2B6 *in vitro*; the clinical relevance is unknown.

Letermovir inhibited efflux transporters P-gp, breast cancer resistance protein (BCRP), bile salt export pump (BSEP), multidrug resistance-associated protein 2 (MRP2), OAT3, and hepatic uptake transporter OATP1B1/3 *in vitro*. Co-administration of letermovir with substrates of OATP1B1/3 transporters (e.g. atorvastatin, a known substrate of CYP3A, OATP1B1/3, and potentially BCRP) may result in a clinically relevant increase in plasma concentrations of OATP1B1/3 substrates (see Table 5). There were no clinically relevant changes in plasma concentrations of digoxin, a P-gp substrate, or acyclovir, an OAT3 substrate, following co-administration with letermovir in clinical studies (see

Table **4**). The effect of letermovir on BCRP, BSEP, and MRP2 substrates was not evaluated in clinical studies; the clinical relevance is unknown.

Based on *in vitro* results letermovir is not an inhibitor of CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, UGT1A4, UGT1A6, UGT1A9, or UGT2B7 and is not an inducer of CYP1A2. Letermovir is not an inhibitor of MRP2, OATP2B1, BSEP, OCT1, OCT2, or OAT1 *in vitro*.

Table 3: Drug Interactions: Changes in Pharmacokinetics of Letermovir in the Presence of Co-administered Drug

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	Geometric Mean Ratio [90% CI] of Letermovir PK with/without Co-administered Drug (No Effect=1.00)		
			AUC	Cmax	C24hr*
Immunosuppressants					
cyclosporine	200 mg single dose PO	240 mg once daily PO	2.11 (1.97, 2.26)	1.48 (1.33, 1.65)	2.06 (1.81, 2.35)
mycophenolate mofetil	1 g single dose PO	480 mg once daily PO	1.18 (1.04, 1.32)	1.11 (0.93, 1.34)	1.39 (1.12, 1.74)
tacrolimus	5 mg single dose PO	80 mg twice daily PO	1.02 (0.97, 1.07)	0.92 (0.84, 1.00)	1.02 (0.93, 1.12)
Abbreviations: PO= oral * C12hr for tacrolimus					

Table 4: Drug Interactions: Changes in Pharmacokinetics for Co-administered Drug in the Presence of Letermovir

Co-administered Drug	Regimen of Co-administered Drug	Letermovir Regimen	Geometric Mean Ratio [90% CI] of Co-administered Drug PK with/without Letermovir (No Effect=1.00)		
			AUC	Cmax	C24hr*
CYP3A Substrates					
midazolam	1 mg single dose IV	240 mg once daily PO	1.47 (1.37, 1.58)	1.05 (0.94, 1.17)	2.74 (2.16, 3.49)
midazolam	2 mg single dose PO	240 mg once daily PO	2.25 (2.04, 2.49)	1.72 (1.54, 1.92)	Not available
P-gp Substrates					
digoxin	0.5 mg single dose PO	240 mg twice daily PO	0.88 (0.80, 0.96)	0.75 (0.63, 0.89)	0.90 (0.84, 0.96)
Immunosuppressants					
cyclosporine	50 mg single dose PO	240 mg once daily PO	1.66 (1.51, 1.82)	1.08 (0.97, 1.19)	2.19 (1.80, 2.66)
mycophenolate mofetil	1 g single dose PO	480 mg once daily PO	1.08 (0.97, 1.20)	0.96 (0.82, 1.12)	1.04 (0.86, 1.27)
tacrolimus	5 mg single dose PO	480 mg once daily PO	2.42 (2.04, 2.88)	1.57 (1.32, 1.86)	2.53 (2.12, 3.03)
sirolimus	2 mg single dose PO	480 mg once daily PO	3.40 (3.01, 3.85)	2.76 (2.48, 3.06)	3.15 (2.80, 3.55)
Antifungals and Antivirals					
acyclovir	400 mg single dose PO	480 mg once daily PO	1.02 (0.87, 1.2)	0.82 (0.71, 0.93)	1.13 (0.94, 1.36)
posaconazole	300 mg single dose PO	480 mg once daily PO	0.98 (0.82, 1.17)	1.11 (0.95, 1.29)	1.10 (0.94, 1.30)
voriconazole	200 mg twice daily PO	480 mg once daily PO	0.56 (0.51, 0.62)	0.61 (0.53, 0.71)	0.49 (0.42, 0.57)
HMG-CoA Reductase Inhibitors					
atorvastatin	20 mg single dose PO	480 mg once daily PO	3.29 (2.84, 3.82)	2.17 (1.76, 2.67)	3.62 (2.87, 4.55)
Oral Contraceptives					
ethinyl estradiol (EE) /levonorgestrel (LNG)	0.03 mg EE single dose PO	480 mg once daily PO	1.42 (1.32, 1.52)	0.89 (0.83, 0.96)	1.57 (1.45, 1.70)
	0.15 mg LNG single dose PO		1.36 (1.30, 1.43)	0.95 (0.86, 1.04)	1.38 (1.32, 1.46)

Abbreviations: PO=oral
* C12hr reported for voriconazole.

Table 5: Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Drug Interaction Studies or Predicted Interactions* (Information in the Table Applies to Co-administration of Letermovir and the Concomitant Drug without Cyclosporine, Unless Otherwise Indicated)

Concomitant Drug Class and/or Clearance Pathway: Drug Name	Effect on Concentration†	Clinical 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 letermovir.
Anticoagulants		
warfarin	↓ warfarin	When letermovir is co-administered with warfarin, frequently monitor International Normalized Ratio (INR)§.
Anticonvulsants		
phenytoin	↓ phenytoin	When letermovir is co-administered with phenytoin, frequently monitor phenytoin concentrations§.
Antidiabetic agents		
Examples: glyburide, repaglinide, rosiglitazone	↑ glyburide ↑ repaglinide ↑ rosiglitazone	When letermovir is co-administered with glyburide, repaglinide, or rosiglitazone, frequently monitor glucose concentrations§. When letermovir is co-administered with cyclosporine, use of repaglinide is not recommended.
Antifungals		
voriconazole‡	↓ voriconazole	If concomitant administration of voriconazole is necessary, closely monitor for reduced effectiveness of voriconazole§.
Antimycobacterial		
rifampin	↓ letermovir	Co-administration of letermovir and rifampin is not recommended.
Antipsychotics		

pimozide	↑ pimozide	Co-administration is **contraindicated** due to risk of QT prolongation and torsades de pointes
Ergot alkaloids		
ergotamine, dihydroergotamine	↑ ergotamine, dihydroergotamine	Co-administration is **contraindicated** due to risk of ergotism
HMG-CoA Reductase Inhibitors		
atorvastatin‡	↑ atorvastatin	When letermovir is co-administered with atorvastatin, do not exceed an atorvastatin dosage of 20 mg daily§. Closely monitor patients for myopathy and rhabdomyolysis. When letermovir is co-administered with cyclosporine, use of atorvastatin is not recommended.
pitavastatin, simvastatin	↑ HMG-CoA reductase inhibitors	Co-administration of letermovir and pitavastatin or simvastatin is not recommended. When letermovir is co-administered with cyclosporine, 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 letermovir is co-administered with these statins, a statin dosage reduction may be necessary§. Closely monitor patients for myopathy and rhabdomyolysis. When letermovir is co-administered with cyclosporine, use of lovastatin is not recommended. When letermovir is co-administered with cyclosporine, refer to the statin prescribing information for specific statin dosing recommendations.
Immunosuppressants		
cyclosporine‡	↑ cyclosporine ↑ letermovir	Decrease the dosage of letermovir to 240 mg once daily Frequently monitor cyclosporine whole blood concentrations during treatment and after discontinuation of letermovir and adjust the dose of cyclosporine accordingly§.

sirolimus‡	↑ sirolimus	When letermovir is co-administered with sirolimus, frequently monitor sirolimus whole blood concentrations during treatment and after discontinuation of letermovir and adjust the dose of sirolimus accordingly§. When letermovir is co-administered with cyclosporine 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 letermovir 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.
CYP3A Substrates		
Examples: alfentanil, fentanyl, midazolam, and quinidine	↑ CYP3A substrate	When letermovir is co-administered with a CYP3A substrate, refer to the prescribing information for dosing of the CYP3A substrate with a moderate CYP3A inhibitor§. When letermovir is co-administered with cyclosporine, 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**

* This table is not all inclusive.
† ↓ =decrease, ↑=increase
‡ These interactions have been studied *[see Package Insert: Clinical Pharmacology (12.3)]*.
§ Refer to the respective prescribing information.

8.4 Preparation, Storage, and Administration: Oral Formulation

Letermovir tablets are supplied in two formulations:

- Letermovir 240 mg tablet: yellow oval tablet with “591” on one side and Merck logo on the other side.
- Letermovir 480 mg tablet: pink oval, bi-convex tablet with “595” on one side and Merck logo on the other side.

Letermovir tablets contain either 240 mg or 480 mg of letermovir and the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone 25, and film-coated with a coating material containing the following inactive ingredients: hypromellose 2910, iron oxide red (only for 480 mg tablets), iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin, Carnauba wax is added as a polishing agent.

Tablets should be swallowed whole with or without food.

Store letermovir tablets in the original package until use.

Store letermovir tablets at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F)

8.5 Preparation, Storage, and Administration: Intravenous formulation

Letermovir injection is supplied in 30 mL single-dose vials containing either 240 mg/12 mL per vial (20 mg/mL) or 480 mg/24 mL per vial (20 mg/mL). The preparation and administration instructions are the same for either dose.

Letermovir vials are for single use only. Discard any unused portion.

Preparation and Administration Instructions

- Letermovir must be diluted prior to intravenous (IV) use.
- Inspect vial contents for discoloration and particulate matter prior to dilution. Letermovir injection is a clear colorless solution. Do not use the vial if the solution is discolored or contains visible particles.
- Do not shake letermovir vial.
- Add one single-dose vial of letermovir injection into a 250 mL pre-filled IV bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP and mix bag gently. Do not shake. Only 0.9% Sodium Chloride and 5% Dextrose are chemically and physically compatible with letermovir injection.
- Use compatible IV bags and infusion set materials. Letermovir injection is compatible with the following IV bags and infusion set materials. Letermovir injection is not recommended with any IV bags or infusion set materials not listed below (note that letermovir injection is not recommended for use with polyurethane-containing IV administration set tubing).

  IV Bags Materials:

  Polyvinyl chloride (PVC), ethylene vinyl acetate (EVA) and polyolefin (polypropylene and polyethylene)

  Infusion Sets Materials:

  PVC, polyethylene (PE), polybutadiene (PBD), silicone rubber (SR), styrene–butadiene copolymer (SBC), styrene-butadiene-styrene copolymer (SBS), polystyrene (PS)

  Plasticizers:

Diethylhexyl phthalate (DEHP), tris (2-ethylhexyl) trimellitate (TOTM), benzyl butyl phthalate (BBP)

Catheters:

Radiopaque polyurethane

- Once diluted, the solution of letermovir is clear, and ranges from colorless to yellow. Variations of color within this range do not affect the quality of the product. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Discard if discoloration or visible particles are observed.
- The diluted solution is stable for up to 24 hours at room temperature or up to 48 hours under refrigeration at 2°C to 8°C (36°F to 46°F) (this time includes storage of the diluted solution in the intravenous bag through the duration of infusion).
- Administer the entire contents of the intravenous bag by intravenous infusion via a peripheral catheter or central venous line at a constant rate over 1 hour. Do not administer as an IV bolus injection.

Compatible Drug Products:

The physical compatibility of letermovir injection with selected injectable drug products was evaluated in two commonly available diluents. Letermovir should not be co-administered through the same intravenous line (or cannula) with other drug products and diluent combinations except those listed below. Refer to the respective prescribing information of the co-administered drug(s) to confirm compatibility of simultaneous co-administration.

List of Compatible Drug Products when letermovir and Drug Products are Prepared in 0.9% Sodium Chloride Injection, USP:

Ampicillin sodium, ampicillin sodium/sulbactam sodium, anti-thymocyte globulin, caspofungin, daptomycin, fentanyl citrate, fluconazole, furosemide, human insulin, magnesium sulfate, methotrexate, micafungin.

List of Compatible Drug Products when letermovir and Drug Products are Prepared in 5% Dextrose Injection, USP:

Amphotericin B (lipid complex)*, anidulafungin, cefazolin sodium, ceftaroline, ceftriaxone sodium, doripenem, famotidine, folic acid, ganciclovir sodium, hydrocortisone sodium succinate, morphine sulfate, norepinephrine bitartrate, pantoprazole sodium, potassium chloride, potassium phosphate, tacrolimus, telavancin, tigecycline.

*Amphotericin B (lipid complex) is compatible with letermovir. However, Amphotericin B (liposomal) is incompatible (see below)

Incompatible Drug Products

Letermovir injection is physically incompatible with amiodarone hydrochloride, amphotericin B (liposomal), aztreonam, cefepime hydrochloride, ciprofloxacin, cyclosporine, diltiazem hydrochloride, filgrastim, gentamicin sulfate, levofloxacin, linezolid, lorazepam, midazolam HCl, mycophenolate mofetil hydrochloride, ondansetron, palonosetron.

Storage

Store letermovir injection vials at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F).

Store in the original carton to protect from exposure to light.

8.6 Non Clinical Toxicology

8.6.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Letermovir was not genotoxic in *in vitro* or *in vivo* assays, including microbial mutagenesis assays, chromosomal aberration in Chinese hamster ovary cells, and in an *in vivo* mouse micronucleus study.

Carcinogenicity studies with letermovir have not been conducted.

Impairment of Fertility

In a fertility and early embryonic development study in rats, no effects of letermovir on female fertility were observed at letermovir exposures (AUC) approximately 5 times higher than human exposure at the RHD.

In male rat fertility studies, decreased fertility associated with irreversible testicular toxicity was observed at

≥180 mg/kg/day (greater than or equal to 3 times the human exposure at the RHD). No fertility or testicular effects were observed at dose levels resulting in letermovir exposures (AUC) similar to human exposure at the RHD [see Nonclinical Toxicology (13.2)].

8.6.2 Animal Toxicology and Pharmacology

Testicular toxicity in rats observed at ≥180 mg/kg/day (greater than or equal to 3 times the human exposure at the RHD) was characterized by decreased testis weight, bilateral seminiferous tubular degeneration, decreased sperm count and motility, and resultant decreased male fertility. Male reproductive system toxicities were not observed in either a monkey testicular toxicity study up to 240 mg/kg/day (approximately 2 times higher than human exposure at the RHD), or a general toxicology study in mice up to 250 mg/kg/day (approximately 3 times higher than human exposure at the RHD).

8.7 Clinical Studies

To evaluate letermovir prophylaxis as a preventive strategy for CMV infection or disease in transplant recipients at high risk for CMV reactivation, the efficacy of letermovir was assessed in a multicenter, double-blind, placebo-controlled Phase 3 Trial (P001, NCT02137772) in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). Subjects were randomized (2:1) to receive either letermovir at a dose of 480 mg once daily adjusted to 240 mg when co-administered with cyclosporine, or placebo. Randomization was stratified by investigational site and risk level for CMV reactivation at the time of study entry. Study drug was initiated after HSCT (at any time from Day 0 to Day 28 post-transplant) and continued through Week 14 post-transplant. Study drug was administered either orally or

intravenously; the dose of letermovir was the same regardless of the route of administration. Subjects received CMV DNA monitoring weekly until post-transplant Week 14 and then bi-weekly until post- transplant Week 24, with initiation of standard-of-care CMV pre-emptive therapy if CMV viremia was considered clinically significant. Subjects had continued follow-up through Week 48 post-transplant.

Among the 565 treated subjects, 70 subjects were found to have CMV viremia prior to study drug initiation and were therefore excluded from the efficacy analyses. The efficacy population consisted of 325 subjects who received letermovir (including 91 subjects who received at least one IV dose) and 170 who received placebo (including 41 subjects who received at least one IV dose). The IV formulation of letermovir was used at investigators' discretion in subjects who were unable to take oral therapy (e.g., unable to tolerate oral intake). The median time to starting study drug was 8 days after transplantation. Thirty-four percent (34%) of subjects were engrafted at baseline. The median age was 55 years (range: 18 to 76 years); 57% were male; 84% were White; 9% were Asian; 2% were Black or African American; and 7% were Hispanic or Latino.

At baseline, 30% of all subjects had one or more of the following factors associated with increased risk for CMV reactivation (high risk stratum): Human Leukocyte Antigen (HLA)-related donor with at least one mismatch at one of the following three HLA-gene loci: HLA-A, -B or –DR; haploidentical donor; unrelated donor with at least one mismatch at one of the following four HLA-gene loci: HLA-A, -B, -C and -DRB1; use of umbilical cord blood as stem cell source; use of ex vivo T-cell-depleted grafts; Grade 2 or greater Graft- Versus-Host Disease (GVHD) requiring systemic corticosteroids. The remaining 70% of subjects did not meet any of these high risk stratum criteria and were therefore included in the low risk stratum. Additionally, 48% of subjects received a myeloablative regimen, 51% were receiving cyclosporine, and 43% were receiving tacrolimus. The most common primary reasons for transplant were acute myeloid leukemia (38%), myelodysplastic syndrome (16%), and lymphoma (12%).

Clinically Significant CMV Infection

The primary efficacy endpoint of Trial P001 was the incidence of clinically significant CMV infection through Week 24 post-transplant (prophylaxis failure). Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV pre-emptive therapy (PET) based on documented CMV viremia (using the Roche COBAS® AmpliPrep/COBAS TaqMan® assay, LLoQ is 137 IU/mL, which is approximately 150 copies/mL) and the clinical condition of the subject. The protocol-

specified guidance for CMV DNA thresholds for the initiation of PET during the treatment period was ≥ 150 copies/mL or > 300 copies/mL for subjects in the high and low risk strata, respectively. From Week 14 through Week 24, the threshold was >300 copies/mL for both high and low risk strata subjects. The Non- Completer=Failure (NC=F) approach was used, where subjects who discontinued from the trial prior to Week 24 post-transplant or had a missing outcome at Week 24 post-transplant were counted as failures.

Efficacy results from Trial P001 are shown in .

748 **Table 6**.

Table 6: Trial P001 Efficacy Results in HSCT Recipients (NC=F Approach, FAS Population) Through Week 24

Parameter	Letermovir (N=325)	Placebo (N=170)
Proportion of subjects who failed prophylaxis	**38%**	**61%**
Reasons for failures*		
Clinically significant CMV infection by Week 24†	18%	42%
Initiation of PET based on documented CMV viremia	16%	40%
CMV end-organ disease	2%	2%
Discontinued from study before Week 24‡	17%	16%
Missing outcome in Week 24 visit window	3%	3%
Stratum-adjusted treatment difference (Letermovir-Placebo)§		
Difference (95% CI)	-23.5 (-32.5, -14.6)¶	

* The categories of failure are mutually exclusive and based on the hierarchy of categories in the order listed.

† Through Week 14, 8% of subjects in the letermovir group and 39% of subjects in the placebo group experienced clinically significant CMV infection.

‡ Reasons for discontinuation included adverse event, death, lost to follow-up, physician decision, and withdrawal by subject.

§ 95% CI and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).

¶ p-value <0.0001.

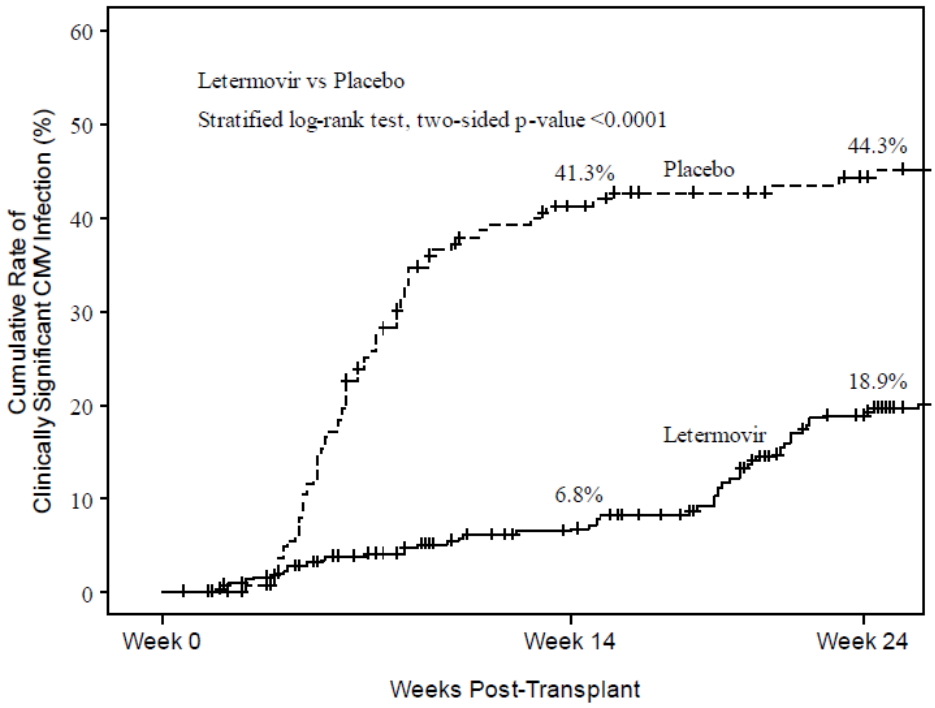
Note: FAS=Full analysis set; FAS includes randomized subjects who received at least one dose of study medication, and excludes subjects with detectable CMV DNA at baseline. Approach to handling missing values: Non-Completer=Failure (NC=F) approach. With NC=F approach, failure was defined as all subjects who developed clinically significant CMV infection or prematurely discontinued from the study or had a missing outcome through Week 24 post-transplant visit window.

Efficacy results were consistent across high and low risk strata for CMV reactivation. The time to clinically significant CMV infection is shown in

754 Figure **1**.

755

Figure 1: P001: Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection Through Week 24 Post-Transplant in HSCT Recipients (FAS Population)



Number of Subjects at Risk			
Letermovir	325	270	212
Placebo	170	85	70

Post-hoc analysis demonstrated that among letermovir-treated subjects, inclusion in the high risk stratum for CMV reactivation at baseline, occurrence of GVHD, and steroid use at any time after randomization may be associated with the development of clinically significant CMV infection between Week 14 and Week 24 post-transplant.

Mortality

The Kaplan-Meier event rate for all-cause mortality in the letermovir vs. placebo groups was 12% vs. 17% at Week 24 post-transplant, and 24% vs. 28% at Week 48 post-transplant.

8.8 Adverse Events

Adult CMV-seropositive Recipients [R+] of an Allogeneic HSCT

The safety of letermovir was evaluated in one Phase 3 randomized, double-blind, placebo-controlled trial (P001) in which 565 subjects were randomized and treated with letermovir (N=373) or placebo (N=192) through Week 14 post-transplant. Adverse events were those reported while subjects were on study medication or within two weeks of study medication completion/discontinuation. The mean time for reporting adverse events and laboratory abnormalities was approximately 22% longer in the letermovir arm compared to the placebo arm.

Cardiac Adverse Events:

The cardiac adverse event rate (regardless of investigator-assessed causality) was higher in subjects receiving letermovir (13%) compared to subjects receiving placebo (6%). The most common cardiac adverse events were tachycardia (reported in 4% of letermovir subjects and in 2% of placebo subjects) and atrial fibrillation (reported in 3% of letermovir subjects and in 1% of placebo subjects). Among those subjects who experienced one or more cardiac adverse events, 85% of letermovir and 92% of placebo subjects had events reported as mild or moderate in severity.

Common Adverse Events

The rate of adverse events occurring in at least 10% of subjects in the letermovir group and at a frequency at least 2% greater than placebo are outlined in Table 7.

Table 7: Trial P001 All Grade Adverse Events Reported in ≥ 10% of Letermovir-Treated HSCT Recipients at a Frequency at least 2% Greater than Placebo

Adverse Events	Letermovir (N=373)	Placebo (N=192)
nausea	27%	23%
diarrhea	26%	24%
vomiting	19%	14%
peripheral edema	14%	9%
cough	14%	10%
headache	14%	9%
fatigue	13%	11%
abdominal pain	12%	9%

Overall, similar proportions of subjects in each group discontinued study medication due to an adverse event (13% of letermovir subjects vs. 12% of placebo subjects). The most frequently reported adverse event that led to study drug discontinuation was nausea, occurring in 2% of letermovir subjects and 1% of placebo subjects. Hypersensitivity reaction, with associated moderate dyspnea, occurred in one subject following the first infusion of IV letermovir after switching from oral letermovir, leading to treatment discontinuation.

Laboratory Abnormalities

Selected laboratory abnormalities reported during treatment or within 2 weeks of stopping treatment are presented in Table 8.

Table 8: Trial P001 Selected Laboratory Abnormalities

	Letermovir N=373	Placebo N=192
Absolute neutrophil count (cells/μL)		
< 500	19%	19%

500 – < 750	4%	7%
750 – < 1000	8%	9%
Hemoglobin (g/dL)		
< 6.5	2%	1%
6.5 – < 8.0	14%	15%
8.0 – < 9.5	41%	43%
Platelets (cells/µL)		
< 25000	27%	21%
25000 – < 50000	17%	18%
50000 – < 100000	20%	30%
Serum creatinine (mg/dL)		
> 2.5	2%	3%
> 1.5 – 2.5	17%	20%

The median time to engraftment (defined as absolute neutrophil count ≥ 500/mm3 on 3 consecutive days after transplantation) was 19 days in the letermovir group and 18 days in the placebo group.

9 REGULATORY AND REPORTING REQUIREMENTS

9.1 Adverse Events (AEs)

Definition: any unfavorable medical occurrence in a human subject including any abnormal sign, symptom, or disease.

For the purposes if this study, “Adverse Event” or “AE” shall mean any untoward medical occurrence iin a Study subject who is administered the Study Drug (letermovir) regardless of whether or not a causal relationship with the Study Drug exists. By way of example and without limitation, an AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of the Study Drug.

Grading: the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for all toxicity reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website.

Attribution (relatedness), Expectedness, and Seriousness: the definitions for the terms listed that should be used are those provided by the Department of Health and Human Services’ Office for Human Research Protections (OHRP). A copy of this guidance can be found on OHRP’s website:

http://www.hhs.gov/ohrp/policy/advevntguid.html

Unanticipated Problems Definition:

- unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB- approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research);
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

9.2 Serious Adverse Events (SAEs)

"**Serious Adverse Event**" or "**SAE**" shall mean any untoward medical occurrence in a Study subject who is administered the Study Drug (letermovir) which meets one or more of the seriousness criteria outlined below.

An adverse event should be classified as a serious adverse event if the following seriousness criteria are met:

- It results in death (i.e., the adverse event actually causes or leads to death)
- It is life threatening (i.e., the adverse event, in the view of the investigator, places the subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.).
- It requires or prolongs inpatient hospitalization.
- It results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the subject's ability to conduct normal life functions).
- It results in a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to the IMP.
- It is considered a significant medical event by the investigator based on medical judgment (e.g., may jeopardize the subject or may require medical/surgical intervention to prevent one of the outcomes listed above).

"**Suspected Unexpected Serious Adverse Reaction**" or "**SUSAR**" shall mean any Serious Adverse Event, the nature, severity or frequency of which is not consistent with information in the most current Summary of Product Characteristics (SPC) or Package Insert.

9.3 Noncompliance

Definition: failure to follow any applicable regulation or institutional policies that govern human subjects research or failure to follow the determinations of the IRB. Noncompliance may occur due to lack of knowledge or due to deliberate choice to ignore regulations, institutional policies, or determinations of the IRB.

9.4 Serious Noncompliance

Definition: noncompliance that materially increases risks, that results in substantial harm to subjects or others, or that materially compromises the rights or welfare of participants.

9.5 Reporting to the OSU IRB

The OSU PI is required to promptly notify the IRB of the following events:

- Any unanticipated problems involving risks to participants or others which occur at OSU, or that impacts participants or the conduct of the study.
- Noncompliance with federal regulations or the requirements or determinations of the IRB.
- Receipt of new information that may impact the willingness of participants to participate or continue participation in the research study.

These events must be reported to the IRB within the time frames outlined in the IRB policy.

9.6 Reporting to the sponsor

Principal investigator shall forward to Merck's Global Pharmacovigilance ("Merck GPV") group, any SAE or SUSAR, including, but not limited to, all initial and follow up information involving any study subject in the study. Notification shall be in the form of a completed CIOMS I/MedWatch (or other mutually agreed upon format) within two (2) business days of but not longer than three (3) calendar days of receipt of this information. This information shall be transmitted to Merck GPV using the contact information provided below or such other modified contact information as provided by Merck in writing. All information shall be transmitted in the English language and contain the reporter's name and the study subject identifier code. SUSAR information will be reported unblinded if the study drug has been blinded in the study. Randomization codes for all other SAEs will be provided to Merck GPV at end of study if the Study Drug has been blinded in the study.

SAE reports and any other relevant safety information are to be forwarded to Merck GPV facsimile number: 215-661-6229.

9.7 Reporting to the FDA

The conduct of the study will comply with all FDA safety reporting requirements. **PLEASE NOTE THAT REPORTING REQUIREMENTS FOR THE FDA DIFFER FROM REPORTING REQUIREMENTS FOR THE IRB.** It is the responsibility of the investigator to report any unanticipated problem to the FDA as follows:

- Report any unexpected fatal or life-threatening adverse experiences associated with use of the drug (i.e., there is a reasonable possibility that the experience may have been caused by the drug) by telephone or fax no later than 7 calendar days after initial receipt of the information. A life-threatening adverse experience is defined as any adverse drug experience that places the subject (in the view of the investigator) at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

- Report any serious, unexpected adverse experiences, as well as results from animal studies that suggest significant clinical risk within 15 calendar days after initial receipt of this information. A serious adverse drug experience is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:
    - Death
    - A life-threatening adverse drug experience
    - Inpatient hospitalization or prolongation of existing hospitalization
    - A persistent or significant disability/incapacity (i.e., a substantial disruption of a person's ability to conduct normal life functions)
    - A congenital anomaly/birth defect
    - Any other experience which, based upon appropriate medical judgment, may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above

An unexpected adverse drug experience is defined as any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or risk information, if an IB is not required or available).

All MedWatch forms will be sent by the investigator or investigator's team to the FDA (refer to the FDA website to obtain the current address and fax number for the Center for Drug Evaluation and Research Division of Oncology Drug Products).

9.8 Timeframe for Reporting Required Events

Reportable adverse events will be tracked for 30 days following the last day of study treatment.

Deaths	
Any reportable death while on study or within 30 days of study	Immediately, within 24 hours, to PI and the IRB
Any reportable death while off study	Immediately, within 24 hours, to PI and the IRB
Adverse Events/Unanticipated Problems	
Any reportable adverse events as described in Sections 9.1 and 9.2 (other than death) and 9.9	Immediately, within 24 hours to PI and within required time frame to the IRB (per local policy) and within 7 or 15 calendar days to the FDA
All adverse events regardless of grade and attribution should be submitted cumulatively	Include in DSM report
Noncompliance and Serious Noncompliance	

All noncompliance and serious noncompliance as described in Sections 9.3 and 9.4	Immediately, within 24 hours, to PI and within required time frame to the IRB (per local policy)

9.9 Overdose

In this trial, an overdose is any dose higher than two times the dose specified in section 4.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met. If a dose of Sponsor's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect." All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper.

There is no specific antidote for overdose with letermovir. In case of overdose, it is recommended that the patient be monitored for adverse reactions and appropriate symptomatic treatment be instituted.

It is unknown whether dialysis will result in meaningful removal of letermovir from systemic circulation.

9.10 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a woman occurring while on study or within 28 days of her last dose of study drug are considered immediately reportable events. Protocol therapy is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported within 24 hours.

All subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). CRFs will be used to report pregnancies and pregnancy outcomes.

9.11 Data and safety monitoring

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at the regular protocol review meeting at least monthly. The PI of the trial will review toxicities and responses of the trial where applicable and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with sponsors, to determine if the trial should be terminated before completion. Serious adverse events and responses will also be reviewed by the OSUCCC Data

and Safety Monitoring Committee (DSMC). The PI will also submit a progress report that will be reviewed by the committee per the DSMC plan. All reportable Serious Adverse Events (SAE) will be reported to the IRB of record as per the policies of the IRB.

9.11.1 Data Submission

The study will be managed per OSU Clinical Trial Office. Data will be directly entered into the OSU OnCore database.

9.11.2 Auditing

As the study sponsor, The Ohio State University Comprehensive Cancer Center (OSUCCC) will audit the trial per OSU policies. Audits will be performed by the OSUCCC Clinical Research Audit Team.

9.12 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. Investigators and study staff will undergo training on Good Clinical Practice (GCP) through the Collaborative Institutional Training Initiative (CITI). GCP training sets the standard for the design, conduct, recording, and reporting of studies involving human subjects, ensuring that study subjects rights, safety, and well-being are protected. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and wellbeing of the patients. The study will only be conducted at sites where IRB approval has been obtained. The protocol, informed consent form, written information given to the patients (including pill diaries), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator, as allowable by local regulations. The principal investigator will ensure that the study will be conducted according to the protocol and all applicable regulations. The protection of each subject’s rights and welfare will be maintained.

9.13 Retention of records

FDA regulations (21 CFR § 312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the United States under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

10 STATISTICAL METHODS

10.1 Study Design and Sample Size Justification

The primary objective of this single center, single arm phase II study is to determine the efficacy of letermovir prophylaxis in PLL, CLL, PTCL or CTCL patients treated with alemtuzumab. The efficacy will be measured through the CMV reactivation rate during letermovir prophylaxis (3

months after completion of alemtuzumab therapy). All eligible patients who receive any letermovir will be included in the safety analysis, and all patients who receive ≥90% of planned letermovir doses are evaluable for the efficacy analysis.

Fleming's two-stage design[80] will be followed to conduct the study. Previous trials reported CMV reactivation rate of 30% in a similar patient population, and our own institutional data revealed a similar pattern. Based on these data, we determined that a CMV reactivation rate of 30% or higher is not acceptable, which leads to our null hypothesis of a 70% safety rate. In a pivotal phase 3 trial, letermovir prophylaxis resulted in a clinically significant 23.1% absolute reduction (61.6% relative risk reduction) in CMV infection rate compared with placebo in recipients of allogeneic hematopoietic stem cell transplantation without evidence of hematologic toxicity [67]. Therefore, we hypothesized that letermovir prophylaxis will reduce the CMV by 20% in our patient population to a 10% reactivation rate, which translates to an alternative hypothesis of 90% safety rate.

With a one-sided type I error rate of 5% and 85% power, Fleming's two-stage design allows a first-stage analysis after the first 14 patients are enrolled and evaluated. If 4 or more patients have CMV reactivation during letermovir prophylaxis period, the regimen will be considered inefficacious, and the study will be terminated early due to futility. On the other hand, if none of the 14 patients experiences CMV reactivation, letermovir will be declared effective in preventing CMV reactivation, and the study will be ended early with rejection of the null hypothesis as the final conclusion. If CMV infection is observed in between 1 to 3 patients among the first 14, then the study will continue to accrue to a total of 28 patients. By the end of the study, if at least 24 out of the 28 patients are CMV free, we will conclude the regimen effective to warrant further investigation.

To account for the possibility that some patients might not be evaluable, we will allow a 5% over-accrual for a total target enrollment of 30 patients. With an anticipated accrual rate of 1.5 patients a month, the study is expected to complete enrolling for the first stage in 10 months. With another 7 months for the primary endpoint evaluation, the first stage will finish in about 17 months. If the second stage were to continue, the whole study can last as long as 27 months.

10.2 Analysis of Primary Objective

1. For efficacy analysis, the CMV reactivation rate will be defined as the proportion of patients who experience CMV reactivation (CMV DNA by real time polymerase chain reaction >500 IU/mL) during prophylaxis period among all patients who receive ≥90% of planned letermovir doses. The rate will be provided with 95% binomial confidence interval.

10.3 Analysis of Secondary Objectives

1. All eligible patients who receive any letermovir prophylaxis will be included in the tolerability analysis. Adverse event data will be described and graded per the NCI CTCAE v5.0 guidelines. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns, especially for grade 3 or above adverse events. To assess tolerability, we also capture the proportion of patients who require dose reduction as well as those who go off treatment due to adverse events.

2. Clinically significant CMV reactivation be determined per the Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum [71] (Appendix 12.1).

3. OS of patients treated with alemtuzumab after letermovir prophylaxis will be calculated from trial enrollment to the occurrence of (death due to any cause), censoring event-free patients at time of last follow-up. OS will be estimated with the method of Kaplan-Meier (KM), where KM curves will be drawn to aid with visualization and estimates provided with 95% confidence intervals.

10.4 Analysis of Exploratory Objectives

CMV DNA Sequence Analysis to be performed only in subjects with CMV reactivation. Resistance to letermovir will be monitored by retrospective genotypic analysis of the CMV terminase gene UL56 in CMV DNA extracts from selected plasma samples collected at the time of diagnosed CMV reactivation. Samples will be analyzed by standard population sequencing technology through an established contract laboratory with validated protocols in place. If no mutations are noted in UL56, then genotype testing will reflex to UL51 and UL89 (less frequent resistance mutations have been reported in these genes).

11 REFERENCES

1. Foss, F.M., et al., *Peripheral T-cell lymphoma.* Blood, 2011. **117**(25): p. 6756-6767.
2. Vose, J., et al., *International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes.* J Clin Oncol, 2008. **26**(25): p. 4124-30.
3. Morgensztern, D., et al., *Lack of survival improvement in patients with peripheral T-cell lymphoma: a Surveillance, Epidemiology, and End Results analysis.* Leuk Lymphoma, 2011. **52**(2): p. 194-204.
4. Weisenburger, D.D., et al., *Peripheral T-cell lymphoma, not otherwise specified: a report of 340 cases from the International Peripheral T-cell Lymphoma Project.* Blood, 2011. **117**(12): p. 3402-8.
5. Abouyabis, A.N., et al., *Incidence and outcomes of the peripheral T-cell lymphoma subtypes in the United States.* Leuk Lymphoma, 2008. **49**(11): p. 2099-107.
6. Morton, L.M., et al., *Lymphoma incidence patterns by WHO subtype in the United States, 1992-2001.* Blood, 2006. **107**(1): p. 265-76.
7. Hristov, A.C., T. Tejasvi, and R.A. Wilcox, *Mycosis fungoides and Sezary syndrome: 2019 update on diagnosis, risk-stratification, and management.* Am J Hematol, 2019. **94**(9): p. 1027-1041.
8. Agar, N.S., et al., *Survival outcomes and prognostic factors in mycosis fungoides/Sezary syndrome: validation of the revised International Society for Cutaneous Lymphomas/European Organisation for Research and Treatment of Cancer staging proposal.* J Clin Oncol, 2010. **28**(31): p. 4730-9.
9. Duvic, M., et al., *Bexarotene is effective and safe for treatment of refractory advanced-stage cutaneous T-cell lymphoma: multinational phase II-III trial results.* J Clin Oncol, 2001. **19**(9): p. 2456-71.
10. Olsen, E.A., et al., *Phase IIb multicenter trial of vorinostat in patients with persistent, progressive, or treatment refractory cutaneous T-cell lymphoma.* J Clin Oncol, 2007. **25**(21): p. 3109-15.
11. Mann, B.S., et al., *Vorinostat for treatment of cutaneous manifestations of advanced primary cutaneous T-cell lymphoma.* Clin Cancer Res, 2007. **13**(8): p. 2318-22.

12. Whittaker, S.J., et al., *Final results from a multicenter, international, pivotal study of romidepsin in refractory cutaneous T-cell lymphoma.* J Clin Oncol, 2010. **28**(29): p. 4485-91.
13. Piekarz, R.L., et al., *Phase II Multi-Institutional Trial of the Histone Deacetylase Inhibitor Romidepsin As Monotherapy for Patients With Cutaneous T-Cell Lymphoma.* Journal of Clinical Oncology, 2009. **27**(32): p. 5410-5417.
14. Prince, H.M., et al., *Brentuximab vedotin or physician's choice in CD30-positive cutaneous T-cell lymphoma (ALCANZA): an international, open-label, randomised, phase 3, multicentre trial.* Lancet, 2017. **390**(10094): p. 555-566.
15. Kim, Y.H., et al., *Mogamulizumab versus vorinostat in previously treated cutaneous T-cell lymphoma (MAVORIC): an international, open-label, randomised, controlled phase 3 trial.* Lancet Oncol, 2018. **19**(9): p. 1192-1204.
16. Matutes, E., et al., *Clinical and laboratory features of 78 cases of T-prolymphocytic leukemia.* Blood, 1991. **78**(12): p. 3269-74.
17. Sud, A. and C. Dearden, *T-cell Prolymphocytic Leukemia.* Hematol Oncol Clin North Am, 2017. **31**(2): p. 273-283.
18. Dearden, C.E., et al., *Alemtuzumab therapy in T-cell prolymphocytic leukemia: comparing efficacy in a series treated intravenously and a study piloting the subcutaneous route.* Blood, 2011. **118**(22): p. 5799-802.
19. Pawson, R., et al., *Treatment of T-cell prolymphocytic leukemia with human CD52 antibody.* J Clin Oncol, 1997. **15**(7): p. 2667-72.
20. Ferrajoli, A., et al., *Phase II study of alemtuzumab in chronic lymphoproliferative disorders.* Cancer, 2003. **98**(4): p. 773-8.
21. Keating, M.J., et al., *Campath-1H treatment of T-cell prolymphocytic leukemia in patients for whom at least one prior chemotherapy regimen has failed.* J Clin Oncol, 2002. **20**(1): p. 205-13.
22. Dearden, C.E., et al., *High remission rate in T-cell prolymphocytic leukemia with CAMPATH-1H.* Blood, 2001. **98**(6): p. 1721-6.
23. Krishnan, B., et al., *Stem cell transplantation after alemtuzumab in T-cell prolymphocytic leukaemia results in longer survival than after alemtuzumab alone: a multicentre retrospective study.* Br J Haematol, 2010. **149**(6): p. 907-10.
24. Wiktor-Jedrzejczak, W., et al., *Hematopoietic stem cell transplantation in T-prolymphocytic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation and the Royal Marsden Consortium.* Leukemia, 2012. **26**(5): p. 972-6.
25. Guillaume, T., et al., *Allogeneic hematopoietic stem cell transplantation for T-prolymphocytic leukemia: a report from the French society for stem cell transplantation (SFGM-TC).* Eur J Haematol, 2015. **94**(3): p. 265-9.
26. Kalaycio, M.E., et al., *Allogeneic hematopoietic cell transplant for prolymphocytic leukemia.* Biol Blood Marrow Transplant, 2010. **16**(4): p. 543-7.
27. Poggio, T., J. Duyster, and A. Illert, *Current Immunotherapeutic Approaches in T Cell Non-Hodgkin Lymphomas.* Cancers, 2018. **10**(9): p. 339.
28. Enblad, G., et al., *A pilot study of alemtuzumab (anti-CD52 monoclonal antibody) therapy for patients with relapsed or chemotherapy-refractory peripheral T-cell lymphomas.* Blood, 2004. **103**(8): p. 2920-4.
29. Stewart, J.R., et al., *Alemtuzumab is an effective third-line treatment versus single-agent gemcitabine or pralatrexate for refractory Sezary syndrome: a systematic review.* Eur J Dermatol, 2018. **28**(6): p. 764-774.
30. Bernengo, M.G., et al., *Low-dose intermittent alemtuzumab in the treatment of Sezary syndrome: clinical and immunologic findings in 14 patients.* Haematologica, 2007. **92**(6): p. 784-94.

31. Watanabe, R., et al., *Alemtuzumab therapy for leukemic cutaneous T-cell lymphoma: diffuse erythema as a positive predictor of complete remission.* JAMA Dermatol, 2014. **150**(7): p. 776-9.
32. Kluin-Nelemans, H.C., et al., *Intensified alemtuzumab-CHOP therapy for peripheral T-cell lymphoma.* Ann Oncol, 2011. **22**(7): p. 1595-600.
33. Roswarski, J., et al., *Phase 1/2 study of alemtuzumab with dose-adjusted EPOCH in untreated aggressive T and NK cell lymphomas.* Leuk Lymphoma, 2019. **60**(8): p. 2062-2066.
34. Ravandi, F., et al., *Phase II study of alemtuzumab in combination with pentostatin in patients with T-cell neoplasms.* J Clin Oncol, 2009. **27**(32): p. 5425-30.
35. Cannon, M.J., D.S. Schmid, and T.B. Hyde, *Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection.* Rev Med Virol, 2010. **20**(4): p. 202-13.
36. Borst, E.M., et al., *The human cytomegalovirus UL51 protein is essential for viral genome cleavage-packaging and interacts with the terminase subunits pUL56 and pUL89.* J Virol, 2013. **87**(3): p. 1720-32.
37. Boeckh, M., et al., *Cytomegalovirus in hematopoietic stem cell transplant recipients: Current status, known challenges, and future strategies.* Biol Blood Marrow Transplant, 2003. **9**(9): p. 543-58.
38. El Chaer, F., D.P. Shah, and R.F. Chemaly, *How I treat resistant cytomegalovirus infection in hematopoietic cell transplantation recipients.* Blood, 2016. **128**(23): p. 2624-2636.
39. Allice, T., et al., *Valganciclovir as pre-emptive therapy for cytomegalovirus infection post-allogenic stem cell transplantation: implications for the emergence of drug-resistant cytomegalovirus.* J Antimicrob Chemother, 2009. **63**(3): p. 600-8.
40. Hantz, S., et al., *Drug-resistant cytomegalovirus in transplant recipients: a French cohort study.* J Antimicrob Chemother, 2010. **65**(12): p. 2628-40.
41. Sharma, K., et al., *Phase II Study of Alemtuzumab (CAMPATH-1) in Patients with HTLV-1-Associated Adult T-cell Leukemia/lymphoma.* Clin Cancer Res, 2017. **23**(1): p. 35-42.
42. Kim, J.G., et al., *Alemtuzumab plus CHOP as front-line chemotherapy for patients with peripheral T-cell lymphomas: a phase II study.* Cancer Chemother Pharmacol, 2007. **60**(1): p. 129-34.
43. Binder, C., et al., *CHO(E)P-14 followed by alemtuzumab consolidation in untreated peripheral T cell lymphomas: final analysis of a prospective phase II trial.* Ann Hematol, 2013. **92**(11): p. 1521-8.
44. Weidmann, E., et al., *A phase II study of alemtuzumab, fludarabine, cyclophosphamide, and doxorubicin (Campath-FCD) in peripheral T-cell lymphomas.* Leuk Lymphoma, 2010. **51**(3): p. 447-55.
45. Hopfinger, G., et al., *Sequential chemoimmunotherapy of fludarabine, mitoxantrone, and cyclophosphamide induction followed by alemtuzumab consolidation is effective in T-cell prolymphocytic leukemia.* Cancer, 2013. **119**(12): p. 2258-67.
46. Kuan, J.W., et al., *The Outcome of HyperCVAD Combined with Alemtuzumab for the Treatment of Aggressive T-Cell and NK-Cell Neoplasms.* Indian J Hematol Blood Transfus, 2011. **27**(3): p. 136-45.
47. Intragumtornchai, T., et al., *Alemtuzumab in Combination with CHOP and ESHAP as First-Line Treatment in Peripheral T-Cell Lymphoma.* Blood, 2006. **108**(11): p. 4740-4740.
48. Kim, S.J., et al., *Dose modification of alemtuzumab in combination with dexamethasone, cytarabine, and cisplatin in patients with relapsed or refractory peripheral T-cell lymphoma: analysis of efficacy and toxicity.* Invest New Drugs, 2012. **30**(1): p. 368-75.

49. Rupoli, S., et al., *Alemtuzumab in Combination with Interferon-α or Gemcitabine in Aggressive and Advanced Cutaneous T-Cell Lymphomas: Report of Preliminary Results.* Blood, 2008. **112**(11): p. 5000-5000.
50. de Masson, A., et al., *Long-term efficacy and safety of alemtuzumab in advanced primary cutaneous T-cell lymphomas.* Br J Dermatol, 2014. **170**(3): p. 720-4.
51. Dumitriu, B., et al., *Alemtuzumab in T-cell large granular lymphocytic leukaemia: interim results from a single-arm, open-label, phase 2 study.* Lancet Haematol, 2016. **3**(1): p. e22-9.
52. Alinari, L., et al., *Subcutaneous alemtuzumab for Sezary Syndrome in the very elderly.* Leuk Res, 2008. **32**(8): p. 1299-303.
53. Nguyen, D.D., et al., *Cytomegalovirus viremia during Campath-1H therapy for relapsed and refractory chronic lymphocytic leukemia and prolymphocytic leukemia.* Clin Lymphoma, 2002. **3**(2): p. 105-10.
54. Querfeld, C., et al., *Alemtuzumab for relapsed and refractory erythrodermic cutaneous T-cell lymphoma: a single institution experience from the Robert H. Lurie Comprehensive Cancer Center.* Leuk Lymphoma, 2009. **50**(12): p. 1969-76.
55. Zinzani, P.L., et al., *Preliminary observations of a phase II study of reduced-dose alemtuzumab treatment in patients with pretreated T-cell lymphoma.* Haematologica, 2005. **90**(5): p. 702-3.
56. Kennedy, G.A., et al., *Treatment of patients with advanced mycosis fungoides and Sezary syndrome with alemtuzumab.* Eur J Haematol, 2003. **71**(4): p. 250-6.
57. Lundin, J., et al., *Phase 2 study of alemtuzumab (anti-CD52 monoclonal antibody) in patients with advanced mycosis fungoides/Sezary syndrome.* Blood, 2003. **101**(11): p. 4267-72.
58. Clark, R.A., et al., *Skin effector memory T cells do not recirculate and provide immune protection in alemtuzumab-treated CTCL patients.* Sci Transl Med, 2012. **4**(117): p. 117ra7.
59. Novelli, S., et al., *Alemtuzumab treatment for Sezary syndrome: A single-center experience.* J Dermatolog Treat, 2016. **27**(2): p. 179-81.
60. Buckstein, R., et al., *Alemtuzumab and CHOP Chemotherapy for the Treatment of Aggressive Histology Peripheral T Cell Lymphomas: A Multi-Center Phase I Study.* Clin Lymphoma Myeloma Leuk, 2016. **16**(1): p. 18-28 e4.
61. Kim, S.J., et al., *Alemtuzumab and DHAP (A-DHAP) is effective for relapsed peripheral T-cell lymphoma, unspecified: interim results of a phase II prospective study.* Ann Oncol, 2009. **20**(2): p. 390-2.
62. Wulf, G.G., et al., *Reduced intensity conditioning and allogeneic stem cell transplantation after salvage therapy integrating alemtuzumab for patients with relapsed peripheral T-cell non-Hodgkin's lymphoma.* Bone Marrow Transplant, 2005. **36**(3): p. 271-3.
63. Beltran-Garate, B., et al., *Alemtuzumab in Patients with Advanced Mycosis Fungoides and Sezary Syndrome.* Blood, 2007. **110**(11): p. 3425-3425.
64. Oliveira, A., et al., *Sezary syndrome presenting with leonine facies and treated with low-dose subcutaneous alemtuzumab.* Dermatol Online J, 2011. **17**(11): p. 6.
65. Fernandes, I.C., et al., *Can the level of CD52 expression on Sezary cells be used to predict the response of Sezary syndrome to alemtuzumab?* J Am Acad Dermatol, 2012. **67**(5): p. 1083-5.
66. Kim, S.J., et al., *Non-bacterial infections in Asian patients treated with alemtuzumab: a retrospective study of the Asian Lymphoma Study Group.* Leuk Lymphoma, 2012. **53**(8): p. 1515-24.
67. Marty, F.M., et al., *Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation.* N Engl J Med, 2017. **377**(25): p. 2433-2444.

68. Goldner, T., et al., *The novel anticytomegalovirus compound AIC246 (Letermovir) inhibits human cytomegalovirus replication through a specific antiviral mechanism that involves the viral terminase.* J Virol, 2011. **85**(20): p. 10884-93.
69. Lischka, P., et al., *In vitro and in vivo activities of the novel anticytomegalovirus compound AIC246.* Antimicrob Agents Chemother, 2010. **54**(3): p. 1290-7.
70. Ljungman, P., et al., *A Mortality Analysis of Letermovir Prophylaxis for Cytomegalovirus (CMV) in CMV-Seropositive Recipients of Allogeneic Hematopoietic-Cell Transplantation.* Clin Infect Dis, 2019.
71. Ljungman, P., et al., *Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials: Table 1.* Clinical Infectious Diseases, 2017. **64**(1): p. 87-91.
72. Chou, S., *A third component of the human cytomegalovirus terminase complex is involved in letermovir resistance.* Antiviral Res, 2017. **148**: p. 1-4.
73. Lischka, P., D. Michel, and H. Zimmermann, *Characterization of Cytomegalovirus Breakthrough Events in a Phase 2 Prophylaxis Trial of Letermovir (AIC246, MK 8228).* J Infect Dis, 2016. **213**(1): p. 23-30.
74. Chou, S., L.E. Satterwhite, and R.J. Ercolani, *New Locus of Drug Resistance in the Human Cytomegalovirus UL56 Gene Revealed by In Vitro Exposure to Letermovir and Ganciclovir.* Antimicrob Agents Chemother, 2018. **62**(9).
75. Chou, S., *Rapid In Vitro Evolution of Human Cytomegalovirus UL56 Mutations That Confer Letermovir Resistance.* Antimicrob Agents Chemother, 2015. **59**(10): p. 6588-93.
76. Goldner, T., et al., *Geno- and phenotypic characterization of human cytomegalovirus mutants selected in vitro after letermovir (AIC246) exposure.* Antimicrob Agents Chemother, 2014. **58**(1): p. 610-3.
77. Chou, S., *Comparison of Cytomegalovirus Terminase Gene Mutations Selected after Exposure to Three Distinct Inhibitor Compounds.* Antimicrob Agents Chemother, 2017. **61**(11).
78. Lischka, P., et al., *Impact of glycoprotein B genotype and naturally occurring ORF UL56 polymorphisms upon susceptibility of clinical human cytomegalovirus isolates to letermovir.* Antiviral Res, 2016. **132**: p. 204-9.
79. Goldner, T., H. Zimmermann, and P. Lischka, *Phenotypic characterization of two naturally occurring human Cytomegalovirus sequence polymorphisms located in a distinct region of ORF UL56 known to be involved in in vitro resistance to letermovir.* Antiviral Res, 2015. **116**: p. 48-50.
80. Fleming, T.R., *One-sample multiple testing procedure for phase II clinical trials.* Biometrics, 1982. **38**(1): p. 143-51.

12 APPENDICES

12.1 CMV Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum

CMV Disease	Diagnostic criteria	Notes
Pneumonia	Clinical symptoms and/or signs of pneumonia such as new infiltrates on imaging, hypoxia, tachypnea, and/or dyspnea **AND**	• PCR may be too sensitive, so detection of CMV by PCR alone is insufficient for the diagnosis of CMV pneumonia.

	CMV documented in BAL or lung tissue by virus isolation, rapid culture, histopathology, IHC, or DNA hybridization techniques	• Detection of fungal co-pathogens like Aspergillus spp. + "halo" sign (radiology) indicates fungal, rather than CMV pneumonia. • Superinfection or coinfection with other pathogens may occur and should be noted when present.
GI	Upper and/or lower gastrointestinal (GI) symptoms **AND** macroscopic mucosal lesions **AND** CMV documented in tissue by histopathology, virus isolation, rapid culture, IHC, or DNA hybridization techniques.	• PCR may be too sensitive, so detection of CMV by PCR alone is insufficient for the diagnosis of CMV GI disease • Studies should give information regarding the presence or absence of GI GVHD in HSCT recipients.
Hepatitis	Abnormal liver function tests **AND** CMV documented in tissue by histopathology, IHC, virus isolation, rapid culture, or DNA hybridization techniques **AND** Absence of other documented cause of hepatitis, including DILI	• Studies should give information regarding the presence or absence of hepatic GVHD in HSCT recipients.
CNS	CNS symptoms **AND** Detection of CMV in CNS tissue by virus isolation, rapid culture, IHC, in situ hybridization, or (preferably) quantitative PCR.	• Probable disease requires CNS symptoms plus detection of CMV in CSF without visible contamination of blood plus abnormal imaging results or evidence of encephalitis on electroencephalography.
Retinitis	Typical ophthalmological signs judged by an ophthalmologist experienced with the diagnosis of CMV retinitis **OR** CMV documented in vitreous fluid by NAT (for example PCR)	
Nephritis	Renal dysfunction **AND** Detection of CMV by virus isolation, rapid culture, IHS, or in situ hybridization in a kidney biopsy specimen **AND** Identification of histologic features of CMV infection	• The detection of CMV in urine by PCR or culture is not sufficient for the diagnosis of CMV nephritis as asymptomatic viral shedding in urine is common.

Cystitis	Signs/symptoms of cystitis **AND** Detection of CMV by virus isolation, rapid culture, IHC, or in situ hybridization in a bladder biopsy specimen **AND** Histologic features of CMV infection.	• The detection of CMV in urine by PCR or culture is not sufficient for the diagnosis of CMV cystitis as asymptomatic viral shedding in urine is common.
Myocarditis	Signs/symptoms of myocarditis **AND** Detection of CMV by virus isolation, rapid culture, IHC, or in situ hybridization in a myocardial biopsy specimen **AND** Histologic features of CMV infection.	
Pancreatitis	Signs/symptoms of myocarditis **AND** Detection of CMV by virus isolation, rapid culture, IHC, or in situ hybridization in a pancreatic biopsy specimen **AND** Histologic features of CMV infection.	
Other	Presence of compatible symptoms in other organs **AND** Detection of CMV by virus isolation, rapid culture, IHC, or in situ hybridization in a biopsy specimen	
Reference [71]. BAL= bronchoalveolar lavage; CMV = cytomegalovirus; CNS = central nervous system; DILI = drug induced liver injury; GI = gastrointestinal; GVHD = graft versus host disease; HSCT = hematopoietic stem cell transplant; IHC = immunohistochemistry; NAT = nucleic acid testing; PCR = polymerase chain reaction		

12.2 Eastern Cooperative Oncology Group Performance Status Scale

ECOG	**Description**
0	Asymptomatic (Fully active, able to carry on all predisease activities without restriction)
1	Symptomatic but completely ambulatory (Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature. For example, light housework, office work)
2	Symptomatic, <50% in bed during the day (Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours)
3	Symptomatic, >50% in bed, but not bedbound (Capable of only limited self-care, confined to bed or chair 50% or more of waking hours)
4	Bedbound (Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair)

5	Death

12.3 Child-Pugh Classification of liver disease

	Scoring by Anomaly		
Signs or symptom	**1 point**	**2 points**	**3 points**
Hepatic encephalopathy[1]	Absent	Grade 1 or 2	Grade 3 or 4
Ascites	Absent	Mild	Moderate
Bilirubin (µmol/L)	< 2 mg/dL	2 – 3 mg/dL	> 3 mg/dL
Albumin (g/dL)	> 3.5 g/dL	2.8 – 3.5 g/dL	< 2.8 g/dL
Prothrombin time (INR)	< 1.7	1.7 – 2.3	> 2.3

[1]Hepatic encephalopathy grading:
Grade 1: Altered mood/confusion
Grade 2: Inappropriate behavior, impending stupor, somnolence
Grade 3: Markedly confused, stuporous but arousable
Grade 4: Comatose/unresponsive

Child-Pugh Score interpretation	
5-6 points	Child-Pugh Stage A (mild hepatic insufficiency)
	Child-Pugh Stage B (moderate hepatic insufficiency*)
	Child-Pugh Stage C (severe hepatic insufficiency)

*If hypoalbuminemia is the only abnormality noted, the subject will need to have a score of ≥7 to qualify for moderate hepatic insufficiency for this study