frontiers | Frontiers in Pediatrics

TYPE Mini Review
PUBLISHED 12 September 2025
DOI 10.3389/fped.2025.1663600

Check for updates

OPEN ACCESS

EDITED BY
Juan Tong,
Anhui Provincial Hospital, China

REVIEWED BY
Alexis Kuhn,
Mayo Clinic, United States

*CORRESPONDENCE
Ramia Zakhour
✉ ramia.g.zakhour@uth.tmc.edu

RECEIVED 10 July 2025
ACCEPTED 29 August 2025
PUBLISHED 12 September 2025

CITATION
Hiskey L, Hijano DR and Zakhour R (2025) Revisiting cytomegalovirus in pediatric allogeneic hematopoietic stem cell transplant recipients: current strategies for prevention and management in the letermovir era. Front. Pediatr. 13:1663600. doi: 10.3389/fped.2025.1663600

COPYRIGHT
© 2025 Hiskey, Hijano and Zakhour. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.

Revisiting cytomegalovirus in pediatric allogeneic hematopoietic stem cell transplant recipients: current strategies for prevention and management in the letermovir era

Lisa Hiskey[1], Diego R. Hijano[1,2] and Ramia Zakhour[3]*

[1]Department of Infectious Diseases, St. Jude Children's Research Hospital, Memphis, TN, United States, [2]Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN, United States, [3]Division of Infectious Diseases, Department of Pediatrics, McGovern Medical Center at UTHealth Houston, Children's Memorial Hermann Hospital, Houston, TX, United States

CMV infection remains the most common clinically significant infection in pediatric allogeneic hematopoietic stem cell (HCT) recipients, with seropositive recipients of transplants from seronegative donors at the highest risk for complications. In recent years, letermovir, a novel antiviral with a favorable toxicity profile, was approved first for adults and more recently for pediatric patients for the primary prophylaxis of CMV infection and disease in high-risk HCT recipients. Growing evidence from real-life data regarding the safety and efficacy of letermovir has transformed the landscape of CMV disease in HCT transplant recipients and led to a paradigm shift from a preemptive approach to prophylaxis. Other novel additions to the diagnosis, risk stratification, and treatment of CMV include the measurement of CMV-specific cellular-mediated immunity and the approval of maribavir as a treatment option for resistant/refractory CMV infection and disease. Other prevention and treatment modalities currently under development include virus-specific T cells, monoclonal antibodies, and vaccines. Despite these promising advancements, additional pediatric-specific studies are needed to better understand the viral and immunological implications of these novel preventive and therapeutic methods in this patient population.

KEYWORDS

CMV, antiviral, hematopoietic cell transplant, pediatric, letermovir

Highlights

Letermovir, a novel antiviral agent with a favorable toxicity profile, has transformed CMV disease management in hematopoietic stem cell transplant recipients, shifting the approach from preemptive treatment to prophylaxis in high-risk patients.

10.3389/fped.2025.1663600

Introduction

Cytomegalovirus (CMV) is a double-stranded DNA virus of the herpesvirus family that establishes latency in the host after primary infection and can reactivate during periods of immunosuppression. CMV infection is the most common clinically significant infection following allogeneic hematopoietic stem cell transplantation (HCT) (1–3). Infection usually results from reactivation in seropositive recipients, and seropositive recipients with seronegative donors are considered to be at the highest risk of infection and disease (4). In the absence of appropriate prevention and timely treatment, CMV causes significant morbidity and mortality following HCT. Beyond the direct effect of CMV disease and the organ dysfunction it causes, CMV has indirect and immune-modulating effects on the host, as manifested by an increased risk of other opportunistic infections (including fungal infections) (5–7), a bidirectional relationship with graft-versus-host disease (GVHD) (8, 9), and increased non-relapse mortality (10). In the absence of prophylaxis, up to 80% of seropositive patients undergoing allogeneic HCT experience CMV reactivation (11).

Over the years, different approaches to CMV infection post-HCT have been adopted, including prophylaxis and preemptive therapy (PET). In this review, we provide an overview of CMV infection in pediatric HCT recipients, focusing on the most recent developments in prevention, risk stratification, and management.

Epidemiology and risk factors

CMV is a ubiquitous virus (12). Primary infection occurs via various modes of transmission: person-to-person through virus-containing secretions, mother-to-infant transmission, receipt of blood products, and solid organ transplantation or HCT (12–14). After primary infection, the virus establishes a lifelong latency in hematopoietic progenitor cells, blood monocytes, and tissue cells (12, 14).

In the United States, approximately 50% of the population is CMV seropositive, with varying prevalence depending on age, sex, birthplace, and socioeconomic status (15, 16). Approximately 30% of pediatric HCT recipients develop CMV infection between days +30–100 post-HCT (17).

An important risk factor for CMV infection and disease in HCT recipients is the combination of donor and recipient serostatus (18). HCT recipients are at the highest risk when the recipient is seropositive and the donor is seronegative (1, 18). Other risk factors for CMV infection and disease include lymphopenia, immunosuppressive therapy (including steroid use and post-HCT cyclophosphamide) (19), type of transplant, and post-transplant complications (such as GVHD) (1). Recipients of T-cell-depleted umbilical cord blood, matched unrelated, mismatched, and haploidentical transplants are at a higher risk than recipients of matched-related transplants (1, 18).

Diagnosis and definitions

The initial determination of CMV serostatus in recipients and donors is determined by serologic measurement of CMV-IgG. Currently, post-HCT diagnosis of CMV infection relies on molecular testing to detect CMV DNA in whole blood, serum, and plasma. The definitions of CMV infection and disease are based on consensus by a group of expert panels and are updated regularly for clinical trial purposes. The most recent definitions were published in 2024: *CMV infection* is defined as CMV detection in the blood or CMV DNAemia (CMV DNA detection by qPCR). *Clinically significant CMV infection (csCMVi)* is defined as the development of CMV disease or the need to initiate anti-CMV preemptive therapy for DNAemia above a certain threshold. *CMV disease* is defined as an end-organ disease; that is, CMV infection of a specific organ is demonstrated by the presence of symptoms in the setting of CMV infection and, ideally, documentation of the presence of CMV or CMV-related changes in tissue. End-organ diseases include pneumonia, gastrointestinal disease, hepatitis, central nervous system infection, retinitis, nephritis, cystitis, myocarditis, and pancreatitis. End-organ disease can be classified as proven, probable, or possible, depending on the availability of histological findings and CMV documentation in tissue.

Refractory CMV infection is defined as a CMV DNAemia increase of more than 1 $\log_{10}$ from the peak viral load or persistence after at least two weeks of appropriate antiviral therapy.

Refractory CMV end-organ disease is defined as worsening signs and symptoms, progression to end-organ disease during treatment, or lack of improvement after at least two weeks of appropriate antiviral therapy. *Resistant CMV infection* is defined as refractory CMV infection, in addition to viral genetic alterations that decrease susceptibility to one or more antiviral drugs (20).

Initial management

Preemptive therapy and prophylaxis

The initial approaches to CMV infection in HCT recipients consist of PET, antiviral prophylaxis, or a combination of both. PET aims to detect CMV DNAemia early through frequent (usually weekly) monitoring and initiation of antiviral therapy before the development of CMV disease at predefined thresholds. Prophylaxis involves administering antiviral therapy to high-risk patients early in the post-transplant course and throughout the period of the highest risk of CMV reactivation (21).

Historically, antivirals for the management of CMV infection have carried undesirable side effects, such as myelosuppression from ganciclovir and valganciclovir and nephrotoxicity from foscarnet and cidofovir. These toxicity profiles, in the absence of

other alternatives and the widespread availability of PCR, frequently favor PET.

In 2017, a phase 3 clinical trial showed that letermovir, a CMV viral terminase complex inhibitor, started prophylactically within 28 days of HCT and continued for up to 100 days post-transplant, resulted in a significant reduction in csCMVi in CMV-seropositive adult allogeneic HCT recipients. Letermovir was accordingly approved by the United States Food and Drug Administration (FDA) as a safe and effective medication for primary CMV prophylaxis in CMV seropositive adult allogeneic HCT recipients in the first 100 days post-transplant (22), and this has since become of the standard of care in this population (1) More recently, the duration of letermovir has been extended to 200 days in higher-risk in higher risk patients based on individualized criteria (23). Studies including adult participants suggest that although PET may prevent development of CMV disease, patients with CMV viremia prompting PET have higher overall and non-relapse related mortality compared to patients with no CMV reactivation and not requiring PET (24). Moreover, one study showed that adult patients on letermovir had lower rates of csCMVi and hospitalization, with no incidence of CMV disease compared to aa ~5% incidence of CMV disease in patients receiving PET (25).

In 2024, the FDA approval of letermovir was expanded to include pediatric allogenic HCT recipients aged ≥6 months and weighing ≥6 kg. This approval was based on the results of a small phase 2b, single-arm, non-comparative study (NCT03940586). Data from a clinical trial that included 28 adolescents 12–18 years of age demonstrated a favorable safety profile and comparable rates of csCMVi as seen in the pivotal phase 3 adult study: 24% through week 24 post-HCT (26). Until recently, data on the use of letermovir in pediatrics remained anecdotal through its use as salvage therapy in single patients or case series. A recently published meta-analysis of letermovir prophylaxis in pediatric HCT recipients reviewed 12 observational studies, including a pooled population of 253 pediatric HCT recipients (27). Letermovir was given for 92–221 days and the CMV infection rate was 10.9%. No CMV disease was reported during letermovir prophylaxis, and there were no CMV-related deaths. For the four studies that included a control group (using acyclovir or valacyclovir), the incidence of CMV infection was significantly lower in the letermovir group (RR 0.29, 95% CI 0.16–0.56, $p < 0.001$). The rate of letermovir discontinuation was low (2.4%), and adverse events were mild and infrequent, with no reported myelosuppression or nephrotoxicity (27). Dosing was weight-based, and the dose was reduced by 50% in the case of concurrent cyclosporine administration.

Additional articles reporting the use of letermovir in pediatric HCT have been published in 2025. These studies have supported the safety and tolerability of letermovir compared to valganciclovir and ganciclovir (27), provided additional efficacy data in higher-risk umbilical cord and haploidentical HCT recipients, supported early vs. later initiation of letermovir (28), and demonstrated lower cumulative CMV reactivation up to 1-year post-transplant. as well as the potential for delayed immune reconstitution in letermovir recipients (29).

FDA approval for pediatric use, as well as the results of a recent meta-analysis and other publications, highlight the importance and safety of using letermovir prophylaxis in pediatric HCT recipients in the first 100 days post-transplant, in line with the current adult guidelines. The recently published ECIL-10 guidelines for management of CMV in patient undergoing allogeneic stem cell transplant has incorporated this data and recommends considering letermovir prophylaxis in high risk pediatric patients (28). This is expected to be reflected as well in the recommendations of the upcoming updated ASTCT guidelines for CMV prevention in HCT.

Viral and immune-response monitoring

Concerns regarding letermovir prophylaxis include breakthrough infection and the potential for delayed CMV-specific cellular reconstitution, leading to late-onset CMV, which may be due to decreased CMV antigen exposure (29).

The initial study prompting FDA approval of letermovir demonstrated the potential for breakthrough CMV DNAemia while receiving prophylactic treatment. Consequently, the current guidelines recommend continued CMV monitoring during letermovir prophylaxis. Monitoring is usually recommended for up to 6 months post-HCT, based on the initial letermovir trial showing significant rates of reactivation up to day 180 after discontinuation of letermovir, as supported by other real-life studies suggesting the same. Letermovir prophylaxis and monitoring for CMV DNAemia may be extended in patients assessed to be at high risk of viral reactivation. Monitoring may have to be extended to select patients receiving letermovir prophylaxis for longer periods or those deemed to have risk factors for the later development of csCMVi. The cut-offs for the initiation of PET are institution-dependent and patient-specific. Studies have shown success in preventing the progression to CMV disease using thresholds of 2–3 $\log_{10}$ IU/ml (30). One pediatric study performed prior to routine letermovir prophylaxis demonstrated that initiation of PET at ≥1,000 IU/ml (≥3$\log_{10}$) vs. <1,000 IU/ml resulted in a higher peak viral load and longer duration of viremia, though without significant differences in end-organ disease, overall survival, or non-relapse-related mortality at 12 months post-HCT (31).

Measuring CMV-specific T-cell-mediated immunity (CMV CMI) has been explored to identify patients at risk for reactivation following discontinuation of prophylaxis and CMV-seropositive or viremic patients at risk of progression to csCMVi. CMV CMI combined with an assessment of patient risk factors may allow for individualized plans for primary and secondary prophylaxis, thresholds for PET, and duration of letermovir prophylaxis (32). This is mostly based on adult studies that explored the role of CMV CMI in stratifying the risk of CMV infection over time through serial monitoring and predicting the progression of DNAemia to csCMVi. Few pediatric studies have explored the role of CMV CMI in predicting the risk of CMV infection and recurrence. Although

these studies had small sample sizes, they showed promising results for the clinical use of CMV CMI therapy (33, 34).

Adult studies suggest that letermovir prophylaxis results in delayed development of CMV-specific cellular immunity, with a 100-day delay in the development of CMV-specific immunity and lower CMV-specific CD4 cells noted up to 1-year post-transplant in the letermovir group (29, 35).

Treatment approaches

Breakthrough infection on letermovir

Breakthrough CMV reactivation on letermovir can occur even in the absence of known genotypic resistance (36, 37). Breakthrough infection often results in low-level viremia and is typically managed with alternative antiviral therapy if the viral load reaches a predetermined threshold or if CMV disease develops (36). Risk factors for breakthrough infection include higher cumulative steroid exposure, GVHD prophylaxis with post-transplant cyclophosphamide or calcineurin inhibitors in combination with mycophenolate, low-grade CMV replication (21–149 IU/ml) at the time of letermovir initiation or during prophylaxis, and acute GVHD (36, 38).

As noted above, CMV reactivation following letermovir discontinuation has been documented in several studies, occurring in 12%–45% of patients (39–41). Risk factors for late CMV infection after letermovir discontinuation include severe neutropenia on the day of stem cell infusion, HLA-mismatched donors, and CMV-seronegative donors (42, 43).

Management of resistant and refractory CMV infection

Refractory and resistant CMV infections occur in 19%–39% and 1.7 to14.5% of adult allogeneic HCT recipients, respectively (17, 44, 45). Limited data in pediatric allogeneic HCT recipients suggest resistance in 4%–10% (17). Resistance typically involves mutations in UL97 (conferring resistance to ganciclovir and valganciclovir) or UL54 (potentially conferring resistance to ganciclovir, valganciclovir, foscarnet, and cidofovir) (45).

The initial evaluation and management of refractory CMV infection or end-organ disease involves optimizing the immune status (e.g., decreasing immune suppression) when feasible, ensuring that antiviral therapy is appropriately dosed, and evaluating antiviral drug resistance (44). Alternative antiviral dosing or therapy may be explored if antiviral resistance is detected and/or when testing is pending (44).

Maribavir is a novel antiviral agent that received FDA approval in 2021 for the management of refractory/resistant CMV infection and end-organ disease (46). Maribavir is a benzimidazole antiviral that inhibits multiple stages of CMV replication (47). Maribavir has been associated with a lower treatment effect in patients with higher baseline viral loads, acute graft-versus-host disease, and T-cell depletion (48, 49). Adverse effects include dysgeusia and gastrointestinal distress (e.g., nausea, vomiting, and diarrhea) (46). In the AURORA trial, a multicenter, double-blind, randomized, phase 3 trial comparing maribavir to valganciclovir for first asymptomatic CMV infection in HCT recipients 16 years and older, maribavir showed less neutropenia and discontinuation of therapy and comparable CMV viremia clearance to that of valganciclovir during post-treatment follow-up, although it failed to achieve non-inferiority (49). The SOLSTICE trial, a phase 3, randomized, open-label trial comparing maribavir to investigator assigned therapy (IAT: valganciclovir/ganciclovir, foscarnet, or cidofovir) for the treatment of refractory CMV infection with or without resistance in HCT and solid organ transplant recipients showed superiority of maribavir for CMV viremia clearance and symptom control (50). Similarly, maribavir appears to be as effective as foscarnet for viral clearance, with similar resistance rates (51). Pediatric data are limited, although case reports and series have shown results like those in adults in terms of safety and efficacy (52, 53).

Future directions

Virus-specific T-cells (VSTs)

Given the limited antiviral options available, alternative treatment strategies have been investigated. One promising innovation is the use of virus-specific T-cells (VSTs). This therapy involves manufacturing or isolating T-cells that recognize specific viral epitopes, and the cells can be collected from a patient's HCT donor or from a third party (54–56). VSTs are manufactured by stimulating donor peripheral blood mononuclear cells (PBMCs) with virus-specific peptides. T cells are then selectively amplified and expanded in culture (55). Alternatively, T-cells can be isolated from seropositive donors, stimulated with viral peptides, and antigen-specific cells can be isolated (55).

Current research suggests that CMV-specific VSTs are effective in treating CMV viremia and end-organ diseases (55). One study of pediatric allogeneic HCT recipients treated with VSTs for CMV and other double-stranded DNA viruses showed no difference in clinical response between donor-derived and third-party VSTs (54).

Vaccine

Triplex® is a recombinant attenuated poxvirus vaccine (modified vaccinia Ankara) that expresses immunodominant CMV antigens (57). A multicenter, double-blind, randomized, placebo-controlled phase II trial was performed, which included 102 CMV-seropositive adult allogeneic HCT recipients (57). The study participants received the Triplex vaccine or placebo on days +28 and +56 following HCT. Vaccine recipients showed a reduction in clinically relevant CMV events, higher levels of CMV-specific T-cells in the first 100 days post-HCT, and no

vaccine-related deaths, infections, or serious adverse events were observed (57).

Another small study evaluated the feasibility, safety, and immunogenicity of vaccinating matched-related HCT donors with the Triplex vaccine. This phase 1 trial showed that the vaccine was feasible and safe, with no effects on recipient engraftment. Although the vaccine was not ultimately powered to assess efficacy, the results indicated a higher frequency of functionally activated CMV-specific T-cells early post-HCT in pairs with vaccinated donors and continued expansion of the T-cell population during immune reconstitution (58). Phase 1 and 2 studies of CMV-seropositive pediatric allogeneic transplant recipients are ongoing (NCT03354728).

Monoclonal antibodies

Fistasovimab (NPC-21) is a fully human, neutralizing monoclonal antibody that targets the epitope of CMV glycoprotein B (59). An *in vitro* study has shown a significant anti-CMV effect (60). A phase 2 study in adult renal transplant recipients showed a lower incidence of CMV disease in patients who received the antibody administered monthly as an intramuscular injection, although there was no significant benefit in preventing CMV infection (59).

Discussion

CMV remains the most common and clinically significant infection in pediatric HCT recipients. Despite significant advancements and ongoing research, additional well-designed, larger pediatric-specific studies are still needed to optimize the diagnosis, prevention, risk stratification, and treatment of CMV infection in this patient population. The approval of letermovir has been the most significant development in the prevention of CMV disease in pediatric HCT recipients in recent years. More long-term longitudinal real-world data on CMV infection and disease during and after discontinuation of letermovir are needed, including studies on immune reconstitution in the context of letermovir prophylaxis.

Additional information on the use of CMV CMI and its integration in clinical practice in the pediatric population is needed, although this seems to hold promise as a good guidance measure in tailoring the need and duration of prophylaxis, as well as the need and frequency of monitoring and threshold for PET in selected patients.

In addition to a growing armamentarium of antiviral drugs with the approval of maribavir in recent years, CMV vaccines, monoclonal antibodies, and VSTs hold hope for additional means to prevent and treat CMV disease and change its landscape in HCT recipients, allowing for continued improved outcomes and reduced mortality.

Author contributions

LH: Conceptualization, Data curation, Investigation, Methodology, Writing – original draft. DH: Conceptualization, Methodology, Resources, Supervision, Writing – review & editing. RZ: Conceptualization, Data curation, Investigation, Methodology, Project administration, Writing – original draft.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declare that no Generative AI was used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

References

1. Hakki M, Aitken SL, Danziger-Isakov L, Michaels MG, Carpenter PA, Chemaly RF, et al. American Society for transplantation and cellular therapy series: #3-prevention of cytomegalovirus infection and disease after hematopoietic cell transplantation. *Transplant Cell Ther.* (2021) 27(9):707–19. doi: 10.1016/j.jtct.2021.05.001

2. Rauwolf KK, Pichler H. Virus infections after allogeneic stem cell transplantation in children. *Rev EJC Paediatr Oncol.* (2023) 2:100131. doi: 10.1016/j.ejcped.2023.100131

3. Lau CE, DiTullio DJ, Wilhalme H, Bowles L, Moore TB, De Oliveira SN. Prevalence of viral infections and serious complications in pediatric hematopoietic stem cell transplant patients: a ten-year single-institution retrospective study. *J Hematol.* (2025) 14(1):1–13. doi: 10.14740/jh1376

4. Eberhardt KA, Jung V, Knops E, Heger E, Wirtz M, Steger G, et al. CMV-IgG pre-allogeneic hematopoietic stem cell transplantation and the risk for CMV reactivation and mortality. *Bone Marrow Transplant.* (2023) 58(6):639–46. doi: 10.1038/s41409-023-01944-2

5. Chuleerarux N, Nematollahi S, Thongkam A, Dioverti MV, Manothummetha K, Torvorapanit P, et al. The association of cytomegalovirus infection and cytomegalovirus serostatus with invasive fungal infections in allogeneic haematopoietic stem cell transplant recipients: a systematic review and meta-analysis. *Clin Microbiol Infect.* (2022) 28(3):332–44. doi: 10.1016/j.cmi.2021.10.008

6. Yong MK, Ananda-Rajah M, Cameron PU, Morrissey CO, Spencer A, Ritchie D, et al. Cytomegalovirus reactivation is associated with increased risk of late-onset invasive fungal disease after allogeneic hematopoietic stem cell transplantation: a multicenter study in the current era of viral load monitoring. *Biol Blood Marrow Transplant.* (2017) 23(11):1961–7. doi: 10.1016/j.bbmt.2017.07.025

7. Yong MK, Slavin MA, Kontoyiannis DP. Invasive fungal disease and cytomegalovirus infection: is there an association? *Curr Opin Infect Dis.* (2018) 31(6):481–9. doi: 10.1097/QCO.0000000000000502

8. Kielsen K, Møller DL, Pedersen AE, Nielsen CH, Ifversen M, Ryder LP, et al. Cytomegalovirus infection is associated with thymic dysfunction and chronic graft-versus-host disease after pediatric hematopoietic stem cell transplantation. *Clin Immunol.* (2024) 265:110302. doi: 10.1016/j.clim.2024.110302

9. Bueno F, Solano C, Vázquez L, Giménez E, de la Cámara R, Albert E, et al. Assessment of the association between cytomegalovirus DNAemia and subsequent acute graft-versus-host disease in allogeneic peripheral blood stem cell transplantation: a multicenter study from the Spanish hematopoietic transplantation and cell therapy group. *Transpl Infect Dis.* (2021) 23(4):e13627. doi: 10.1111/tid.13627

10. Klejmont LM, Mo X, Milner J, Harrison L, Morris E, van de Ven C, et al. Risk factors associated with survival following ganciclovir prophylaxis through day +100 in cytomegalovirus at-risk pediatric allogeneic stem cell transplantation recipients: development of cytomegalovirus viremia associated with significantly decreased 1-year survival. *Transplant Cell Ther.* (2024) 30(1):103.e1–e8. doi: 10.1016/j.jtct.2023.09.025

11. Foolad F, Aitken SL, Chemaly RF. Letermovir for the prevention of cytomegalovirus infection in adult cytomegalovirus-seropositive hematopoietic stem cell transplant recipients. *Expert Rev Clin Pharmacol.* (2018) 11(10):931–41. doi: 10.1080/17512433.2018.1500897

12. American Academy of pediatrics committee on infectious diseases, cytomegalovirus infection. In: Kimberlin DW, Barnett ED, Lynfield R, Sawyer MH, editors. *Red Book: 2024–2027 Report of the Committee on Infectious Diseases*. 33rd edn. Itasca, IL: American Academy of Pediatrics (2024). p. 344–52.

13. Balegamire SJ, McClymont E, Croteau A, Dodin P, Gantt S, Besharati AA, et al. Prevalence, incidence, and risk factors associated with cytomegalovirus infection in healthcare and childcare worker: a systematic review and meta-analysis. *Syst Rev.* (2022) 11(1):131. doi: 10.1186/s13643-022-02004-4

14. Forte E, Zhang Z, Thorp EB, Hummel M. Cytomegalovirus latency and reactivation: an intricate interplay with the host immune response. *Front Cell Infect Microbiol.* (2020) 10:130. doi: 10.3389/fcimb.2020.00130

15. Bate SL, Dollard SC, Cannon MJ. Cytomegalovirus seroprevalence in the United States: the national health and nutrition examination surveys, 1988–2004. *Clin Infect Dis.* (2010) 50(11):1439–47. doi: 10.1086/652438

16. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients-guidelines of the American society of transplantation infectious diseases community of practice. *Clin Transplant.* (2019) 33(9):e13512. doi: 10.1111/ctr.13512

17. Song E. Case report: approaches for managing resistant cytomegalovirus in pediatric allogeneic hematopoietic cell transplantation recipients. *Front Pediatr.* (2024) 12:1394006. doi: 10.3389/fped.2024.1394006

18. Hiskey L, Madigan T, Ristagno EH, Razonable RR, Ferdjallah A. Prevention and management of human cytomegalovirus in pediatric HSCT recipients: a review. *Front Pediatr.* (2022) 10:1039938. doi: 10.3389/fped.2022.1039938

19. Goldsmith SR, Abid MB, Auletta JJ, Bashey A, Beitinjaneh A, Castillo P, et al. Posttransplant cyclophosphamide is associated with increased cytomegalovirus infection: a CIBMTR analysis. *Blood.* (2021) 137(23):3291–305. doi: 10.1182/blood.2020009362

20. Ljungman P, Chemaly RF, Khawaya F, Alain S, Avery R, Badshah C, et al. Consensus definitions of cytomegalovirus (CMV) infection and disease in transplant patients including resistant and refractory CMV for use in clinical trials: 2024 update from the transplant associated virus infections forum. *Clin Infect Dis.* (2024) 79(3):787–94. doi: 10.1093/cid/ciae321

21. Einsele H, Ljungman P, Boeckh M. How I treat CMV reactivation after allogeneic hematopoietic stem cell transplantation. *Blood.* (2020) 135(19):1619–29. doi: 10.1182/blood.2019000956

22. Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med.* (2017) 377(25):2433–44. doi: 10.1056/NEJMoa1706640

23. Russo D, Schmitt M, Pilorge S, Stelljes M, Kawakita T, Teal VL, et al. Efficacy and safety of extended duration letermovir prophylaxis in recipients of haematopoietic stem-cell transplantation at risk of cytomegalovirus infection: a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Haematol.* (2024) 11(2):e127–35. doi: 10.1016/S2352-3026(23)00344-7

24. Green ML, Leisenring W, Xie H, Mast TC, Cui Y, Sandmaier BM, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. *Lancet Haematol.* (2016) 3(3):e119–27. doi: 10.1016/S2352-3026(15)00289-6

25. Johnsrud JJ, Nguyen IT, Domingo W, Narasimhan B, Efron B, Brown J(. Letermovir prophylaxis decreases burden of cytomegalovirus (CMV) in patients at high risk for CMV disease following hematopoietic cell transplant. *Biol Blood Marrow Transplant.* (2020) 26(10):1963–70. doi: 10.1016/j.bbmt.2020.07.002

26. Groll AH, Schulte JH, Antmen AB, Fraser CJ, Teal VL, Haber B, et al. Pharmacokinetics, safety, and efficacy of letermovir for cytomegalovirus prophylaxis in adolescent hematopoietic cell transplantation recipients. *Pediatr Infect Dis J.* (2024) 43(3):203–8. doi: 10.1097/INF.0000000000004208

27. Aldalati AY, Hussein AM, Balbaa E, Hammadeh BM, idrees M, Aloudat O, et al. Efficacy and safety of letermovir for cytomegalovirus prophylaxis in pediatric hematopoietic stem cell transplantation recipients: a systematic review, meta-analysis, and meta-regression. *Transpl Infect Dis.* (2025) 27(2):e70006. doi: 10.1111/tid.70006

28. Ljungman P, Alain S, Chemaly RF, Einsele H, Galaverna F, Hirsch HH, et al. Recommendations from the 10th European conference on infections in leukaemia for the management of cytomegalovirus in patients after allogeneic haematopoietic cell transplantation and other T-cell-engaging therapies. *Lancet Infect Dis.* (2025) 25(8):e451–62. doi: 10.1016/S1473-3099(25)00069-6

29. Zamora D, Duke ER, Xie H, Edmison BC, Akoto B, Kiener R, et al. Cytomegalovirus-specific T-cell reconstitution following letermovir prophylaxis after hematopoietic cell transplantation. *Blood.* (2021) 138(1):34–43. doi: 10.1182/blood.2020009396

30. Sadowska-Klasa A, Leisenring WM, Limaye AP, Boeckh M. Cytomegalovirus viral load threshold to guide preemptive therapy in hematopoietic cell transplant recipients: correlation with cytomegalovirus disease. *J Infect Dis.* (2024) 229(5):1435–9. doi: 10.1093/infdis/jiad386

31. Gutierrez V, Stanek J, Ardura MI, Song E. Cytomegalovirus viral load at initiation of pre-emptive antiviral therapy impacts cytomegalovirus dynamics in pediatric allogeneic hematopoietic cell transplantation recipients. *Transpl Infect Dis.* (2024) 26(6):e14358. doi: 10.1111/tid.14358

32. Otto WR, Vora SB, Dulek DE. Cytomegalovirus cell-mediated immunity assays in pediatric transplantation. *J Pediatric Infect Dis Soc.* (2024) 13(Suppl 1):S22–30. doi: 10.1093/jpids/piae005

33. Seo E, Choi ES, Kim JH, Kim H, Koh K-N, Im HJ, et al. Immunologic monitoring of cytomegalovirus (CMV) enzyme-linked immune absorbent spot (ELISPOT) for controlling clinically significant CMV infection in pediatric allogeneic hematopoietic stem cell transplant recipients. *PLoS One.* (2021) 16(2):e0246191. doi: 10.1371/journal.pone.0246191

34. Paouri B, Soldatou A, Petrakou E, Theodosaki M, Tsentidis C, Kaisari K, et al. Quantiferon-Cytomegalovirus assay: a potentially useful tool in the evaluation of CMV-specific CD8+ T-cell reconstitution in pediatric hematopoietic stem cell transplant patients. *Pediatr Transplant.* (2018) 22(5):e13220. doi: 10.1111/petr.13220

35. Gabanti E, Borsani O, Colombo AA, Zavaglio F, Binaschi L, Caldera D, et al. Human cytomegalovirus-specific T-cell reconstitution and late-onset cytomegalovirus infection in hematopoietic stem cell transplantation recipients following letermovir prophylaxis. *Transplant Cell Ther.* (2022) 28(4):211.e1–e9. doi: 10.1016/j.jtct.2022.01.008

36. Perchetti GA, Biernacki MA, Xie H, Castor J, Joncas-Schronce L, Ueda Oshima M, et al. Cytomegalovirus breakthrough and resistance during letermovir prophylaxis. *Bone Marrow Transplant.* (2023) 58(4):430–6. doi: 10.1038/s41409-023-01920-w

37. Shigle TL, Handy VW, Foolad F, Khawaja F, Aitken SL, Chemaly RF. Breakthrough CMV infections on letermovir prophylaxis in CMV-seropositive allogeneic hematopoietic cell transplant (allo-HCT) recipients. *Biol Blood Marrow Transplant*. (2019) 25(3):S276. doi: 10.1016/j.bbmt.2018.12.341

38. Royston L, Royston E, Masouridi-Levrat S, Chalandon Y, Van Delden C, Neofytos D. Predictors of breakthrough clinically significant cytomegalovirus infection during letermovir prophylaxis in high-risk hematopoietic cell transplant recipients. *Immun Inflamm Dis*. (2021) 9(3):771–6. doi: 10.1002/iid3.431

39. Chavaz L, Royston L, Masouridi-Levrat S, Mamez A-C, Giannotti F, Morin S, et al. CMV Infection after letermovir primary prophylaxis discontinuation in allogeneic hematopoietic cell transplant recipients. *Open Forum Infect Dis*. (2023) 10(4):ofad169. doi: 10.1093/ofid/ofad169

40. Galaverna F, Baccelli F, Zama D, Tridello G, Masetti R, Soncini E, et al. Letermovir for cytomegalovirus infection in pediatric patients undergoing allogenic hematopoietic stem cell transplantation: a real-life study by the infectious diseases working group of Italian association of pediatric hematology-oncology (AIEOP). *Bone Marrow Transplant*. (2024) 59(4):505–12. doi: 10.1038/s41409-024-02209-2

41. Little JS, Prockop S. Immune milestones to predict CMV after letermovir. *Blood Adv*. (2024) 8(11):2964–6. doi: 10.1182/bloodadvances.2024012849

42. Hopff SM, Wingen-Heimann SM, Classen AY, Blau I-W, Bug G, Hebermehl C, et al. Real-world experience with letermovir for cytomegalovirus-prophylaxis after allogeneic hematopoietic cell transplantation: a multi-centre observational study. *J Infect*. (2024) 89(2):106220. doi: 10.1016/j.jinf.2024.106220

43. Mori Y, Harada T, Yoshimoto G, Shima T, Numata A, Jinnouchi F, et al. Risk factors for late cytomegalovirus infection after completing letermovir prophylaxis. *Int J Hematol*. (2022) 116(2):258–65. doi: 10.1007/s12185-022-03348-2

44. El Chaer F, Shah DP, Chemaly RF. How I treat resistant cytomegalovirus infection in hematopoietic cell transplantation recipients. *Blood*. (2016) 128(23):2624–36. doi: 10.1182/blood-2016-06-688432

45. Sassine J, Khawaja F, Shigle TL, Handy V, Foolad F, Aitken SL, et al. Refractory and resistant cytomegalovirus after hematopoietic cell transplant in the letermovir primary prophylaxis era. *Clin Infect Dis*. (2021) 73(8):1346–54. doi: 10.1093/cid/ciab298

46. United States Food and Drug Administration. LIVTENCITY (maribavir) label (2021).

47. Valencia Deray KG, Danziger-Isakov LA, Downes KJ. Current and emerging antiviral agents in the prevention and treatment of cytomegalovirus in pediatric transplant recipients. *J Pediatric Infect Dis Soc*. (2024) 13(Suppl 1):S14–21. doi: 10.1093/jpids/piad059

48. Daher M, Khawaja F, Spallone A, Shigle TL, Bhatti M, Vuong NN, et al. Real-World experience with maribavir for treatment of refractory or resistant cytomegalovirus infection in hematopoietic cell transplant recipients and hematologic malignancy patients. *Transpl Infect Dis*. (2025) 27(2):e14444. doi: 10.1111/tid.14444

49. Papanicolaou GA, Avery RK, Cordonnier C, Duarte RF, Haider S, Maertens J, et al. Treatment for first cytomegalovirus infection post-hematopoietic cell transplant in the AURORA trial: a multicenter, double-blind, randomized, phase 3 trial comparing maribavir with valganciclovir. *Clin Infect Dis*. (2024) 78(3):562–72. doi: 10.1093/cid/ciad709

50. Avery RK, Alain S, Alexander BD, Blumberg EA, Chemaly RF, Cordonnier C, et al. Maribavir for refractory cytomegalovirus infections with or without resistance post-transplant: results from a phase 3 randomized clinical trial. *Clin Infect Dis*. (2022) 75(4):690–701. doi: 10.1093/cid/ciab988

51. Ogawa L, Morinishi C, Multani A, Gaynor P, Beaird OE, Pham C, et al. Real-World comparison of maribavir to foscarnet for the treatment of cytomegalovirus in solid organ and hematopoietic stem cell transplant recipients. *Viruses*. (2024) 16(12):1889. doi: 10.3390/v16121889

52. Doshi S, Dassner A, Hanisch B. Maribavir use in pediatric immunocompromised hosts: a case series to talk about real-world experience. *J Pediatric Infect Dis Soc*. (2024) 13(4):26–7. doi: 10.1093/jpids/piae093.071

53. Fisher JE, Mulieri K, Finch E, Ericson JE. Use of maribavir for multidrug resistant cytomegaloviremia in a pediatric oncology patient. *J Pediatr Hematol Oncol*. (2024) 46(3):e244–7. doi: 10.1097/MPH.0000000000002841

54. Galletta TJ, Galletta TJ, Lane A, Lutzko C, Leemhuis T, Cancelas JA, et al. Third-Party and patient-specific donor-derived virus-specific T cells demonstrate similar efficacy and safety for management of viral infections after hematopoietic stem cell transplantation in children and young adults. *Transplant Cell Ther*. (2023) 29(5):305–10. doi: 10.1016/j.jtct.2023.01.027

55. Green A, Rubinstein JD, Grimley M, Pfeiffer T. Virus-Specific T cells for the treatment of systemic infections following allogeneic hematopoietic cell and solid organ transplantation. *J Pediatric Infect Dis Soc*. (2024) 13(Suppl 1):S49–57. doi: 10.1093/jpids/piad077

56. Jiang W, Jiang W, Clancy LE, Avdic S, Sutrave G, Street J, et al. Third-party CMV- and EBV-specific T-cells for first viral reactivation after allogeneic stem cell transplant. *Blood Adv*. (2022) 6(17):4949–66. doi: 10.1182/bloodadvances.2022007103

57. Aldoss I, La Rosa C, Baden LR, Longmate J, Ariza-Heredia EJ, Rida WN, et al. Poxvirus vectored cytomegalovirus vaccine to prevent cytomegalovirus viremia in transplant recipients: a phase 2, randomized clinical trial. *Ann Intern Med*. (2020) 172(5):306–16. doi: 10.7326/M19-2511

58. La Rosa C, Aldoss I, Park Y, Yang D, Zhou Q, Gendzekhadze K, et al. Hematopoietic stem cell donor vaccination with cytomegalovirus triplex augments frequencies of functional and durable cytomegalovirus-specific T cells in the recipient: a novel strategy to limit antiviral prophylaxis. *Am J Hematol*. (2023) 98(4):588–97. doi: 10.1002/ajh.26824

59. Ichimaru N, Natori Y, Alloway RR, Wojciechowski D, Castillo Almeida NE, Futamura K, et al. Phase 2, randomized, double-blind, placebo-controlled study of fiztasovimab (NPC-21) for kidney transplant recipients at high risk of cytomegalovirus infection (LionHeart21). *Transplantation*. (2025) 109(6):985–93. doi: 10.1097/TP.0000000000005260

60. Okamoto M, Kurino R, Miura R, Takada K. A fully human neutralizing monoclonal antibody targeting a highly conserved epitope of the human cytomegalovirus glycoprotein B. *PLoS One*. (2023) 18(5):e0285672. doi: 10.1371/journal.pone.0285672

Journal of the Pediatric Infectious Diseases Society

SUPPLEMENT ARTICLE

Current and Emerging Antiviral Agents in the Prevention and Treatment of Cytomegalovirus in Pediatric Transplant Recipients

Kristen G. Valencia Deray,[1] Lara A. Danziger-Isakov,[2,3] and Kevin J. Downes[4,5]

[1]Department of Pediatrics, Division of Infectious Diseases, Baylor College of Medicine, Houston, Texas, USA, [2]Division of Infectious Disease, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA, [3]Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio, USA, [4]Division of Infectious Diseases, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA, [5]Department of Pediatrics, Perelman School of Medicine of the University of Pennsylvania, Philadelphia, Pennsylvania, USA

Despite current prophylaxis regimens, cytomegalovirus (CMV) is common in hematopoietic cell transplantation (HCT) and solid organ transplantation (SOT) and remains a significant cause of morbidity and mortality. Newer antiviral medications are reshaping the landscape for prevention and treatment of CMV DNAemia, infection, and disease. Letermovir is approved for CMV prevention in adult HCT patients and is attractive due to the absence of marrow suppression seen with ganciclovir/valganciclovir. Letermovir should not be routinely used for CMV treatment due to its low threshold for resistance. Maribavir is approved for the treatment of refractory or resistant CMV disease in HCT and SOT recipients ≥12 years of age, though it has no current role in CMV prevention. More research is needed to fully elucidate the roles, efficacy, and safety of these newer agents in prevention and treatment of CMV in pediatric transplant recipients.

Key words. antiviral; cytomegalovirus; pediatric; resistance; transplantation.

INTRODUCTION

Cytomegalovirus (CMV) continues to cause significant morbidity after solid organ transplantation (SOT) and hematopoietic cell transplantation (HCT) with recent reports showing CMV disease rates of up to 5% [1, 2] and 7% [3], respectfully. The risk of posttransplant CMV is affected by donor and recipient serostatus, organ or graft type, T-cell depletion, immunosuppressive agent, and intensity [4, 5]. Prevention strategies and newer treatment options provide effective options to diminish the impact of this virus.

As it is not possible to avoid CMV in HCT recipients (highest risk individuals are seropositive prior to transplant) and preferential use of CMV seronegative HCT and SOT donors is not routinely feasible, alternative prevention strategies are needed to mitigate risk. Further, no current antivirals eliminate latent virus, requiring ongoing monitoring and/or prevention for at-risk patients posttransplant. Several strategies have emerged and are endorsed in guidance documents including prophylaxis, monitoring with preemptive therapy, or a combination of these strategies, also referred to as surveillance after prophylaxis [4, 5]. Prophylaxis entails giving an antiviral medication, usually ganciclovir/valganciclovir at present, for a predetermined amount of time with the goal of preventing CMV DNAemia. Prophylaxis is generally targeted based on the CMV risk profile, including donor and recipient serostatus, where the highest risk exists when CMV R− SOT receive seropositive (D+) organs or CMV R+ HCT receive D− grafts. The major drawbacks of this strategy include the side effects of the antiviral medications, specifically bone marrow suppression with the use of ganciclovir/valganciclovir, and late-onset CMV disease after prophylaxis is discontinued [4, 5]. Preemptive therapy includes monitoring for CMV DNAemia at routine times posttransplant and initiating antiviral therapy if DNAemia is found at a predetermined threshold. This strategy avoids unnecessary antiviral side effects, though studies have shown that it does not prevent the indirect effects of CMV DNAemia such as graft dysfunction and all-cause mortality [4, 5]. Many experts use surveillance after prophylaxis in patients at risk for developing CMV DNAemia, such as those with a high-risk CMV profile. Secondary prophylaxis is the use of antiviral prophylaxis, after treatment for CMV DNAemia or disease, for prevention of recurrent CMV.

The optimal prevention strategy for each organ and HCT subgroup is not fully elucidated, and data support several approaches. In pediatric HCT, primary prophylaxis with valganciclovir, ganciclovir, or foscarnet may be considered in some populations; however, monitoring with preemptive therapy is also a reasonable option [6], as it may avoid the toxicities associated with the use of these agents. In the adult HCT population, letermovir has emerged as the primary

Received 22 May 2023; editorial decision 8 August 2023; accepted 16 August 2023

Corresponding Author: Kristen G. Valencia Deray, MD, Department of Pediatrics, Division of Infectious Diseases, Baylor College of Medicine, 1102 Bates Street Suite 1120, Houston, Texas 77030, USA. E-mail: Kristen.ValenciaDeray@bcm.edu

Journal of the Pediatric Infectious Diseases Society 2024;13(S1):S14–S21

© The Author(s) 2024. Published by Oxford University Press on behalf of The Journal of the Pediatric Infectious Diseases Society. All rights reserved. For permissions, please e-mail: journals.permissions@oup.com.

https://doi.org/10.1093/jpids/piad059

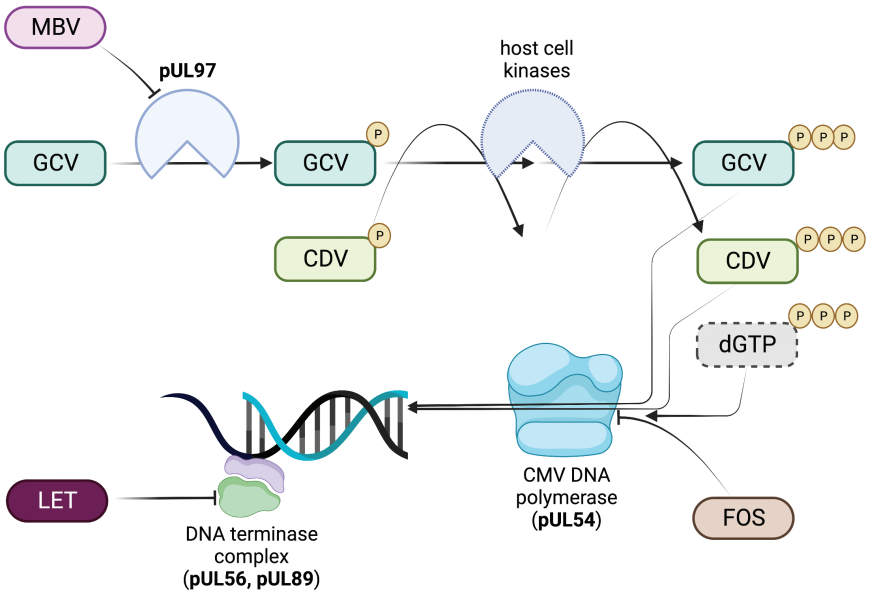


Figure 1. Mechanisms of activity of anti-CMV antivirals. Ganciclovir (GCV) is a nucleoside analog that requires initial phosphorylation by the viral protein kinase encoded by UL97. It is subsequently di- and tri-phosphorylated by host cellular kinases. Ganciclovir triphosphate inhibits CMV DNA polymerase (UL54) activity and also serves as substrate for the enzyme, substituting for deoxyguanosine triphosphate (dGTP) during chain elongation, slowing viral DNA synthesis. Cidofovir (CDV) is not a substrate for UL97 but is di- and tri-phosphorylated by host kinases, as with GCV monophosphate, and serves as competitive inhibitor of DNA polymerase. Foscarnet (FOS) is a noncompetitive inhibitor of CMV DNA polymerase, blocking the pyrophosphate binding site and preventing cleavage of deoxynucleotide triphosphates. Maribavir (MBV) is a potent inhibitor of the UL97 kinase, which is involved in phosphorylation of a number of viral proteins, leading to inhibition of multiple stages of CMV DNA replication, viral encapsulation, and nuclear egress. Letermovir (LET) inhibits the CMV DNA terminase complex by binding to its pUL56 subunit. The enzymatic targets are also the main sites of resistance for each drug: GCV–UL97 > UL54; CDV–UL54; FOS–UL54; MBV–UL97; LET–UL56 > UL89. Figure was made using Biorender. Abbreviations: CDV, cidofovir; CMV, cytomegalovirus; FOS foscarnet; GCV, ganciclovir; LET, letermovir; MBV, maribavir; NUC, nucleotide.

prophylactic agent, but limited pediatric data have restricted its use to small cohorts to date (covered subsequently in this review). For pediatric SOT, monitoring with preemptive therapy has been successfully reported primarily in pediatric liver transplant recipients [7, 8], while the bulk of the published data support the use of universal prophylaxis in other pediatric SOT populations [1, 2, 9–11]. However, challenges exist related to optimal prophylaxis durations [12] and dosing strategies [13, 14], as well as frequent medication side effects [15, 16], which highlight the need for additional therapeutic options for both prevention and treatment.

Despite CMV prevention strategies, CMV DNAemia and disease continue to occur. Occasionally, CMV DNAemia does not respond to traditional antiviral agents either due to drug resistant or refractory disease. Refractory CMV is defined as CMV DNAemia that continues to increase despite 2 weeks of adequately dosed antiviral medication [17]. Cytomegalovirus is considered resistant if it has a genetic mutation that decreases susceptibility to one or more antiviral drugs [17]. Limited treatment strategies are available to treat resistant/refractory disease, but maribavir, a novel CMV antiviral, is now FDA approved for this indication in individuals 12 years of age and older. This article explores the potential therapeutic uses and challenges of maribavir and letermovir, two newer CMV antivirals, in addition to traditional CMV agents.

TRADITIONAL AGENTS

Ganciclovir was the first drug to be approved for the treatment and prevention of CMV DNAemia and disease. It is a nucleoside analog that requires phosphorylation by UL97 kinase and host kinases to inhibit viral DNA polymerase, therefore inhibiting the synthesis of CMV DNA (Figure 1) [18–20]. Valganciclovir is an oral prodrug of ganciclovir with excellent bioavailability [21]. Ganciclovir and valganciclovir are currently the drugs of choice for the prevention and treatment of CMV in HCT and SOT recipients [5, 22, 23], though their use is limited by significant toxicities including myelosuppression, predominantly neutropenia, and acute kidney injury, which both have been associated with dose modification and early cessation of therapy [15, 24, 25]. This is of particular concern with valganciclovir as optimal dosing in the pediatric population is controversial. The FDA recommended dosing for valganciclovir is based on body surface area and creatinine, but adverse effects with this dosing strategy are common [15, 16]. Therefore, in 2018, the FDA updated its dosing guidance to prevent supratherapeutic

concentrations [26]. A PK study by Peled et al. showed that weight-based dosing produced more appropriate area under the curve values with continued clinical efficacy [14]. Subsequently, numerous pediatric centers have changed their dosing strategy to weight-based and achieved similar results [13].

Foscarnet is a pyrophosphate analog that binds reversibly to DNA polymerase, stopping the elongation of CMV DNA [27]. Foscarnet can be used as preemptive therapy in HCT or treatment for CMV disease in HCT or SOT, in an effort to avoid the myelosuppressive effects of ganciclovir/valganciclovir [5, 22]. The most common adverse event is nephrotoxicity [27], caused by both renal tubule toxicity [28] and formation of crystal nephropathy [29]. Other toxicities include electrolyte abnormalities, seizures, genital ulcerations, anemia, and nausea [27].

Cidofovir is a nucleotide analog that inhibits CMV DNA polymerase, slowing DNA synthesis and destabilizing viral DNA [30]. Cidofovir is a second-line agent for CMV treatment and a third-line agent for CMV prevention in HCT recipients [22]. It is a third-line treatment agent in SOT recipients, but is not recommended for prophylaxis in this population [23]. Nephrotoxicity limits its use primarily to patients intolerant of other medications or with resistant or refractory infections [30]. Brincidofovir, an oral lipid prodrug of cidofovir with less nephrotoxic potential, is not currently available for treatment of CMV.

The development of CMV resistance to these agents is a major concern. The primary ganciclovir resistance mechanism is via a mutation in the UL97 phosphotransferase gene, which prevents the initial phosphorylation step required for antiviral activity [31]. A less common ganciclovir resistance mechanism, mutation in the UL54 DNA polymerase, also confers resistance to foscarnet or cidofovir [31]. Resistant and refractory CMV infection in HCT and SOT recipients remains a challenge given the limited number of traditional antiviral agents and their associated toxicities. The development of newer antiviral agents for the prevention and treatment of CMV infection and disease is paramount to improve outcomes in pediatric HCT and SOT patients. Pertinent prescribing information for antivirals discussed is located in Table 1.

MARIBAVIR

Maribavir is a benzimidazole riboside that competitively inhibits the protein kinase activity of CMV enzyme pUL97, which results in the inhibition of phosphorylation of proteins [34, 35] and inhibition of multiple stages of CMV DNA replication, viral encapsulation, and nuclear egress [36–41]. Maribavir differs from ganciclovir/valganciclovir in that it is a UL97 inhibitor rather than a UL97 substrate [31], thus it can antagonize the antiviral activity of ganciclovir/valganciclovir and should not be used simultaneously [42]. Foscarnet, cidofovir, and letermovir have no activity at pUL97 and therefore, can be used concurrently with maribavir. Mutations that confer resistance to ganciclovir, valganciclovir, foscarnet, and cidofovir generally do not affect maribavir activity as the UL97 mutations conferring resistance to maribavir and ganciclovir/valganciclovir have limited overlap and differential resistance levels [43], and maribavir does not have action against the UL54 CMV DNA polymerase utilized by foscarnet and cidofovir [44]. Low-level maribavir resistance has been seen with UL27 mutations [45], though these are felt to have less of an impact on susceptibility than UL97 mutations [43]. Notably, maribavir is a CMV-specific antiviral agent; other antiviral agents should be used to treat or prevent non-CMV herpesvirus infections during maribavir administration.

Early adult trials of maribavir focused on CMV DNAemia prophylaxis. A phase II, randomized, double-blind, placebo-controlled study in CMV-seropositive HCT recipients found that maribavir was more effective than placebo for reducing the incidence of CMV DNAemia (CMV DNA polymerase chain reaction [PCR]: 7%–19% vs 46%; all $P < .05$), and CMV disease was only seen in three patients, all in the placebo group [46]. However, separate phase III prophylaxis trials in HCT and high-risk D+/R− liver transplant recipients found maribavir was not superior to placebo and oral ganciclovir, respectively [47, 48]. Based on these results, the evaluation for use of maribavir shifted toward treatment of CMV disease.

The pivotal SOLSTICE trial, a phase III, randomized, open-label, active-controlled trial, compared the safety and efficacy of 400 mg of maribavir twice daily to investigator-assigned therapy (valganciclovir/ganciclovir, foscarnet, or cidofovir) for refractory or resistant CMV in HCT and SOT recipients [49]. Significantly more patients in the maribavir group met the primary endpoint of confirmed CMV DNAemia clearance by week 8 of therapy (55.7% vs 23.9%; $P < .01$) and the secondary endpoint of CMV DNAemia clearance by week 8 with maintenance of clearance and symptom control through week 16 (18.7% vs 10.3%, $P = .01$) [49]. Notably, significantly more patients in the maribavir group met the primary end point even when controlling for early discontinuation of investigator-assigned therapy; therefore, maribavir's superiority is not solely the result of better tolerance and adherence. Unfortunately, despite eligibility of patients ≥12 years, no children under 18 years of age were enrolled in the trial. Subsequently, a pharmacokinetic simulation was performed and supported adult dosing in children ≥12 years of age [50]. A phase III trial with the aim of determining the safety, tolerability, and pharmacokinetics of maribavir in children 0 to <18 years of age (NCT05319353) is planned [51]. In November 2021, the U.S. FDA approved maribavir as the first drug for treatment of resistant or refractory CMV infection in HCT and SOT recipients ≥12 years of age and weighing at least 35 kg (Table 1) [52].

Maribavir is well-tolerated with the most common side effect being dysgeusia seen in 37.2% of participants in the SOLSTICE

trial [49]. Participants on maribavir also had a lower rate of marrow suppression than the valganciclovir group (24.8% vs 53.5%) and less acute kidney injury than the foscarnet group (8.5% vs 21.3%) [49]. Notably, maribavir is currently offered in a 200 mg tablet form, which can make dosing a challenge for critically ill patients where intravenous formulation may

Table 1. Antiviral Drugs for the Prevention and Treatment of Cytomegalovirus in Pediatric Hematopoietic Stem Cell and Solid Organ Transplant Recipients

Agent	Indications in Transplant Recipients	Dosing for CMV Prevention in Pediatric Transplant	Dosing for CMV Treatment in Pediatric Transplant	Comments/Challenges to Use
Valganciclovir	First line for treatment and prevention of CMV DNAemia and disease	7 × BSA × creatinine clearance with upper limit of creatinine clearance of 150 mL/min PO daily (max dose 900 mg PO daily) or 16 mg/kg PO daily (max dose 900 mg PO daily)	7 × BSA × creatinine clearance with upper limit of creatinine clearance of 150 mL/min PO BID (max dose 900 mg PO BID) or 16 mg/kg PO BID (max dose 900 mg PO BID)	Causes myelosuppression, predominately leukopenia Requires dose adjustment for renal dysfunction Oral formulations available as a tablet and a suspension
Ganciclovir	First line for treatment and prevention of CMV DNAemia and disease	5 mg/kg IV once daily	5 mg/kg IV every 12 h	Causes myelosuppression, predominately leukopenia Requires dose adjustment for renal dysfunction Intravenous administration
Foscarnet	Second-line agent for therapy in SOT recipients First-line agent for HCT recipients who can't tolerate marrow suppression from ganciclovir/valganciclovir	Currently not indicated for prevention in SOT recipients 90 mg/kg IV every 24 h for prevention in HCT	90 mg/kg IV every 12 h	Highly nephrotoxic Requires dose adjustment for renal dysfunction Intravenous administration Used for UL97-mutant ganciclovir-resistant CMV DNAemia or disease
Cidofovir	Third-line agent for treatment of CMV DNAemia and disease in SOT recipients Second-line agent for prevention and treatment of CMV DNAemia and disease in HCT recipients	Currently not indicated for prevention in SOT recipients 5 mg/kg/dose IV once weekly for 2 consecutive weeks followed by 5 mg/kg/dose IV once every 2 weeks, in combination with probenecid in HCT [32]	5 mg/kg/dose IV once weekly for 2 consecutive weeks followed by 5 mg/kg/dose IV once every 2 weeks, in combination with probenecid	Highly nephrotoxic Requires dose adjustment for renal dysfunction Intravenous administration Second-line agent for UL97-mutant ganciclovir-resistant CMV DNAemia or disease
Maribavir	Refractory CMV DNAemia or disease (with or without resistance to traditional agents) age 12 and older	Currently not indicated for CMV prevention	400 mg PO twice daily for patients ≥12 years of age and ≥35 kg [33]	Well-tolerated (GI side effects including taste disturbance are most common) Primarily metabolized by CYP3A4 and can increase the concentration of common immunosuppressant. Therefore, monitor immunosuppression levels closely Recommend reviewing contaminant medications as it has numerous other drug–drug interactions Oral tablet formulation only. Can be crushed and placed through orogastric or nasogastric tubes No dose adjustment is needed for impaired renal or mild to moderate hepatic function Do not coadminister with ganciclovir/valganciclovir due to concerns for antagonism No CNS penetration
Letermovir	Prophylaxis of CMV infection and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant	480 mg PO or IV administered once daily (over 1 h) through 100 days posttransplant; dose should be reduced to 240 mg if coadministered with cyclosporine	Currently not indicated for treatment	Generally well-tolerated (GI side effects most common) Oral formulation only available as a tablet that must be swallowed whole CYP3A4 inhibitor and has notable drug interactions (cyclosporine, tacrolimus, and statins) that require dose adjustments and/or close monitoring when coadministered

Abbreviations: BID, twice daily; BSA, body surface area; CMV, cytomegalovirus; HCT, hemopoietic cell transplantation; IV, intravenous; kg, kilograms; mg, milligrams; mL, milliliter; min, minute; PO, orally; SOT, solid organ transplant.

be preferable. However, alternative administration via an orogastric or nasogastric tube after crushing the tablet is feasible [33]. Maribavir is primarily metabolized by CYP3A4 so drugs that are strong inducers of this pathway, specifically many anticonvulsants, can decrease the concentration of maribavir and dose adjustments may be warranted [33]. Similarly, concentrations of immunosuppressants that are CYP3A4 substrates, such as mTOR inhibitors, may increase when taken concomitantly with maribavir so immunosuppression levels should be monitored closely [33]. Importantly, maribavir does not cross the blood–brain barrier [53].

LETERMOVIR

Letermovir is a CMV DNA terminase complex (subunit pUL56) inhibitor with potent activity against human CMV [54]. Because of its site and mechanism of action, it does not inhibit CMV DNA replication and, thus, may lead to accumulation of concatemeric (ie, nonreplicative) DNA that could cause misleading interpretation of quantitative PCR results [55]. Nevertheless, it acts in a manner distinct from other CMV antiviral agents and does not exhibit cross-resistance with these other drugs. As with maribavir, it is a CMV-specific drug that has no activity against other herpesviruses; other antiviral agents should be coadministered to prevent or treat non-CMV herpesviruses, as appropriate. Letermovir is available in oral and intravenous formulations. However, there are clinically relevant drug–drug interactions between letermovir and other medications metabolized via the cytochrome P450 system that require reduced dosages of letermovir (eg, cyclosporine) [56] or necessitate the use of a reduced dose or diligent therapeutic/clinical monitoring of the coadministered medication (eg, tacrolimus [56, 57], statins [58], and voriconazole [59, 60]).

Letermovir was approved by the FDA in 2017 for the prevention of CMV infection and disease in seropositive (R+) adult allogeneic HCT recipients [61]. Approval came following a phase III, double-blind, placebo-controlled trial in which participants with undetectable CMV DNA at randomization who received 14 weeks of letermovir had fewer clinically significant CMV infections (defined as CMV disease or DNAemia requiring treatment) by week 24 after transplantation than recipients of placebo (37.5% vs 60.6%) [62]. In a secondary analysis evaluating outcomes among trial participants with detectable CMV DNA at randomization, letermovir administration was similarly associated with a lower incidence of clinically significant CMV infection compared to placebo through weeks 14 (33.1% vs 86.6%, $P < .001$) and 24 (64.6% vs 90.9%, $P = .01$) [63]. A post hoc analysis of the trial data showed that all-cause mortality at 24 weeks was significantly lower among letermovir recipients with a trend towards lower mortality at week 48 [64]. In a 2022 systematic review combining data from 48 studies and more than 7100 adult allogeneic HCT patients, Vyas and colleagues determined that letermovir prophylaxis was associated with a significant reduction in CMV reactivation, clinically significant CMV infection, CMV disease, and grade ≥2 graft-versus-host disease, as well as all-cause and nonrelapse mortality beyond day 200 posttransplant [65]. Based on the totality of data, the FDA approved an extension of prophylaxis in high-risk adult HCT patients from 100 to 200 days [66].

A recently completed phase III trial of high-risk (D+/R−) adult kidney transplant recipients determined that letermovir is noninferior to valganciclovir for the prevention of CMV disease [67]. Based on these results, the FDA has also approved letermovir for CMV prevention in high risk (D+/R−) adult kidney transplant recipients [68].

Although letermovir is only approved for primary prophylaxis, there are reports of its use as secondary prophylaxis following a CMV event [69], as well as for treatment of CMV disease in the setting of valganciclovir intolerance or failure [69, 70]. However, treatment of CMV disease does not appear to be the ideal clinical situation for its use. This stems largely from concerns about a low threshold for resistance development, particularly in the setting of high viral loads and/or poor immunologic control [71]. Letermovir's unique mechanism of action and lack of cross-resistance make it a possible option for treatment of refractory or resistant CMV infection or disease [72, 73]; however, clinical failures and development of resistance have been reported [74–76]. As a result, no industry-sponsored CMV treatment trials are active for this drug. Additionally, dedicated studies evaluating letermovir's safety and efficacy as secondary prophylaxis are warranted before its routine clinical adoption for this indication.

Off-label use with letermovir has been reported in SOT recipients with valganciclovir intolerance [57, 77]. Off-label use of letermovir in pediatric HCT patients has also been reported, although published data remain limited to small case series [78–81]. In general, outcomes have been favorable. However, despite these reports, the effectiveness of letermovir for primary prophylaxis in pediatric HCT recipients is unknown. Formal investigation is warranted given the differences between pediatric and adult HCT recipients themselves, as well as in outcomes associated with CMV infection in these patient populations. Further, pediatric dosing of letermovir has also not been established. A trial to evaluate this in pediatric allogeneic HCT patients is ongoing (NCT03940586). Preliminary data from adolescent participants of this trial reported at IDWeek 2022 (Washington, DC) suggest that adult dosages (Table 1) are appropriate in the adolescent population (12 to <18) [82], although final dosing recommendations for pediatric patients, particularly younger ones, have yet to be determined.

Letermovir is very well-tolerated with far fewer significant adverse effects than older drugs. In the phase III trial, the rates of hematologic toxicities and acute kidney injury events were

similar between letermovir and placebo recipients, as were other adverse events [62]. Meanwhile, in the recently completed phase 3 trial in adult kidney transplant recipients [67], fewer recipients of letermovir had hematological toxicities (either leukopenia or neutropenia; 26% vs 64%, $P < .0001$). And, in a recent cost effectiveness analysis, with clinical parameters informed mostly from the phase 3 trial data, letermovir prophylaxis in adults HCT was found to be cost effective compared to preemptive treatment alone in a US healthcare setting [83]. With its favorable side effect profile and data supporting its efficacy and cost effectiveness, letermovir is becoming standard of care for CMV prevention in high-risk adult HCT patients.

CURRENT AND POTENTIAL FUTURE CLINICAL APPLICATIONS OF LETERMOVIR AND MARIBAVIR IN PEDIATRIC TRANSPLANT RECIPIENTS

Primary Prophylaxis of CMV

Currently, letermovir is only approved for primary prophylaxis of CMV infection and disease in adult CMV-seropositive allogeneic HCT [61] and high-risk adult kidney transplant recipients [68]. Based on dosing from adolescent PK studies [78], some centers have begun using this agent for primary prophylaxis more routinely among adolescent HCT patients. We anticipate that letermovir will increasingly be used off-label in pediatric HCT, including young patients once dosing is known. This is especially likely in the highest-risk patients (ie, T-cell-depleted grafts) or in patients who have developed toxicities with other antiviral agents. Despite letermovir's appeal, close clinical monitoring for CMV DNAemia with preemptive therapy still remains a viable option in pediatric HCT recipients.

Letermovir may also be attractive for CMV prevention in pediatric SOT recipients. Unfortunately, there are significant drug–drug interactions that may limit its use. As a result, close monitoring of drug concentrations (eg, tacrolimus) or for clinical symptoms of toxicity (eg, myopathy with coadministration of statins) is imperative. We would strongly suggest that dedicated studies be performed to fully understand all clinically relevant drug interactions before letermovir is routinely used for CMV prevention in any patient populations routinely prescribed these medications.

The best way to monitor for breakthrough CMV DNAemia on letermovir prophylaxis has not yet been elucidated. This poses a unique challenge given that letermovir use can result in nonreplicative CMV DNAemia [55], creating challenges to the interpretation of viral loads. Future studies are needed to understand how best to distinguish nonreplicative CMV DNAemia from replicative virus.

Meanwhile, maribavir should not be used as primary prophylaxis in pediatric HCT or SOT. Although it has been studied for this indication in adult populations, primary prophylaxis does not appear to be its greatest utility.

Secondary Prophylaxis

Which pediatric transplant recipients require secondary prophylaxis and, when used, for how long remains controversial. While most experts would offer secondary prophylaxis to a patient who has recovered from CMV disease and is still in the early posttransplant period (ie, when primary prophylaxis would be offered), other scenarios may be more subjective. In our opinion, letermovir could be a viable option when secondary prophylaxis is deemed necessary, particularly for patients who are intolerant of traditional antiviral agents. Due to the low barrier to resistance development, resulting in mutations within the UL56 gene [75, 84], letermovir is best suited as a preventative agent in the absence of ongoing DNAemia, particularly if the patient is significantly immunosuppressed. Meanwhile, maribavir is not currently indicated for secondary prophylaxis. Although the treatment course utilized in the SOLTICE trial (400 mg twice daily for 8 weeks) may have included a period of secondary prophylaxis for individuals whose DNAemia cleared promptly [49], the optimal dosing and duration for this indication are unknown.

Treatment of CMV

Ganciclovir and valganciclovir remain the primary drugs for treatment of CMV infection and disease in children. In the absence of resistant virus or contraindications to one of these agents, they remain as first-line therapy for the majority of CMV infections in pediatric transplant recipients. Maribavir is the first drug approved for treatment of refractory or resistant CMV in patients 12 years of age and older, with an ongoing trial to establish dosing in younger children (NCT05319353). With an improved safety profile compared to foscarnet and cidofovir, maribavir may become the preferred treatment option for refractory or resistant CMV infection/disease in the future.

However, there are several caveats that may temper enthusiasm for the use of maribavir in pediatric transplant recipients. First, the drug is currently only available as 200 mg tablets, which may be challenging to dose accurately in small children (<10 kg). Second, maribavir has poor penetration into the eye and central nervous system. Alternative agents or the use of combination therapy are needed when encephalitis, meningitis, or retinitis are of concern. Lastly, maribavir may not be an ideal agent for treatment of CMV infections with high viral loads. A notable fraction of patients in the phase II trial had recurrence of DNAemia while actively receiving maribavir, some of whom developed maribavir-resistant virus [85]. Ultimately, the optimal strategy for treatment of refractory infections with persistently high viral loads remains to be established.

CONCLUSIONS

Letermovir and maribavir are newer antiviral agents with promise to significantly improve CMV prevention and treatment, respectively, in adult and pediatric HCT and SOT

recipients. With their widespread use in adult transplant recipients, their specific roles in pediatric transplant will become clearer. While off-label use is likely to occur in children given the toxicities associated with traditional anti-CMV agents, dedicated pediatric trials are urgently needed.

Notes

Financial support. K.J.D. is supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development (K23HD091365).

Supplement sponsorship. This article appears as part of the supplement "Advances in Pediatric Transplant Infectious Diseases," sponsored by Eurofins Viracor.

Potential conflicts of interest. K.V.D. is a local investigator for pediatric Pfizer SARS-CoV-2 vaccination trials. L.D.-I. is a consultant for Takeda, Merck, and Roche Diagnostics. L.D.-I. is a site investigator for AiCuris, Ansun BioPharma, Astellas, Merck, Pfizer, and Takeda. K.J.D. has no relevant conflicts of interest to report.

References

1. Deray KGV, Hosek KE, Chilukuri D, et al. Epidemiology and long-term outcomes of cytomegalovirus DNAemia and disease in pediatric solid organ transplant recipients. *Am J Transplant* **2022**; 22:187–98.
2. Downes KJ, Sharova A, Boge CLK, et al. CMV infection and management among pediatric solid organ transplant recipients. *Pediatr Transplant* **2022**; 26:e14220.
3. Wattles BA, Kim AJ, Cheerva AC, Lucas KG, Elder JJ. Cytomegalovirus treatment in pediatric hematopoietic stem cell transplant patients. *J Pediatr Hematol Oncol* **2017**; 39:241–8.
4. Hakki M, Aitken SL, Danziger-Isakov L, et al. American Society for Transplantation and Cellular Therapy Series: #3—Prevention of cytomegalovirus infection and disease after hematopoietic cell transplantation—ScienceDirect [Internet]. [cited 2023 May 4]. https://www.sciencedirect.com/science/article/pii/S2666636721008927?via%3Dihub
5. Kotton CN, Kumar D, Caliendo AM, et al.; The Transplantation Society International CMV Consensus Group. The Third International Consensus Guidelines on the management of cytomegalovirus in solid-organ transplantation. *Transplantation* **2018**; 102:900–31.
6. Bontant T, Sedlaçek P, Balduzzi A, et al. Survey of CMV management in pediatric allogeneic HSCT programs, on behalf of the inborn errors, infectious diseases and pediatric diseases working parties of EBMT. *Bone Marrow Transplant* **2014**; 49:276–9.
7. Arroyo-Orvañanos J, Hernández-Plata JA, Erro-Aboytia R, Nieto-Zermeño J, Reyes-López A, Varela-Fascinetto G. Cytomegalovirus infection and disease in pediatric liver transplantation: burden of disease under a preemptive therapy approach. *Pediatr Transplant* **2023**; 27:e14356.
8. Nicastro E, Giovannozzi S, Stroppa P, et al. Effectiveness of preemptive therapy for cytomegalovirus disease in pediatric liver transplantation. *Transplantation* **2017**; 101:804–10.
9. Das BB, Prusty BK, Niu J, Sue PK. Cytomegalovirus infection and allograft rejection among pediatric heart transplant recipients in the era of valganciclovir prophylaxis. *Pediatr Transplant* **2020**; 24:e13750.
10. Höcker B, Zencke S, Krupka K, et al. Cytomegalovirus infection in pediatric renal transplantation and the impact of chemoprophylaxis with (val-)ganciclovir. *Transplantation* **2016**; 100:862–70.
11. Danziger-Isakov L, Worley S, Michaels M, et al. The risk, prevention & outcome of cytomegalovirus after pediatric lung transplantation. *Transplantation* **2009**; 87:1541–8.
12. Danziger-Isakov L, Bucavalas J. Current prevention strategies against cytomegalovirus in the Studies in Pediatric Liver Transplantation (SPLIT) centers. *Am J Transplant* **2014**; 14:1908–11.
13. Liverman R, Serluco A, Nance G, et al. Incidence of cytomegalovirus DNAemia in pediatric kidney, liver, and heart transplant recipients: efficacy and risk factors associated with failure of weight-based dosed valganciclovir prophylaxis. *Pediatr Transplant* **2023**; 27:e14493.
14. Peled O, Berkovitch M, Rom E, et al. Valganciclovir dosing for cytomegalovirus prophylaxis in pediatric solid-organ transplant recipients: a prospective pharmacokinetic study. *Pediatr Infect Dis J* **2017**; 36:745–50.
15. Hayes M, Boge CLK, Sharova A, et al. Antiviral toxicities in pediatric solid organ transplant recipients. *Am J Transplant* **2022**; 22:3012–20.
16. Pellett Madan R, Allen UD, Green M, et al.; Pediatric Subgroup for the International Consensus Guidelines on the Management of Cytomegalovirus in Solid Organ Transplantation and the International Pediatric Transplant Association Infectious Disease Committee. Pediatric transplantation case conference: update on cytomegalovirus. *Pediatr Transplant* **2018**; 22:e13276.
17. Chemaly RF, Chou S, Einsele H, et al.; Resistant Definitions Working Group of the Cytomegalovirus Drug Development Forum. Definitions of resistant and refractory cytomegalovirus infection and disease in transplant recipients for use in clinical trials. *Clin Infect Dis* **2019**; 68:1420–6.
18. Crumpacker CS. Ganciclovir. *N Engl J Med* **1996**; 335:721–9.
19. Baker R. FDA approves oral ganciclovir as first drug to prevent CMV disease. Food and Drug Administration. *Bull Exp Treat AIDS* **1995**; 8.
20. Ganciclovir prescribing information [Internet]. [cited 2023 March 8]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209347lbl.pdf
21. Valcyte (valganciclovir hydrochloride tablets) package insert. *Roche [Internet]*. [cited 2023 March 9]. ttps://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021304s008,022257s003lbl.pdf
22. Ljungman P, de la Camara R, Robin C, et al.; 2017 European Conference on Infections in Leukaemia Group. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *Lancet Infect Dis* **2019**; 19:e260–72.
23. Razonable RR, Humar A. Cytomegalovirus in solid organ transplant recipients—Guidelines of the American Society of Transplantation Infectious Diseases Community of Practice. *Clin Transplant* **2019**; 33:e13512.
24. McGavin JK, Goa KL. Ganciclovir. *Drugs* **2001**; 61:1153–83.
25. Kimberlin DW, Jester PM, Sánchez PJ, et al.; National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. Valganciclovir for symptomatic congenital cytomegalovirus disease. *N Engl J Med* **2015**; 372:933–43.
26. Research C for DE and FDA Drug Safety Communication: new dosing recommendations to prevent potential Valcyte (valganciclovir) overdose in pediatric transplant patients. *FDA [Internet]*. **2019** [cited 2023 June 27]. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-dosing-recommendations-prevent-potential-valcyte-valganciclovir
27. Wagstaff AJ, Bryson HM. Foscarnet. *Drugs* **1994**; 48:199–226.
28. Trifillis AL, Cui X, Drusano GL. Use of human renal proximal tubule cell cultures for studying foscarnet-induced nephrotoxicity in vitro. *Antimicrob Agents Chemother* **1993**; 37:2496–9.
29. Goldfarb DS, Coe FL. Foscarnet crystal deposition and renal failure. *Am J Kidney Dis* **1998**; 32:519–20.
30. Lea AP, Bryson HM. Cidofovir. *Drugs* **1996**; 52:225–30; discussion 231.
31. Chou S, Waldemer RH, Senters AE, et al. Cytomegalovirus UL97 phosphotransferase mutations that affect susceptibility to ganciclovir. *J Infect Dis* **2002**; 185:162–9.
32. Cidofovir (Lexi-Drugs) prescribing information [Internet]. [cited 2023 May 18]. https://assets.contenthub.wolterskluwer.com/api/public/content/72cbee75ce694e1788322adaaf696e62?v=6b1a2820
33. content.takeda.com.pdf [Internet]. [cited 2023 March 6]. https://content.takeda.com/?contenttype=pi&product=liv&language=eng&country=usa&documentnumber=1
34. Steingruber M, Marschall M. The cytomegalovirus protein kinase pUL97: host interactions, regulatory mechanisms and antiviral drug targeting. *Microorganisms*. **2020**; 8:515.
35. Shannon-Lowe CD, Emery VC. The effects of maribavir on the autophosphorylation of ganciclovir resistant mutants of the cytomegalovirus UL97 protein. *Herpesviridae* **2010**; 1:4.
36. Wolf DG, Courcelle CT, Prichard MN, Mocarski ES. Distinct and separate roles for herpesvirus-conserved UL97 kinase in cytomegalovirus DNA synthesis and encapsidation. *Proc Natl Acad Sci U S A* **2001**; 98:1895–900.
37. Prichard MN. Function of human cytomegalovirus UL97 kinase in viral infection and its inhibition by maribavir. *Rev Med Virol* **2009**; 19:215–29.
38. Bigley TM, Reitsma JM, Mirza SP, Terhune SS. Human cytomegalovirus pUL97 regulates the viral major immediate early promoter by phosphorylation-mediated disruption of histone deacetylase 1 binding. *J Virol* **2013**; 87:7393–408.
39. Gilbert C, Boivin G. Human cytomegalovirus resistance to antiviral drugs. *Antimicrob Agents Chemother* **2005**; 49:873–83.
40. Krosky PM, Baek MC, Coen DM. The human cytomegalovirus UL97 protein kinase, an antiviral drug target, is required at the stage of nuclear egress. *J Virol* **2003**; 77:905–14.
41. Hamirally S, Kamil JP, Ndassa-Colday YM, et al. Viral mimicry of Cdc2/cyclin-dependent kinase 1 mediates disruption of nuclear lamina during human cytomegalovirus nuclear egress. *PLoS Pathog* **2009**; 5:e1000275.
42. Chou S, Marousek GI. Maribavir antagonizes the antiviral action of ganciclovir on human cytomegalovirus. *Antimicrob Agents Chemother* **2006**; 50:3470–2.
43. Chou S, Song K, Wu J, Bo T, Crumpacker C. Drug resistance mutations and associated phenotypes detected in clinical trials of maribavir for treatment of cytomegalovirus infection. *J Infect Dis* **2020**; 226:576–84.

44. Drew WL, Miner RC, Marousek GI, Chou S. Maribavir sensitivity of cytomegalovirus isolates resistant to ganciclovir, cidofovir or foscarnet. *J Clin Virol* **2006**; 37:124–7.
45. Chou S. Diverse cytomegalovirus UL27 mutations adapt to loss of viral UL97 kinase activity under maribavir. *Antimicrob Agents Chemother* **2009**; 53:81–5.
46. Winston DJ, Young JAH, Pullarkat V, et al. Maribavir prophylaxis for prevention of cytomegalovirus infection in allogeneic stem cell transplant recipients: a multicenter, randomized, double-blind, placebo-controlled, dose-ranging study. *Blood* **2008**; 111:5403–10.
47. Marty FM, Ljungman P, Papanicolaou GA, et al.; Maribavir 1263-300 Clinical Study Group. Maribavir prophylaxis for prevention of cytomegalovirus disease in recipients of allogeneic stem-cell transplants: a phase 3, double-blind, placebo-controlled, randomised trial. *Lancet Infect Dis* **2011**; 11:284–92.
48. Winston DJ, Saliba F, Blumberg E, et al.; 1263-301 Clinical Study Group. Efficacy and safety of maribavir dosed at 100 mg orally twice daily for the prevention of cytomegalovirus disease in liver transplant recipients: a randomized, double-blind, multicenter controlled trial. *Am J Transplant* **2012**; 12:3021–30.
49. Avery RK, Alain S, Alexander BD, et al. Maribavir for refractory cytomegalovirus infections with or without resistance post-transplant: results from a phase 3 randomized clinical trial. *Clin Infect Dis* **2021**; 75:690–701.
50. Sun K, Hayes S, Farrell C, Song IH. Population pharmacokinetic modeling and simulation of maribavir to support dose selection and regulatory approval in adolescents with posttransplant refractory cytomegalovirus. *CPT Pharmacomet Syst Pharmacol* **2023**; 12:719–23. https://onlinelibrary.wiley.com/doi/abs/10.1002/psp4.12943
51. Takeda. A Phase 3, open-label, single-arm, repeated-dose study to evaluate the safety and tolerability, pharmacokinetics, and antiviral activity of maribavir for the treatment of cytomegalovirus (CMV) infection in children and adolescents who have received a hematopoietic stem cell transplant (HSCT) or a solid organ transplant (SOT) [Internet]. clinicaltrials.gov; **2022** [cited 2023 March 5]. Report No.: NCT05319353. https://clinicaltrials.gov/ct2/show/NCT05319353
52. Commissioner O of the FDA. FDA approves first treatment for common type of post-transplant infection that is resistant to other drugs. *FDA*. **2021** [cited 2023 March 6]. https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-common-type-post-transplant-infection-resistant-other-drugs
53. Koszalka GW, Johnson NW, Good SS, et al. Preclinical and toxicology studies of 1263W94, a potent and selective inhibitor of human cytomegalovirus replication. *Antimicrob Agents Chemother* **2002**; 46:2373–80.
54. Melendez DP, Razonable RR. Letermovir and inhibitors of the terminase complex: a promising new class of investigational antiviral drugs against human cytomegalovirus. *Infect Drug Resist* **2015**; 8:269–77.
55. Weinberger S, Steininger C. Reliable quantification of cytomegalovirus DNAemia in letermovir treated patients. *Antiviral Res* **2022**; 201:105299.
56. McCrea JB, Macha S, Adedoyin A, et al. Pharmacokinetic drug-drug interactions between letermovir and the immunosuppressants cyclosporine, tacrolimus, sirolimus, and mycophenolate mofetil. *J Clin Pharmacol* **2019**; 59:1331–9.
57. Winstead RJ, Kumar D, Brown A, et al. Letermovir prophylaxis in solid organ transplant—assessing CMV breakthrough and tacrolimus drug interaction. *Transpl Infect Dis* **2021**; 23:e13570.
58. McCrea JB, Menzel K, Adedoyin A, et al. Drug-drug interaction of letermovir and atorvastatin in healthy participants. *Clin Pharmacol Drug Dev* **2022**; 11:420–8.
59. Nakashima T, Inamoto Y, Fukushi Y, et al. Drug interaction between letermovir and voriconazole after allogeneic hematopoietic cell transplantation. *Int J Hematol* **2021**; 113:872–6.
60. Marshall WL, McCrea JB, Macha S, et al. Pharmacokinetics and tolerability of letermovir coadministered with azole antifungals (posaconazole or voriconazole) in healthy subjects. *J Clin Pharmacol* **2018**; 58:897–904.
61. Package insert Prevymis (letermovir) Merck [Internet]. [cited 2023 May 5]. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209939Orig1s000,209940Orig1s000lbl.pdf
62. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med* **2017**; 377:2433–44.
63. Marty FM, Ljungman PT, Chemaly RF, et al. Outcomes of patients with detectable CMV DNA at randomization in the phase III trial of letermovir for the prevention of CMV infection in allogeneic hematopoietic cell transplantation. *Am J Transplant* **2020**; 20:1703–11.
64. Ljungman P, Schmitt M, Marty FM, et al. A mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. *Clin Infect Dis* **2020**; 70:1525–33.
65. Vyas A, Raval AD, Kamat S, LaPlante K, Tang Y, Chemaly RF. Real-world outcomes associated with letermovir use for cytomegalovirus primary prophylaxis in allogeneic hematopoietic cell transplant recipients: a systematic review and meta-analysis of observational studies. *Open Forum Infect Dis* **2023**; 10:ofac687.
66. FDA Accepts Two sNDAs for Merck's Prevymis | FDAnews [Internet]. [cited 2023 May 5]. https://www.fdanews.com/articles/211246-fda-accepts-two-sndas-for-mercks-prevymis
67. Limaye AP, Budde K, Humar A, et al. Letermovir vs valganciclovir for prophylaxis of cytomegalovirus in high-risk kidney transplant recipients: a randomized clinical trial. *JAMA* **2023**; 330:33. [cited 2023 June 29]; https://doi.org/10.1001/jama.2023.9106
68. Merck.com. U.S. FDA approves new indication for Merck's PREVYMIS® (letermovir) for prevention of cytomegalovirus (CMV) disease in high-risk adult kidney transplant recipients [Internet]. [cited 2023 June 29]. https://www.merck.com/news/u-s-fda-approves-new-indication-for-mercks-prevymis-letermovir-for-prevention-of-cytomegalovirus-cmv-disease-in-high-risk-adult-kidney-transplant-recipients/
69. Styczyński J, Tridello G, Xhaard A, et al. Use of letermovir in off-label indications: Infectious Diseases Working Party of European Society of Blood and Marrow Transplantation retrospective study. *Bone Marrow Transplant* **2021**; 56:1171–9.
70. Tsui E, Gonzales JA, Shantha JG, Acharya N, Doan T. Letermovir for the management of cytomegalovirus-associated uveitis. *Ocul Immunol Inflamm* **2021**; 29:169–74.
71. Razonable RR. Oral antiviral drugs for treatment of cytomegalovirus in transplant recipients. *Clin Microbiol Infect [Internet]* **2023**; 29:1144–9. [cited 2023 May 7]. https://www.sciencedirect.com/science/article/pii/S1198743X23001362
72. Boignard A, Augier C, Kheng M, Epaulard O, Germi R. Letermovir use to treat complex cytomegalovirus reactivations in two heart transplant recipients. *Antivir Ther* **2022**; 27:135965352211336.
73. Gonzalez-Bocco IH, Cheng M, Aleissa MM, et al. 733. Letermovir treatment for refractory or resistant cytomegalovirus infection or disease with concurrent organ dysfunction: an interim analysis of a Phase 2 open label study. *Open Forum Infect Dis*. **2022**; 9:ofac492.024.
74. Cherrier L, Nasar A, Goodlet KJ, Nailor MD, Tokman S, Chou S. Emergence of letermovir resistance in a lung transplant recipient with ganciclovir-resistant cytomegalovirus infection. *Am J Transplant* **2018**; 18:3060–4.
75. Hofmann E, Sidler D, Dahdal S, et al. Emergence of letermovir resistance in solid organ transplant recipients with ganciclovir resistant cytomegalovirus infection: a case series and review of the literature. *Transpl Infect Dis* **2021**; 23:e13515.
76. Veit T, Munker D, Barton J, et al. Letermovir in lung transplant recipients with cytomegalovirus infection: a retrospective observational study. *Am J Transplant* **2021**; 21:3449–55.
77. Golob S, Batra J, DeFilippis EM, et al. Letermovir for cytomegalovirus prophylaxis in high-risk heart transplant recipients. *Clin Transplant* **2022**; 36:e14808.
78. Daukshus NP, Cirincione A, Siver M, Mathew S, Kunvarjee B, Chan A, et al. Letermovir for cytomegalovirus prevention in adolescent patients following hematopoietic cell transplantation. *J Pediatr Infect Dis Soc* **2022**; 11:337–40.
79. Kuhn A, Puttkammer J, Madigan T, et al. Letermovir as cytomegalovirus prophylaxis in a pediatric cohort: a retrospective analysis. *Transplant Cell Ther* **2023**; 29:62.e1–4.
80. Körholz KF, Füller MA, Hennies M, et al. Letermovir for prophylaxis and preemptive therapy of cytomegalovirus infection in paediatric allogeneic haematopoietic cell transplant patients. *Pediatr Drugs* **2023**; 25:225–32.
81. Richert-Przygonska M, Jaremek K, Debski R, et al. Letermovir prophylaxis for cytomegalovirus infection in children after hematopoietic cell transplantation. *Anticancer Res* **2022**; 42:3607–12.
82. Groll AH, Schulte JH, Antmen AB, et al. 623. Preliminary dosing for adolescent hematopoietic stem-cell transplant (HSCT) recipients based on pharmacokinetic (PK), safety, and efficacy data of letermovir (LET) for cytomegalovirus (CMV) prophylaxis. *Open Forum Infect Dis*. **2022**; 9:ofac492.675.
83. Sepassi A, Saunders IM, Bounthavong M, Taplitz RA, Logan C, Watanabe JH. Cost effectiveness of letermovir for cytomegalovirus prophylaxis compared with pre-emptive therapy in allogeneic hematopoietic stem cell transplant recipients in the United States. *PharmacoEcon Open [Internet]* **2023**; 7:393–404. [cited 2023 May 5]. https://doi.org/10.1007/s41669-023-00398-y
84. Douglas CM, Barnard R, Holder D, et al. Letermovir resistance analysis in a clinical trial of cytomegalovirus prophylaxis for hematopoietic stem cell transplant recipients. *J Infect Dis* **2020**; 221:1117–26.
85. Papanicolaou GA, Silveira FP, Langston AA, et al. Maribavir for refractory or resistant cytomegalovirus infections in hematopoietic-cell or solid-organ transplant recipients: a randomized, dose-ranging, double-blind, phase 2 study. *Clin Infect Dis* **2019**; 68:1255–64.

Check for updates

Transplant Infectious Disease

WILEY

REVIEW ARTICLE

Efficacy and Safety of Letermovir for *Cytomegalovirus* Prophylaxis in Pediatric Hematopoietic Stem Cell Transplantation Recipients: A Systematic Review, Meta-Analysis, and Meta-Regression

Abdullah Yousef Aldalati[1] | Ayham Mohammad Hussein[2] | Elsayed Balbaa[3] | Bara M. Hammadeh[2] | Muhammad idrees[4] | Osama Aloudat[5] | Moath Albliwi[6] | Mohammad Abuassi[7] | Iyad Sultan[8,9]

[1]Faculty of Medicine, Jordan University of Science and Technology, Irbid, Jordan | [2]Faculty of Medicine, Al- Balqa' Applied University, Salt, Jordan | [3]Faculty of Medicine, Alexandria University, Alexandria, Egypt | [4]Lahore General Hospital, Lahore, Punjab, Pakistan | [5]Department of Pediatrics of Saint Louis University School of Medicine, SSM Health Cardinal Glennon Children's Hospital, St. Louis, Missouri, USA | [6]Department of Internal Medicine, Cleveland Clinic, Cleveland, Ohio, USA | [7]Internal Medicine Department, College of Medicine, University of Central Florida, Gainesville, Florida, USA | [8]Department of Pediatrics, King Hussein Cancer Center, Amman, Jordan | [9]Artificial Intelligence and Data Innovation Office, King Hussein Cancer Center, Amman, Jordan

Correspondence: Abdullah Yousef Aldalati (dalatia29@gmail.com)

Received: 15 January 2025 | **Revised:** 31 January 2025 | **Accepted:** 4 February 2025

Funding: The authors received no specific funding for this work.

Keywords: *cytomegalovirus* | hematopoietic stem cell transplant | letermovir | meta-analysis | pediatrics

ABSTRACT

Objective: Letermovir (LTV) is a novel antiviral agent approved by the FDA in 2017 for CMV prophylaxis in adult CMV-seropositive allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients and approved for pediatric use in 2024. This study systematically evaluates the efficacy and safety of LTV prophylaxis for CMV infection in pediatric allo-HSCT recipients.

Methods: We systematically searched PubMed, Scopus, Web of Science, Embase, and Cochrane Library up to December 2024 for studies that evaluated the use of LTV prophylaxis in pediatric allo-HSCT recipients. We conducted single-arm meta-analysis using Open Meta Analyst software and double-arm meta-analysis using R Studio. We pooled the dichotomous outcomes as event and total using the fixed-effects model.

Results: Twelve articles were included in the analysis. The single-arm meta-analysis indicated that the prophylactic use of LTV against CMV among pediatrics was associated with a 10.9% (95% CI: 0.065, 0.153) infection rate without any disease occurrence. The percentage of patients who discontinued the drug due to adverse reactions was only 2.4% (95% CI: 0.003, 0.045), and all-cause mortality was 7.9% (95% CI: 0.032, 0.126). The double-arm meta-analysis results indicated that the incidence of CMV infection was significantly lower in the LTV group in comparison to the control group (RR: 0.29; 95% CI: 0.16, 0.56; $p < 0.001$).

Conclusion: LTV has demonstrated safety and efficacy in preventing CMV infection and disease among high-risk pediatric patients. Future large scale randomized trials are necessary to validate the findings.

Abbreviations: Allo-HSCT, allogeneic hematopoietic stem cell transplantation; CMV, *Cytomegalovirus*; LTV, letermovir.

© 2025 Wiley Periodicals LLC.

1 | Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an important intervention for pediatric patients with malignant and nonmalignant hematological disorders [1]. Infections remain a significant cause of morbidity and mortality following allo-HSCT [2]. *Cytomegalovirus* (CMV) infection, despite current surveillance and preemptive antiviral therapy, remains a significant driver of morbidity and non-relapse mortality in the pediatric allo-HSCT recipients [3].

The prevention and management of CMV infection is a crucial aspect of posttransplant care for pediatric patients, who are at increased risk due to their immature immune systems [4]. Although antiviral therapies such as ganciclovir, valganciclovir, foscarnet, and cidofovir are effective, yet treating CMV remains challenging due to their toxic side effects. These antivirals effectively prevent CMV disease but often lead to myelosuppression, nephrotoxicity, and electrolyte disturbances, limiting their use, especially in pediatric populations [5, 6]. Foscarnet's nephrotoxicity and the myelosuppression caused by ganciclovir and valganciclovir have limited their use for primary CMV prophylaxis [7, 8].

Letermovir (LTV) is a novel antiviral agent specifically targeting CMV, inhibiting its DNA terminase complex, and preventing viral replication [9]. LTV got approved by the FDA in 2017 for CMV prophylaxis in adult CMV-seropositive allo-HSCT recipients and in 2024 for pediatric use [10], LTV has demonstrated efficacy and safety in preventing CMV activation in both adult and pediatric populations following allo-HSCT [11, 12]. Unlike ganciclovir/valganciclovir, LTV is not associated with myelosuppression and is clinically well-tolerated, even when initiated before engraftment [13].

Although there is substantial evidence supporting the use of LTV in adult patients, its use in pediatric patients lacks a definitive conclusion. To provide a more comprehensive assessment, this systematic review and meta-analysis aimed to evaluate the efficacy and safety of LTV prophylaxis for CMV infection in pediatric allo-HSCT recipients.

2 | Methods

2.1 | Registration

This systematic review and meta-analysis followed the PRISMA guidelines [14]. We registered the protocol of this study on the International Prospective Register of Systematic Reviews (PROSPERO) (No. CRD42024593577).

2.2 | Search Strategy and Eligibility Criteria

We systemically searched PubMed, Scopus, Web of Science, Embase, and Cochrane Library databases up to December 2024. We constructed the search strategy using medical subject headings (MeSH) and keywords including letermovir, cytomegalovirus, pediatric, and transplant. The detailed search strategy for each database is shown in Appendix 1. Furthermore, we reviewed the reference lists of retrieved articles to supplement our extensive search. No restrictions were applied on the language and publication year of articles.

Patient, intervention, comparison, and outcome framework (PICO) was used to develop the inclusion and exclusion criteria. We included studies that use [1] LTV as CMV prophylaxis in [2]; pediatric patients [3]; following allo-HSCT. Studies that did not meet the inclusion criteria were excluded.

2.3 | Study Selection, Data Extraction, and Outcomes

Two authors independently screened the title and abstract of the studies. Then, we obtained the full texts of the potentially eligible studies for more in depth assessment. Any conflicts were resolved by a third author. The final decision to include each paper was reached by consensus among all authors. The same authors extracted data from the studies separately using a standard Excel sheet. Certain data were extracted from the included studies, including the study characteristics (first author, year of publication, journal name, country/region, and study design), baseline data (gender, age, weight, recipient and donor CMV serostatus, and acute graft vs. host disease), efficacy data, and safety data. The outcomes were CMV infection rate (defined as any evidence of CMV activation and a CMV viral load of > 500 IU/mL), CMV disease rate (defined as the presence of CMV infection with concurrent CMV-related impairment of organ function), discontinuation due to adverse effects, and all-cause mortality.

2.4 | Quality Assessment and Risk of Bias

The selected studies were evaluated by two independent authors. We used the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [15], to evaluate the methodological quality of the selected articles. It covers seven key areas of potential bias: confounding factors, selection bias, misclassification of interventions, deviations from intended interventions, missing data, outcome measurement, and selective reporting. Each study's risk of bias was rated across five levels: low, moderate, serious, critical, or insufficient information. Studies rated as having a low or moderate risk of bias across all domains were considered to have high-quality methodology. Any disagreements in quality assessment were resolved by a third independent author.

2.5 | Statistical Analysis

We conducted a single-arm meta-analysis using Open Meta Analyst software (Version 3.13) [16]. We pooled the dichotomous outcomes as event and total and calculated the overall event rate with a 95% confidence interval (CI). A double-arm meta-analysis comparing the incidence of CMV infection between the LTV group and the control group was conducted using R Studio, and we calculated the pooled risk ratio (RR) using the Mantel–Haenszel method. To avoid publication bias, we did not exclude studies with zero events. However, since the logit of 0 is undefined or infinite for studies with zero events, we applied a

13993062, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/tid.70006 by Readcube (Labtiva Inc.), Wiley Online Library on [03/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

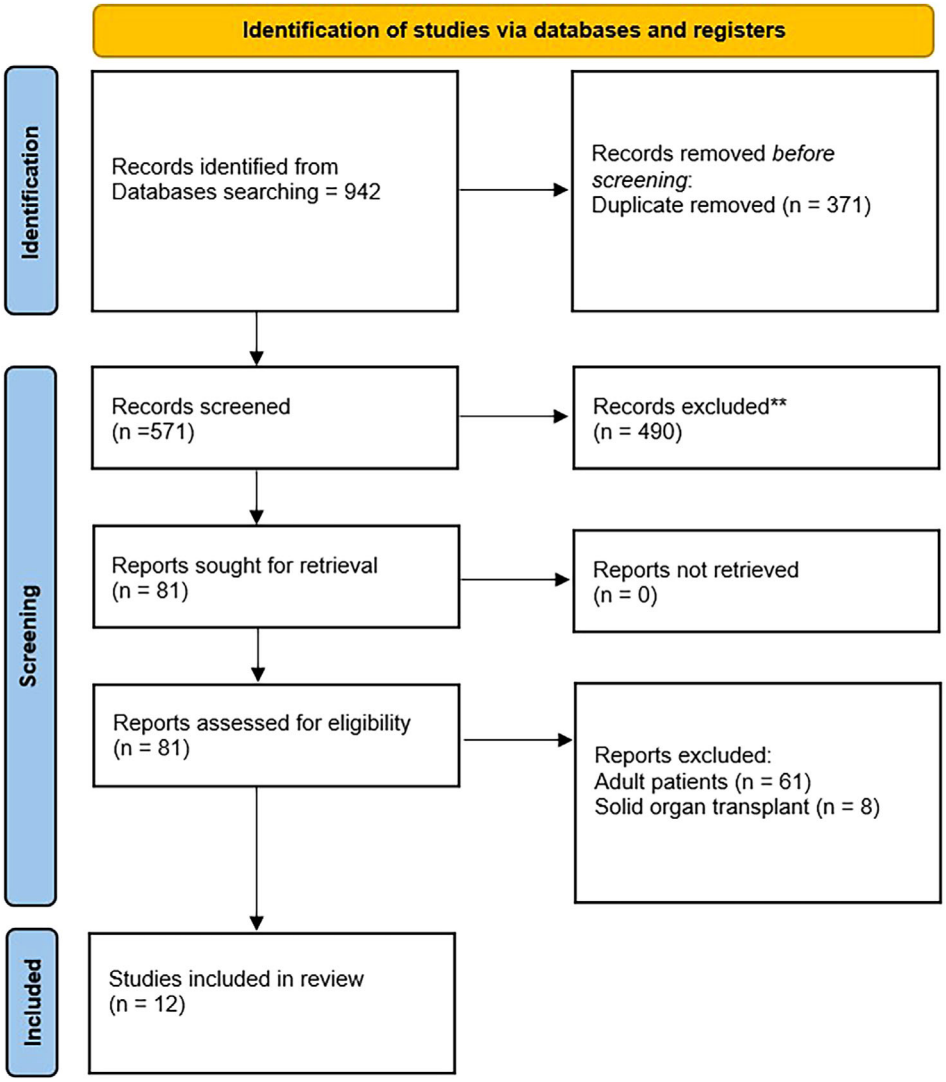


FIGURE 1 | Forest plot of study selection flow chart.

continuity correction by adding 0.5 to the events and nonevents in those studies, ensuring a more conservative effect size. We used the fixed-effects model as low heterogeneity was observed in all outcomes. We used the Cochrane Q chi-square test and the I^2 statistic to assess heterogeneity across the included studies. We considered substantial heterogeneity if $I^2 > 50\%$. Finally, we performed a meta-regression analysis on variables such as age, recipient serostatus, and donor serostatus to identify potential effect modifiers.

3 | Results

3.1 | Study Selection and Characteristics

Our systematic search of the databases retrieved 942 articles. After removing duplicates, 571 articles remained for screening. Following the initial selection process, 81 articles were identified for more detailed assessment based on the full text. Of these, 69 articles did not meet our inclusion criteria and were excluded. Finally, 12 articles [11, 17–27] met our inclusion criteria and were included in our analysis (Figure 1).

The studies included in this analysis were published between 2020 and 2024 and involved a total of 253 pediatric patients receiving LTV prophylaxis. The mean age of the patients ranged from 4 to 17 years and the median duration of LTV prophylaxis ranged from 92 days to 221 days. Five studies were conducted in Europe [11, 17, 18, 25, 26], three in the United States [20–22], three in Asia [23, 24, 27], and one was multicenter [19]. The LTV dose was reduced by 50% when administered with contaminant cyclosporine. The main characteristics of the included studies are reported in Table 1. Transplantation details are summarized in Table 2.

3.2 | CMV Infection Rate

CMV infection was reported in 10 studies [11, 18, 20–27] with 185 pediatric patients. The single arm meta-analysis results indicated that the CMV infection rate was 10.9% (95% CI: 0.065, 0.153) when LTV was used as the prophylactic agent. No clinically important heterogeneity was observed ($I^2 = 0\%$, $p = 0.395$) (Figure 2). The meta-regression analysis was insignificant for age (coefficient = −0.007, 95% CI: −0.017, 0.003, $p = 0.156$), proportion of

13993062, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/id.70006 by Readcube (Labtiva Inc.), Wiley Online Library on [03/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | Characteristics of the included studies and letermovir dosage regimen.

Study ID	Country	Study design	No. of patients (*n*)	Gender (*n*)	Age mean (SD)	Weight mean (SD)	Letermovir dose	Frequency/route of administration
Groll et al. 2024	Multicenters	phase 2b, open-label, single-arm study	28	M = 15 F = 13	13.74 (1.2)	55.79 (16.5)	480 mg half the dose when used with cyclosporine	Daily/IV or PO
Cheng et al. 2022	Taiwan	prospective observational study, with matched control group	4	M = 3 F = 1	14.6 (4)	—	< 30 kg = 240 mg ≥ 30 kg = 480 mg half the dose when used with cyclosporine	Daily/IV or PO
Galaverna et al. 2024	Italy	Retrospective observational study	65	M = 44 F = 21	7.38 (3.6)	36.04 (16.7)	one infnant (8 mo) = 80 mg < 18 kg = 120 mg < 30 kg = 240 mg ≥ 30 kg = 480 mg half the dose when used with cyclosporine	Daily/IV or PO
Korholz et al. 2023	Germany	Retrospective observational study	17	M = 10 F = 7	12.2 (5.1)	39.5 (16.3)	< 18 kg = 120 mg < 30 kg = 240 mg ≥ 30 kg = 480 mg Half the dose when used with cyclosporine	Daily/IV or PO
Daukshus et al. 2022	USA	Retrospective observational study	10	M = 5 F = 5	14.62 (2.5)	51.86 (8.4)	480 mg half the dose when used with cyclosporine	Daily/IV or PO
Cesar et al. 2024	France	Retrospective observational study, with matched control group	31	M = 22 F = 9	4.27 (5.4)	—	480 mg half the dose when used with cyclosporine	Daily/IV or PO

(Continues)

13993062, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/tid.70006 by ReadCube (Labtiva Inc.), Wiley Online Library on [03/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 1 | (Continued)

Study ID	Country	Study design	No. of patients (*n*)	Gender (*n*)	Age mean (SD)	Weight mean (SD)	Letermovir dose	Frequency/route of administration
Chen et al. 2023	USA	Retrospective observational study, with matched control group	41	M = 28 F = 13	17.2 (3.2)	61.28 (19.9)	480 mg half the dose when used with cyclosporine	Daily/IV or PO
Khun et al. 2023	USA	Retrospective observational study	9	M = 4 F = 5	12.91 (5)	—	< 30 kg = 240 mg ≥ 30 kg = 480 mg	Daily/IV or PO
Przygonska et al. 2022	Poland	Retrospective observational study, with matched control group	13	—	12.75 (2.9)	—	< 18 kg = 120 mg < 30 kg = 240 mg ≥ 30 kg = 480 mg half the dose when used with cyclosporine	Daily/IV or PO
Styczynski et al. 2021	Multicenters in Europe	Retrospective observational study	5	—	—	—	< 30 kg = 120 mg ≥ 30 kg = 480 mg	Daily/IV or PO
Zhang et al. 2024	China	prospective observational study, with matched control group	5	—	—	—	480 mg half the dose when used with cyclosporine	Daily/IV or PO
Tatebe et al. 2024	Japan	Retrospective observational study, with matched control group	25	M = 17 F = 8	8.3 (7.1)	26.47 (18)	10–12 mg/kg/d half the dose when used with cyclosporine	Daily/IV or PO

Note: The age is represented in years, weight in kg.

Abbreviations: F = female, M = male, SD = standard deviation.

13993062, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ijd.70006 by Readcube (Labtiva Inc.), Wiley Online Library on [03/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

TABLE 2 | Transplantation details.

	LTV prophylaxis			CMV seropositive (*n*)		Stem cell source (*n*)			HLA matching (*n*)				Indication for the transplantation (*n*)		
Study ID	Median day of initiation after transplant (days)	Median duration (days)	Acute GVHD (*n*)	D	R	Bone marrow	Cord blood	Peripheral blood	MRD	mMRD	MUD	mMUD	ALL	AML	Other causes
Groll et al. 2024	—	—	10	20	28	12	1	15	6	9	9	4	4	7	17
Cheng et al. 2022	—	112	1	0	4	—	—	—	2	0	1	1	2	1	1
Galaverna et al. 2024	6	100	27	29	64	33	1	31	10	—	—	—	—	—	—
Korholz et al. 2023	27.8	139.7	6	17	6	16	0	1	5	—	10	2	—	—	8
Daukshus et al. 2022	19	221	—	4	10	3	3	4	2	—	3	5	5	3	2
Cesar et al. 2024	1	—	9	34	24	28	0	8	5	20	8	3	0	0	36
Chen et al. 2023	1	112	22	11	38	23	14	4	—	—	—	—	11	9	21
Khun et al. 2023	—	182	—	7	7	—	—	—	1	—	5	—	—	—	—
Przygonska et al. 2022	1		—	—	—	—	—	—	—	—	8	—	8	—	—
Styczynski et al. 2020	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Zhang et al. 2024	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Tatebe et al. 2024	1	92	17	15	24	12	6	7	1	0	5	13	9	7	9

Abbreviations: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CMV = *cytomegalovirus*, D = donor, GVHD = graft versus host defense, HLA = human leukocyte antigen, LTV = letermovir, mMRD = mismatched related donor, mMUD = mismatched unrelated donor, MRD = matched related donor, MUD = matched unrelated donor, R = reciepient.

13993062, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/tid.70006 by Readcube (Labtiva Inc.), Wiley Online Library on [03/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

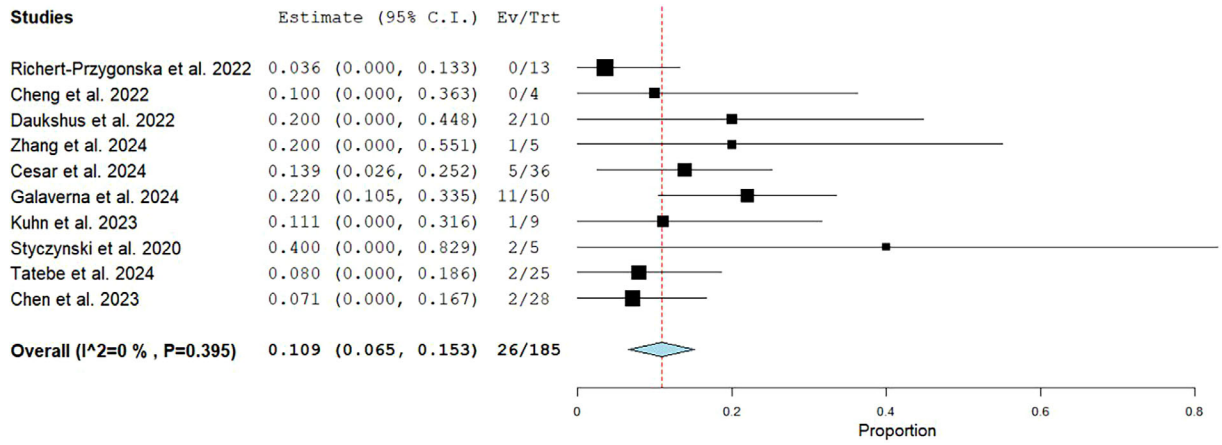


FIGURE 2 | Forest plot of CMV infection rate.

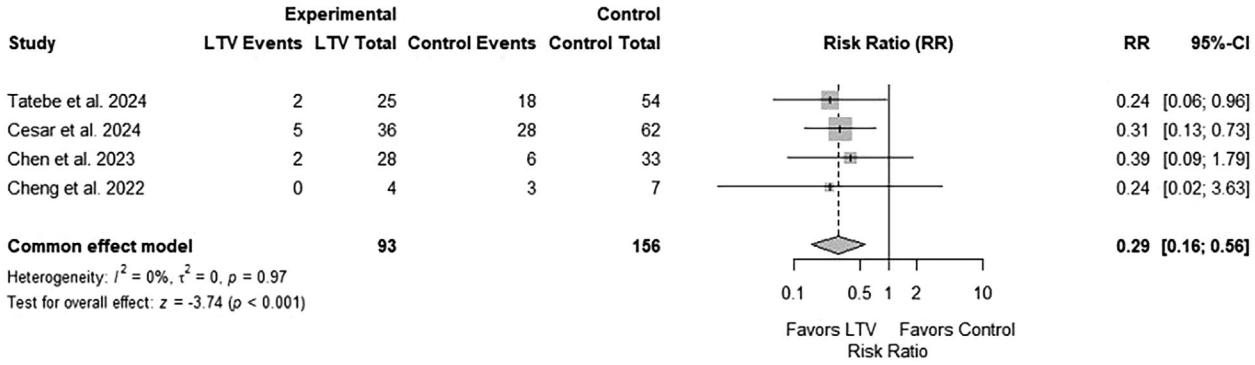


FIGURE 3 | Forest plot comparing the incidence of CMV infection between the LTV group and the control group.

seropositive recipients (coefficient = 0.001, 95% CI: −0.005, 0.007, p = 0.801), and proportion of seropositive donors (coefficient = 0.00, 95% CI: −0.001, 0.002, p = 0.693) (see Appendix 2a–c).

Four studies [18, 21, 24, 27] compared the CMV infection event between the LTV group and the control group. A total of 93 patients were included in the LTV group, while 156 patients were in the control group. The double-arm meta-analysis showed that the LTV group experienced a lower incidence of CMV infection in comparison to the control group (RR: 0.29; 95% CI: 0.16, 0.56; p < 0.001). No clinically important heterogeneity was observed (I^2 = 0%, p = 0.97) (Figure 3).

3.3 | CMV Disease Rate

Eight studies [11, 17–20, 23, 26, 27] with 183 pediatric patients reported CMV disease events. LTV was effective in preventing CMV-related organ dysfunction, as all included studies reported zero CMV disease event (95% CI: −0.002, 0.033) (Figure 4).

3.4 | Discontinuation Due to Adverse Effects

Discontinuation of the drug due to adverse effects was reported in nine studies [11, 17–23, 27] with 189 pediatric patients. Pooled analysis results indicated that the discontinuation rate of LTV was 2.4% (95% CI: 0.003, 0.045). No clinically important heterogeneity was observed (I^2 = 0%, p = 0.404) (Figure 5). The meta-regression analysis was insignificant for age (coefficient = 0.006, 95% CI: −0.002, 0.013, p = 0.157), proportion of seropositive recipients (coefficient = 0.00, 95% CI: −0.001, 0.001, p = 0.819), and proportion of seropositive donors (coefficient = 0.00, 95% CI: −0.001, 0.001, p = 0.501) (see Appendix 3a–c).

Adverse events associated with LTV were generally mild and infrequent such as nausea and headache. None of the studies in this analysis reported clinically significant myelosuppression or nephrotoxicity associated with LTV.

3.5 | All-Cause Mortality

Five studies [11, 18, 19, 24, 25] with 123 pediatric patients reported the all-cause mortality. Pooled analysis showed that the all-cause mortality rate was 7.9% (95% CI: 0.032, 0.126). No clinically important heterogeneity was observed (I^2 = 0%, p = 0.595) (Figure 6). It's important to mention that none of the deaths were caused by CMV infection or disease.

3.6 | Risk of Bias

A quality assessment was performed on all studies that were included in our review to evaluate their inherent risk of bias. No studies were excluded from the systematic review due to

13993062, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/ctd.70006 by Readcube (Labtiva Inc.), Wiley Online Library on [03/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

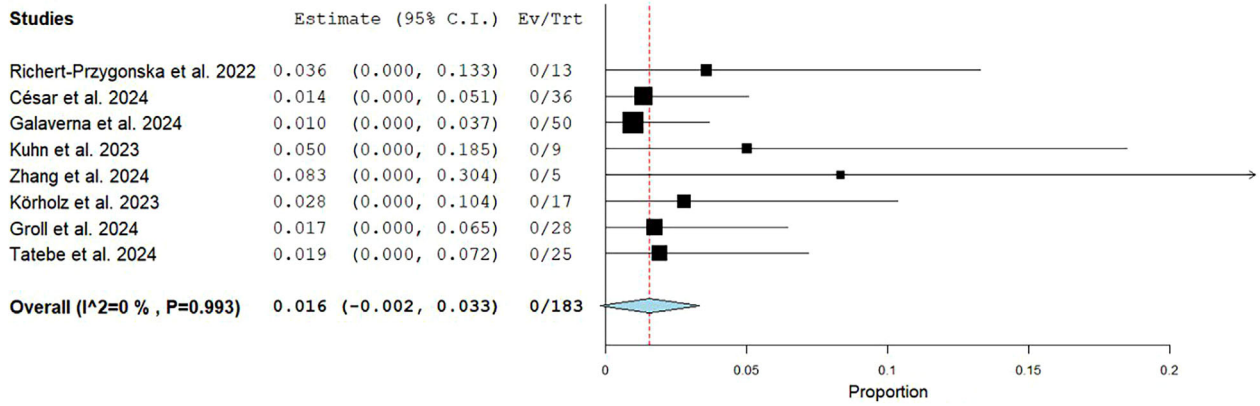


FIGURE 4 | Forest plot of CMV disease rate.

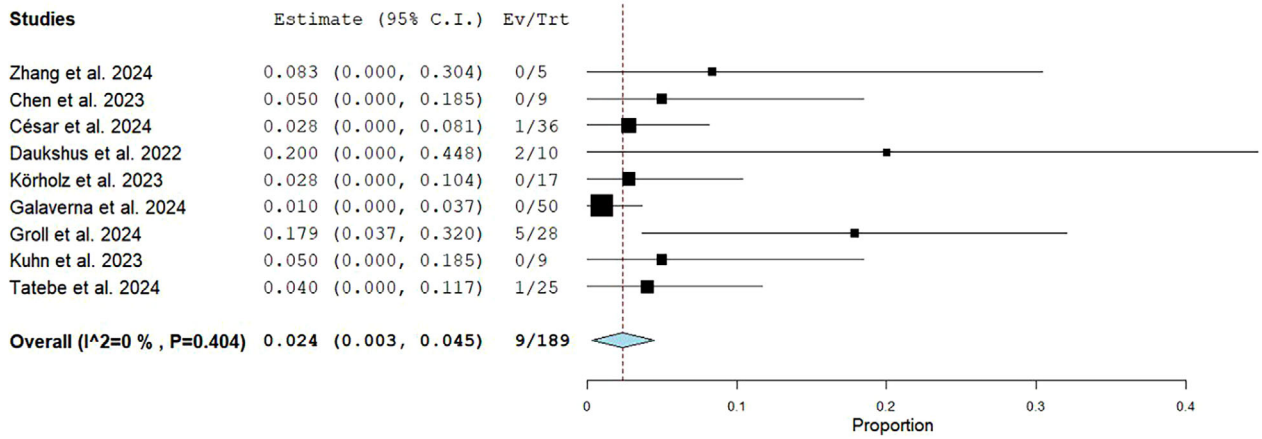


FIGURE 5 | Forest plot of LTV Discontinuation due to adverse effects.

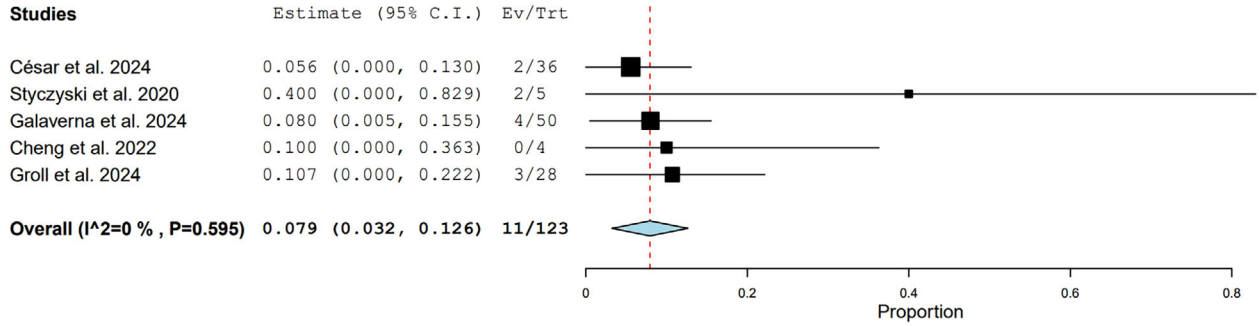


FIGURE 6 | Forest plot of all-cause mortality.

a known risk of bias that could affect the results. Among the included studies, five were judged as having a serious risk, two as moderate, and five as having a low risk of bias. The detailed quality assessment is shown in (see Appendix 4).

4 | Discussion

Allo-HSCT in pediatric patients poses unique challenges due to the distinct physiological, immunological, and developmental characteristics of children [4]. Several preventive measures and prophylactic protocols for pediatrics have been reviewed [28]. We aimed to systematically evaluate the efficacy and safety of LTV prophylaxis in pediatric allo-HSCT recipients to reach a definitive conclusion. Based on our analysis, the prophylactic use of LTV against CMV among pediatric patients was associated with a 10.9% infection rate without any disease occurrence. The percentage of patients who stopped the drug because of adverse reactions was only 2.4%, and all-cause mortality was 7.9%. In addition, the meta-regression analysis showed insignificant results for age, the proportion of seropositive donors, and the proportion of seropositive recipients.

Current clinical guidelines still recommend ganciclovir and its oral prodrug, valganciclovir, for CMV prophylaxis in pediatric populations, despite the significant risk of adverse events associated with these agents [4]. Both drugs exhibit strong anti-CMV activity and have been shown to prevent CMV infection and

13993062, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/tid.70006 by Readcube (Labtiva Inc.), Wiley Online Library on [03/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

disease [29]. Ganciclovir is particularly noted for its myelosuppressive effects, primarily neutropenia, which has been reported in 25%–62% of patients [10]. Similarly, valganciclovir is associated with myelosuppression in addition to gastrointestinal side effects such as nausea and diarrhea [30]. Both medications require close monitoring and dose adjustments in patients with renal impairment owing to their potential nephrotoxicity [31]. Other antiviral drugs, such as acyclovir and valacyclovir, did not significantly reduce CMV infection or disease compared to placebo [10, 29]. Similarly, Maribavir failed to prevent CMV disease in Phase 3 studies involving both adult liver transplant and allo-HSCT recipients [32, 33]. Foscarnet has not been studied as a prophylactic agent in controlled allo-HSCT trials, and its use is restricted by its potential for renal toxicity. This has increased the need for newer and safer antiviral agents to improve patient outcomes and reduce adverse effects [34].

LTV has significant potential as a CMV prophylaxis agent, effectively preventing CMV infection while also exhibiting a favorable side-effect profile. In a Phase 3 trial [13], LTV prophylaxis significantly reduced CMV infection, with minimal side effects in adult patients undergoing allo-HSCT. The LTV group had lower rates of clinically significant CMV infection and all-cause mortality than the placebo group did. Vyas et al. [35] conducted a comprehensive meta-analysis to assess the efficacy and safety of LTV in adults. They found that LTV was effective in reducing the risk of CMV-related complications and mortality beyond Day 200 in adult allo-HCT recipients. These findings demonstrate the favorable use of LTV in adult patients receiving allo-HSCT. Although there is substantial evidence supporting the use of LTV in adult patients, this is not the case in pediatric patients. The application of LTV in pediatrics remains off-label with a limited sample size and follow-up duration. In this systematic review, we analyzed the available data regarding LTV efficacy, safety, and dose regimens for the pediatric population to provide a more comprehensive overview.

The dosage regimen was similar across most included studies. They provided a dose based on the child's weight. 120, 240, or 480 mg were given for pediatrics weighing < 18, 18–30, or ≥ 30 kg, respectively. There was an instance where an infant was administered an 80 mg dose. The results of the Phase 2b pharmacokinetics trial support an LTV dose of 480 mg (240 mg with cyclosporine) in pediatric allo-HCT recipients [19]. LTV dose was reduced by 50% when cyclosporine was concomitantly administered. This was due to cyclosporine's inhibition of cytochrome P450 3A4, which is involved in LTV metabolism [36]. LTV can be administered via oral or intravenous routes without the need for dose adjustments in cases of mild renal impairment and mild liver failure, which distinguishes it from other available options [37].

Our meta-analysis results indicated that the CMV infection rate was 10.9% (95% CI: 0.065, 0.153) when LTV was used as a prophylactic agent. In addition, LTV was effective in lowering the incidence of CMV infection compared to the control group which used acyclovir and valacyclovir ($p < 0.001$). LTV was also effective in preventing CMV disease (95% CI: −0.002, 0.033). These results demonstrate the efficacy of LTV in preventing CMV-related complications in the pediatric population. Reed et al. [38] investigated the use of ganciclovir in adults receiving allo-HSCT and found improved CMV infection up to 33.1% with only a single disease event. Interestingly, LTV offered a lower infection rate as surpassed in our analysis, strongly suggesting its superior efficacy over ganciclovir. In addition, Haastrup et al. [39] reported CMV infection rates and disease events of up to 21.8% and 12.5%, respectively, after acyclovir prophylaxis combined with ganciclovir, which is still significantly higher than that in our pooled analysis. This highlights the potential use of LTV in pediatric patients. However, these results cannot be generalized, as the studies were conducted on different populations.

The primary concern regarding the antiviral agents used for CMV prophylaxis is their adverse effects. Antivirals such as ganciclovir and valganciclovir are associated with myelosuppression, which significantly increases the risk of infection and bleeding [30]. Our meta-analysis showed that LTV was well tolerated, with only 2.4% of pediatric patients discontinuing the drug. Notably, none of the studies included in this analysis reported clinically significant myelosuppression or nephrotoxicity associated with LTV. Some studies have reported very few incidences of liver toxicity, but they were statistically insignificant [20, 25]. This favorable safety profile underscores the potential of LTV as a promising alternative for CMV prophylaxis. In addition to LTV efficacy, incorporating LTV into clinical practice could significantly reduce the risk of leukopenia in high-risk pediatric allo-HSCT recipients, a complication commonly associated with ganciclovir and valganciclovir.

Analysis of the included studies revealed an all-cause mortality rate of 7.9% following allo-HSCT. Notably, neither CMV activation nor disease accounted for any death. Tiera et al. [40] investigated the non-relapse mortality among adults and found that CMV reactivation was associated with higher non-relapse mortality compared to other causes. This raises the importance of preventing CMV activation, particularly in pediatric patients, who have inherently weaker immune systems than adults [41]. Another study by Ljungman et al. [42] reported improved overall survival rates in adults receiving LTV prophylaxis, which was linked to a reduction in CMV reactivation. One possible explanation is that immune reconstitution after allo-HCT gradually improves, and delaying or reducing CMV infection may provide the recovering immune system with a better opportunity to control the infection. Therefore, LTV prophylaxis could offer a mortality benefit by lowering the risk or delaying CMV infection. Another explanation is that LTV prophylaxis may reduce or delay the need for preemptive therapy with other antiviral agents that can lead to serious adverse events, further reducing the mortality. Although our meta-analysis demonstrated low mortality rate in pediatric patients on LTV prophylaxis, data specifically analyzing mortality in pediatric patients are lacking.

CMV serostatus is an important factor that determines the outcomes after allo-HSCT. According to Boeckh et al. [43], positive serology is associated with increased transplant-related mortality, with recipient seropositivity being at the highest risk. In our analysis, the majority of pediatric patients were considered high-risk due to their CMV seropositive status. Many of the studies we reviewed reported a high percentage of seropositive recipients and donors, with some reaching as high as 100%. Although the patients were at high risk, LTV showed excellent results in preventing transplant-related mortality and CMV disease. Meta-regression analysis did not find a significant association between

13993062, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/tid.70006 by Readcube (Labtiva Inc.), Wiley Online Library on [03/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

CMV serostatus and the clinical outcomes we measured. This suggests that LTV offers effective CMV prophylaxis even in high-risk pediatric patients. In addition, LTV prophylaxis was found to be cost-effective compared to preemptive therapy alone, offering potential economic benefits [44].

To our knowledge, this is the first comprehensive analysis to summarize the role of LTV prophylaxis in CMV-related outcomes among pediatric HSCT recipients. This systematic review focused on real-world experiences, with some limitations. The overall sample size of the included studies was relatively small. In addition, the follow-up duration for the included studies was generally short, with most studies reporting follow-up periods of less than 200 days. These studies also varied in terms of patient characteristics. We addressed this limitation by conducting meta-regression analysis. The majority of the studies included in this meta-analysis were observational and nonrandomized, which can introduce bias. Large-scale randomized controlled trials with a control group or head-to-head comparison with other antivirals in pediatric patients are needed, with a primary focus on evaluating CMV disease incidence and adverse events to guide future clinical decision-making.

5 | Conclusion

Based on our analysis, LTV has demonstrated safety and efficacy in preventing CMV infection and disease among high-risk pediatric patients. Future large scale randomized trials are necessary to validate the efficacy and safety of LTV, and identify the most effective parameters for monitoring treatment duration.

Author Contributions

A.Y.A. contributed to conceptualization, methodology, supervision, and drafting the manuscript. A.M.H. conducted data curation, formal analysis, and validation. E.B. contributed to investigation and critical revisions. B.M.H. handled statistical analysis, software, and data visualization. M.I. oversaw project administration and supervision. O.A. contributed to statistical analysis and manuscript review. M.A. participated in systematic literature search and data extraction. M.A.A. managed data acquisition and provided technical input. I.S. supervised the study, conceptualized the systematic review and meta-analysis, and critically revised the manuscript. All authors approved the final submission.

Acknowledgments

The authors have nothing to report.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. M. S. Zinter, R. Brazauskas, J. Strom, et al., "Critical Illness Risk and Long-Term Outcomes Following Intensive Care in Pediatric Hematopoietic Cell Transplant Recipients," *medRxiv* August 5, 2023, https://doi.org/10.1101/2023.07.31.23293444.

2. M. R. Pereira, S. M. Pouch, and B. Scully, "Infections in Allogeneic Stem Cell Transplantation," *Principles and Practice of Transplant Infectious Diseases* (2019): 209–226.

3. N. Jakharia, D. Howard, and D. J. Riedel, "CMV Infection in Hematopoietic Stem Cell Transplantation: Prevention and Treatment Strategies," *Current Treatment Options in Infectious Diseases* 13, no. 3 (2021): 123–140.

4. L. Hiskey, T. Madigan, E. H. Ristagno, R. R. Razonable, and A. Ferdjallah, "Prevention and Management of Human *Cytomegalovirus* in Pediatric HSCT Recipients: A Review," *Frontiers in Pediatrics* 10 (2022): 1039938.

5. S. Y. Cho, D. G. Lee, and H. J. Kim, "*Cytomegalovirus* Infections After Hematopoietic Stem Cell Transplantation: Current Status and Future Immunotherapy," *International Journal of Molecular Sciences* 20, no. 11 (2019): 2666.

6. T. Bontant, P. Sedlaçek, A. Balduzzi, et al., "Survey of CMV Management in Pediatric Allogeneic HSCT Programs, on Behalf of the Inborn Errors, Infectious Diseases and Pediatric Diseases Working Parties of EBMT," *Bone Marrow Transplantation* 49, no. 2 (2014): 276–279.

7. M. Boeckh and P. Ljungman, "How We Treat *Cytomegalovirus* in Hematopoietic Cell Transplant Recipients," *Blood* 113, no. 23 (2009): 5711–5719.

8. M. Boeckh and A. P. Geballe, "*Cytomegalovirus*: Pathogen, Paradigm, and Puzzle," *Journal of Clinical Investigation* 121, no. 5 (2011): 1673–1680.

9. T. L. Shigle, V. W. Handy, and R. F. Chemaly, "Letermovir and Its Role in the Prevention of *Cytomegalovirus* Infection in Seropositive Patients Receiving an Allogeneic Hematopoietic Cell Transplant," *Therapeutic Advances in Hematology* 11 (2020): 2040620720937150.

10. K. Chen, M. P. Cheng, S. P. Hammond, H. Einsele, and F. M. Marty, "Antiviral Prophylaxis for *Cytomegalovirus* Infection in Allogeneic Hematopoietic Cell Transplantation," *Blood Advances* 2, no. 16 (2018): 2159–2175.

11. F. Galaverna, F. Baccelli, D. Zama, et al., "Letermovir for *Cytomegalovirus* Infection in Pediatric Patients Undergoing Allogenic Hematopoietic Stem Cell Transplantation: A Real-Life Study by the Infectious Diseases Working Group of Italian Association of Pediatric Hematology-Oncology (AIEOP)," *Bone Marrow Transplantation* 59, no. 4 (2024): 505–512.

12. D. Beauvais, C. Robin, A. Thiebaut, et al., "Effective Letermovir Prophylaxis of CMV Infection Post Allogeneic Hematopoietic Cell Transplantation: Results From the French Temporary Authorization of Use Compassionate Program," *Journal of Clinical Virology* 148 (2022): 105106.

13. F. M. Marty, P. Ljungman, R. F. Chemaly, et al., "Letermovir Prophylaxis for *Cytomegalovirus* in Hematopoietic-Cell Transplantation," *New England Journal of Medicine* 377, no. 25 (2017): 2433–2444.

14. M. J. Page, J. E. McKenzie, P. M. Bossuyt, et al., "The PRISMA 2020 Statement: An Updated Guideline for Reporting Systematic Reviews," *Bmj* 372 (2021): n71.

15. J. A. Sterne, M. A. Hernán, B. C. Reeves, et al., "ROBINS-I: A Tool for Assessing Risk of Bias in Non-Randomised Studies of Interventions," *Bmj* 355 (2016): i4919.

16. B. C. Wallace, I. J. Dahabreh, T. A. Trikalinos, J. Lau, P. Trow, and C. H. Schmid, "Closing the Gap Between Methodologists and End-Users: R as a Computational Back-End," *Journal of Statistical Software* 49 (2012): 1–15.

17. K. F. Körholz, M. A. Füller, M. Hennies, et al., "Letermovir for Prophylaxis and Pre-Emptive Therapy of *Cytomegalovirus* Infection in Paediatric

13993062, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/tid.70006 by Readcube (Labtiva Inc.), Wiley Online Library on [03/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

Allogeneic Haematopoietic Cell Transplant Patients," *Paediatric Drugs* 25, no. 2 (2023): 225–232.

18. T. César, M. P. Le, R. Klifa, et al., "Letermovir for CMV Prophylaxis in Very High-Risk Pediatric Hematopoietic Stem Cell Transplantation Recipients for Inborn Errors of Immunity," *Journal of Clinical Immunology* 44, no. 1 (2023): 6.

19. A. H. Groll, J. H. Schulte, A. B. Antmen, et al., "Pharmacokinetics, Safety, and Efficacy of Letermovir for *Cytomegalovirus* Prophylaxis in Adolescent Hematopoietic Cell Transplantation Recipients," *Pediatric Infectious Disease Journal* 43, no. 3 (2024): 203–208.

20. A. Kuhn, J. Puttkammer, T. Madigan, et al., "Letermovir as *Cytomegalovirus* Prophylaxis in a Pediatric Cohort: A Retrospective Analysis," *Transplantation and Cellular Therapy* 29, no. 1 (2023): 62.e1–62.e4.

21. T. T. Chen, A. P. David, E. K. Barthelmess, and C. E. MacBrayne, "Letermovir for *Cytomegalovirus* Prophylaxis in Pediatric Hematopoietic Stem Cell Transplantation," *Pediatric Blood and Cancer* 70, no. 11 (2023): e30608.

22. N. P Daukshus, A. Cirincione, M. Siver, et al., "Letermovir for *Cytomegalovirus* Prevention in Adolescent Patients Following Hematopoietic Cell Transplantation," *Journal of the Pediatric Infectious Disease Society* 11, no. 7 (2022): 337–340.

23. Y. Zhang, X. Chen, M. Zhou, et al., "Letermovir Effectively Prevents *Cytomegalovirus* Infection in Patients With Aplastic Anemia After Hematopoietic Stem Cell Transplantation: A Real-World Retrospective Cohort Study," *Infectious Diseases and Therapy* 13, no. 2 (2024): 345–359.

24. C. N. Cheng, S. S. Li, Y. H. Yeh, C. F. Shen, and J. S. Chen, "Letermovir Prophylaxis for *Cytomegalovirus* Reactivation in Children Who Underwent Hematopoietic Stem Cell Transplantation: A Single-Institute Experience in Taiwan," *Journal of Microbiology, Immunology and Infection* 55, no. 2 (2022): 323–327.

25. J. Styczyński, G. Tridello, A. Xhaard, et al., "Use of Letermovir in Off-Label Indications: Infectious Diseases Working Party of European Society of Blood and Marrow Transplantation Retrospective Study," *Bone Marrow Transplantation* 56, no. 5 (2021): 1171–1179.

26. M. Richert-Przygonska, K. Jaremek, R. Debski, et al., "Letermovir Prophylaxis for *Cytomegalovirus* Infection in Children After Hematopoietic Cell Transplantation," *Anticancer Research* 42, no. 7 (2022): 3607–3612.

27. Y. Tatebe, Y. Manabe, Y. Tanaka, et al., "Letermovir at a Prophylactic Dose for *Cytomegalovirus* Infection in Children Undergoing Allogeneic Hematopoietic Stem Cell Transplantation: A Single-Center Retrospective Study in Japan," *Biological and Pharmaceutical Bulletin* 47, no. 9 (2024): 1575–1582.

28. S. S. Balani, S. Sadiq, C. J. Jensen, and S. J. Kizilbash, "Prevention and Management of CMV Infection in Pediatric Solid Organ Transplant Recipients," *Frontiers in Pediatrics* 11 (2023): 1098434.

29. N. Gagelmann, P. Ljungman, J. Styczynski, and N. Kröger, "Comparative Efficacy and Safety of Different Antiviral Agents for *Cytomegalovirus* Prophylaxis in Allogeneic Hematopoietic Cell Transplantation: A Systematic Review and Meta-Analysis," *Biology of Blood and Marrow Transplantation* 24, no. 10 (2018): 2101–2109.

30. K. G. Valencia Deray, L. A. Danziger-Isakov, and K. J. Downes, "Current and Emerging Antiviral Agents in the Prevention and Treatment of *Cytomegalovirus* in Pediatric Transplant Recipients," *Journal of the Pediatric Infectious Diseases Society* 13, no. supplement S1 (2024): S14–S21.

31. A. G. Märtson, A. E. Edwina, J. G. M. Burgerhof, et al., "Ganciclovir Therapeutic Drug Monitoring in Transplant Recipients," *Journal of Antimicrobial Chemotherapy* 76, no. 9 (2021): 2356–2363.

32. F. M. Marty, D. J. Winston, S. D. Rowley, et al., "CMX001 to Prevent *Cytomegalovirus* Disease in Hematopoietic-Cell Transplantation," *New England Journal of Medicine* 369, no. 13 (2013): 1227–1236.

33. F. M. Marty, D. J. Winston, R. F. Chemaly, et al., "A Randomized, Double-Blind, Placebo-Controlled Phase 3 Trial of Oral Brincidofovir for *Cytomegalovirus* Prophylaxis in Allogeneic Hematopoietic Cell Transplantation," *Biology of Blood and Marrow Transplantation* 25, no. 2 (2019): 369–381.

34. M. Foca, S. Demirhan, F. M. Munoz, et al., "Multicenter Analysis of Valganciclovir Prophylaxis in Pediatric Solid Organ Transplant Recipients," *Open Forum Infectious Diseases* 11, no. 7 (2024): ofae353.

35. A. Vyas, A. D. Raval, S. Kamat, K. LaPlante, Y. Tang, and R. F. Chemaly, "Real-World Outcomes Associated With Letermovir Use for *Cytomegalovirus* Primary Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients: A Systematic Review and Meta-Analysis of Observational Studies," *Open Forum Infectious Diseases* 10, no. 1 (2023): ofac687.

36. J. B. McCrea, S. Macha, A. Adedoyin, et al., "Pharmacokinetic Drug–Drug Interactions Between Letermovir and the Immunosuppressants Cyclosporine, Tacrolimus, Sirolimus, and Mycophenolate Mofetil," *Journal of Clinical Pharmacology* 59, no. 10 (2019): 1331–1339.

37. H. N. Imlay and D. R. Kaul, "Letermovir and Maribavir for the Treatment and Prevention of *Cytomegalovirus* Infection in Solid Organ and Stem Cell Transplant Recipients," *Clinical Infectious Diseases* 73, no. 1 (2021): 156–160.

38. D. R. Reed, G. R. Petroni, M. West, et al., "Prophylactic Pretransplant Ganciclovir to Reduce *Cytomegalovirus* Infection After Hematopoietic Stem Cell Transplantation," *Hematology/Oncology and Stem Cell Therapy* 16, no. 1 (2023): 61–69.

39. E. Haastrup, K. Müller, H. Baekgaard, and C. Heilmann, "*Cytomegalovirus* Infection After Allogeneic Stem Cell Transplant in Children," *Pediatric Transplantation* 9, no. 6 (2005): 734–740.

40. P. Teira, M. Battiwalla, M. Ramanathan, et al., "Early *Cytomegalovirus* Reactivation Remains Associated With Increased Transplant-Related Mortality in the Current Era: A CIBMTR Analysis," *Blood* 127, no. 20 (2016): 2427–2438.

41. W. R. Otto, S. B. Vora, and D. E. Dulek, "*Cytomegalovirus* Cell-Mediated Immunity Assays in Pediatric Transplantation," *Journal of the Pediatric Infectious Diseases Society* 13, no. supplement S1 (2024): S22–S30.

42. P. Ljungman, M. Schmitt, F. M. Marty, et al., "A Mortality Analysis of Letermovir Prophylaxis for *Cytomegalovirus* (CMV) in CMV-Seropositive Recipients of Allogeneic Hematopoietic Cell Transplantation," *Clinical Infectious Diseases* 70, no. 8 (2020): 1525–1533.

43. M. Boeckh and W. G. Nichols, "The Impact of *Cytomegalovirus* Serostatus of Donor and Recipient Before Hematopoietic Stem Cell Transplantation in the Era of Antiviral Prophylaxis and Preemptive Therapy," *Blood* 103, no. 6 (2004): 2003–2008.

44. A. Sepassi, I. M. Saunders, M. Bounthavong, R. A. Taplitz, C. Logan, and J. H. Watanabe, "Cost Effectiveness of Letermovir for *Cytomegalovirus* Prophylaxis Compared With Pre-Emptive Therapy in Allogeneic Hematopoietic Stem Cell Transplant Recipients in the United States," *PharmacoEconomics-open* 7, no. 3 (2023): 393–404.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.

13993062, 2025, 2, Downloaded from https://onlinelibrary.wiley.com/doi/10.1111/tid.70006 by Readcube (Labtiva Inc.), Wiley Online Library on [03/03/2026]. See the Terms and Conditions (https://onlinelibrary.wiley.com/terms-and-conditions) on Wiley Online Library for rules of use; OA articles are governed by the applicable Creative Commons License

OPEN

Pharmacokinetics, Safety, and Efficacy of Letermovir for Cytomegalovirus Prophylaxis in Adolescent Hematopoietic Cell Transplantation Recipients

Andreas H. Groll, MD, Johannes H. Schulte, MD,† Ali Bülent Antmen, MD, PhD,‡ Christopher J. Fraser, MD,§ Valerie L. Teal, MS,¶ Barbara Haber, MD,¶ Luzelena Caro, PhD,¶ Jacqueline B. McCrea, PharmD,¶ Craig Fancourt, PhD,¶ Mayankbhai Patel, PhD,¶ Karsten Menzel, PhD,¶ and Cyrus Badshah, MD, PhD¶*

Introduction: Letermovir is a cytomegalovirus (CMV) terminase complex inhibitor approved for prophylaxis of CMV infection and disease in adult CMV-seropositive allogeneic hematopoietic cell transplantation (allo-HCT) recipients (R+). We report pharmacokinetics (PK), safety, and efficacy of letermovir in adolescent (12–18 years) allogeneic HCT recipients from an ongoing clinical study.

Methods: In this phase 2b, multicenter, open-label study (NCT03940586), 28 adolescents received 480 mg letermovir [240 mg with cyclosporin A (CsA)] once daily orally or intravenously. Blood was collected for intensive (n = 14) plasma concentrations of letermovir. Intensive PK data were used for dose confirmation. Target exposure range 34,400–100,000 h × ng/mL for pediatric median exposures was based on model-predicted phase 3 population PK simulations in adult HCT recipients.

Results: All participants were CMV-seropositive (body weight 28.7–95.0 kg). Of 12 PK-evaluable participants, 8 receiving 480 mg letermovir without CsA and 4 receiving 240 mg letermovir with CsA achieved exposures comparable to the adult exposure range. Exposure above the target but below the adult clinical program maximum was observed in 1 patient. Safety was consistent with previously described safety in adults. The proportion of participants with clinically significant CMV infection through week 24 post-HCT was comparable (24%) to that in the pivotal phase 3 study in adults (37.5%).

Conclusions: Administration of adult letermovir doses in this adolescent cohort resulted in exposures within adult clinical program margins and was associated with safety and efficacy similar to adults. Results support a letermovir dose of 480 mg (240 mg with CsA) in adolescent allo-HCT recipients.

Key Words: pharmacokinetics, letermovir, cytomegalovirus, hematopoietic cell transplantation, adolescent

(*Pediatr Infect Dis J* 2024;43:203–208)

Although information on the number of hematopoietic cell transplantations (HCT) by age group among pediatric patients is limited, 2016–2020 data from the Center for International Blood and Marrow Transplant Research, Wisconsin, USA, indicate that approximately 10% of US HCTs are performed in pediatric patients (<18 years old).[1] Clinical manifestations of cytomegalovirus (CMV) disease appear to be similar in adults and children,[2–4] and there is a substantial clinical and economic burden of CMV among pediatric allogeneic HCT (allo-HCT) recipients.[5,6]

CMV seropositivity and reactivation are associated with increased morbidity and mortality in allo-HCT recipients.[7–9] Letermovir is a CMV terminase complex inhibitor. In contrast to current standard-of-care anti-CMV agents, all of which are CMV deoxyribonucleic acid (DNA) polymerase inhibitors, letermovir use is not subject to cross-resistance[10] due to its unique mechanism of action and is not limited by myelosuppression and nephrotoxicity.[11] In the pivotal phase 3 trial in adult CMV-seropositive allo-HCT recipients (R+), letermovir was well tolerated and reduced the risk of clinically significant CMV infection (CS-CMVi) through week 24 post-transplant when compared with placebo.[12] Letermovir was subsequently approved in >60 countries for prophylaxis of CMV infection and disease in adult R+ allo-HCT recipients.[13,14]

Letermovir is expected to have a similar efficacy and safety profile in pediatric populations when administered at doses that achieve exposures observed in adult populations; however, no pharmacokinetic (PK) data are currently available to inform pediatric dosing. PK, safety, and efficacy of letermovir for CMV prophylaxis in allo-HCT recipients from birth to 18 years of age are being assessed in an ongoing study. The PK data obtained in this study will be used to update currently available adult population PK and physiologically-based pharmacokinetics (PBPK) models to support final dosing recommendations in the pediatric population. Here we report data on PK, safety, and efficacy from the cohort of adolescent participants (12 < 18 years old).

METHODS

Study Design and Population

The objectives of this phase 2b, open-label, single-arm study (NCT03940586) were to evaluate PK, safety, and efficacy of

Accepted for publication October 28, 2023

*From the Department of Pediatric Hematology and Oncology, University Children's Hospital Münster, Münster, Germany; †Department of Pediatrics, Division of Oncology and Hematology, Charité Universitätsmedizin Berlin, Berlin, Germany; ‡Department of Pediatric Hematology/Oncology and Bone Marrow Transplantation, Acibadem Adana Hospital, Adana, Turkey; §Blood and Marrow Transplant Service, Queensland Children's Hospital, Brisbane, Queensland, Australia; and ¶Merck & Co., Inc., Rahway, New Jersey.

Trial registration: Clinicaltrials.gov NCT03940586 (registered May 7, 2019).

This work was supported by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ.

A.H.G. has received research support from Gilead Sciences, Merck Sharp & Dohme and Pfizer; is a consultant for Amplyx, Astellas, Basilea, F2G, Gilead Sciences, Merck Sharp & Dohme and Pfizer and served on the speakers' bureau of Astellas, Basilea, F2G, Gilead Sciences, Merck Sharp & Dohme and Pfizer. J.H.S. is supported by the German Cancer Consortium (DKTK). A.B.A. is a consultant for Novo Nordisk, Pfizer, Roche and Takeda. C.J.F. has no potential conflicts of interest to declare. B.H., J.B.M., M.P., K.M. and C.B. are current employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ. V.L.T., C.F. and L.C. are former employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ. C.F. is retired.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.pidj.com).

Address for correspondence: Andreas H. Groll, MD, Department of Pediatric Hematology and Oncology, Universitätsklinikum Münster, Albert-Schweitzer-Campus 1, Gebäude A1, Raum 03.822, 48149 Münster, Germany. E-mail: andreas.groll@ukmuenster.de.

Copyright © 2024 The Author(s). Published by Wolters Kluwer Health, Inc. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

ISSN: 0891-3668/24/433-203208

DOI: 10.1097/INF.0000000000004208

27

letermovir in participants from birth <18 years of age who were at risk of developing CMV infection and/or disease following allo-HCT. Study design is summarized in Figure 1A, Supplemental Digital Content 1, http://links.lww.com/INF/F344. Participants (planned total: N = ~60) were enrolled at 40 centers across 11 countries (Australia, Colombia, France, Germany, Israel, Japan, Mexico, Poland, Spain, Turkey and United States). Study participants were enrolled in 3 age groups (AG): AG1 (adolescents: 12 < 18 years old), AG2 (children: 2 < 12 years old) and AG3 (neonates, infants and toddlers: from birth <2 years). Enrollment began with AG1 participants and moved sequentially to younger age groups based on PK and safety evaluations in the preceding age group (Figure 1B, Supplemental Digital Content 1, http://links.lww.com/INF/F344).

All participants (or their legally acceptable representatives) provided written informed consent before participating in the study. The study protocol was reviewed and approved by the appropriate institutional review board or independent ethics committee at each center. Here we report data from AG1 participants (planned n ≥ 26) enrolled in the ongoing study.

Eligible AG1 participants received a first allo-HCT (bone marrow, peripheral blood stem cell or cord blood) within 28 days before enrollment, were documented as being seropositive for CMV immunoglobin G (R+) within 90 days before enrollment, and had undetectable CMV viremia by DNA polymerase chain reaction (PCR) from a sample collected within 5 days before enrollment. Key exclusion criteria for AG1 participants included CMV end-organ disease within 6 months before enrollment, prior receipt of an allo-HCT, evidence of CMV viremia at any time between signing informed consent or the HCT procedure (whichever was earlier) until enrollment, severe hepatic insufficiency, end-stage renal impairment or the need for renal replacement therapy. A full list of inclusion/exclusion criteria can be found in Supplemental Digital Content 2, http://links.lww.com/INF/F345.

Dose Selection and Pharmacokinetic Exposure Targets

Before the initiation of this study, no PK data existed for letermovir in pediatric patients. Based on accepted principles of ontogeny, the recommended and approved daily adult dose of 480 mg letermovir [adjusted to 240 mg with concomitant cyclosporin A (CsA) administration] was used for the study in adolescent participants. Dose selection was guided by both PBPK and population PK models. The PBPK model was developed based on healthy adult data obtained in a phase 1 study,[15] and it was carried out using a virtual pediatric population in the age range of 12 < 18 years. The population PK model, which characterized letermovir PK at steady state, was previously developed based on adult data from the pivotal phase 3 trial in HCT recipients.[16] The phase 3 adult population PK model was extrapolated to pediatrics using allometric scaling, and the scaled model was used to simulate letermovir PK in AG1 participants. Both modeling approaches (PBPK and Population PK) were used and compared. Based on the comparable body weight range and OATP1B maturation in AG1 and adult participants from the letermovir clinical program (body weight: 35.1 to 141.5 kg), we anticipated that the PK of letermovir in AG1 would behave similarly to those of adults.[16] Predicted exposures in adolescents generally fell within target exposures and were below the highest exposure achieved in the entire clinical program (~328,000 h × ng/mL). There were no weight limits set on adolescent dosing. Results of these modeling analyses suggested that the adult dose would result in letermovir exposures in AG1 comparable to exposures in adults.

The steady-state median target range for the area under the concentration–time curve from 0 to 24 hours postdose (AUC_{0-24}), predicted in adult HCT recipients from the phase 3 population PK model,[16] following administration of oral and intravenous (IV) letermovir 480 mg daily without CsA was 34,400–100,000 h × ng/mL. The lower and upper bounds of the adult HCT exposure range were 16,900 h × ng/mL (10th AUC_{0-24} percentile following administration of 480 mg oral letermovir) and 148,000 h × ng/mL (90th AUC_{0-24} percentile following 480 mg IV letermovir), respectively.[16]

Treatment, PK Sampling, and Follow-up

Participants were screened from up to 15 days before transplant to 28 days post-transplant and enrolled within 28 days post-transplant (Figure 1A, Supplemental Digital Content 1, http://links.lww.com/INF/F344), with weekly confirmation of the absence of CMV viremia by DNA PCR before enrollment.

For oral administration, participants received either currently marketed oral adult tablets or a newly developed age-appropriate pediatric oral granule formulation, which is bio-equivalent to the tablets. Oral letermovir administration was preferred, with IV administration being reserved for participants who could not tolerate oral intake (eg, due to mucositis, vomiting or gastrointestinal graft-versus-host disease). An initial cohort of participants (n = 6; Panel A) was evaluated to determine optimum dosing for oral letermovir in the absence of CsA before enrolling additional participants in the same age group (Panel B). The final dose selected in Panel A simultaneously triggered initiation of enrollment in Panel B for the same age group and Panel A for the next youngest age group. Use of CsA and/or IV letermovir were permitted in Panel B only. Letermovir 480 mg (adjusted to 240 mg with concomitant CsA administration) was administered once daily (QD) through week 14 post-transplant.

Both intensive and sparse PK sampling were performed. For intensive PK sampling, samples were collected predose and at 1, 2.5, 8 and 24 hours postdose on day 7 for participants who received the oral formulation and on day 5 for those who received the IV formulation for ≥5 consecutive days (excluding participants who had already undergone intensive PK sampling while receiving the oral formulation). The interim analysis was based on participants with intensive PK data only.

Participants were followed through week 24 post-transplant for efficacy and through week 48 post-transplant for safety and tolerability. CMV disease was assessed at every visit from screening through week 24 post-transplant. CMV DNA PCR testing was performed using qualitative or quantitative assays done at the local laboratory, using the same methodology throughout the study. Cases of investigator-reported CMV disease were confirmed by an independent clinical adjudication committee. All adverse events (AEs), serious AEs and other reportable safety events were reported by the investigator from the time of treatment allocation/randomization through 28 days following cessation of treatment. Thereafter, only serious AEs related to study medication or leading to death were collected through week 48 post-transplant.

Analysis

There was no formal hypothesis testing in this study. PK parameters were assessed in participants who complied with the protocol in a manner ensuring that the data were likely to exhibit the effects of treatment (per-protocol population). Noncompartmental analysis was performed on the subset of participants who underwent intensive PK sampling. The primary objective of this ongoing study is to evaluate letermovir PK in pediatric patients grouped by age based on PK endpoints including steady-state AUC_{0-24} for letermovir, maximum plasma concentration (C_{max}) for participants receiving the oral formulation [concentration at the end of infusion (C_{EOI}) for participants receiving the IV

© 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

formulation], time to C_{max} (T_{max}) for participants receiving the oral formulation, and half-life ($t½$). For this interim analysis, intensive PK data were used to calculate PK parameters of interest (AUC_{0-24}, C_{max}, C_{EOI} and $t½$) at day 7, which were summarized by dose level, with geometric means based on natural log-transformed values and t-distribution. Individual AUC values were plotted by weight band.

Safety was evaluated in the all-participants-as-treated population, comprising those who received ≥1 dose of study drug. Safety and tolerability were assessed by clinical review of relevant parameters, including summation of the proportions of participants with AEs, serious AEs, drug-related AEs, discontinuations due to AEs and AEs with fatal outcomes.

Efficacy was evaluated as a secondary study objective, based on the proportion of participants with CS-CMVi through weeks 14 and 24 post-transplant. The primary efficacy population, the full analysis set, consisted of participants who received ≥1 dose of study drug and had no detectable CMV viral DNA on day 1 of treatment. CS-CMVi was defined as the onset of CMV end-organ disease adjudicated by an independent committee, and/or initiation of anti-CMV preemptive therapy based on documented CMV viremia and the participant's clinical condition. The primary missing data approach used was the noncompleter = failure approach, where participants who prematurely discontinued the study, or who had missing efficacy data at weeks 14 or 24 post-transplant, were also imputed as having reached the efficacy endpoint. To estimate proportion of participants with CS-CMVi through week 14 and week 24 post-transplant, 95% confidence interval was calculated based on the exact binomial method of Clopper and Pearson.

Interim analyses of PK and safety (by external data monitoring committee) following the completion of intensive PK sampling by Panel A participants from AG1 were prespecified, with a pause in enrollment for reevaluation of the initial dose.

RESULTS

Participants

Between August 8, 2019 and July 18, 2021 (data cutoff for this analysis), 28 adolescents (12 < 18 years of age) enrolled in AG1 received study medication, and 17 (60.7%) completed treatment (Table 1). The most common reasons for discontinuation of study medication were AEs (17.9%) and lack of efficacy (17.9%). Although enrollment for AG1 has been completed, the study is ongoing; data from AG2 and AG3 will be reported separately.

AG1 participant demographics and baseline characteristics are summarized in Table 2. The median age of the population was

TABLE 1. Disposition of Participants

Participants, n (%)	Age Group 1 (N = 28)
Treated	28 (100.0)
Completed study medication	17 (60.7)
Discontinued study medication	11 (39.3)
Adverse event	5 (17.9)
Lack of efficacy*	5 (17.9)
Withdrawal by parent or guardian	1 (3.6)
Completed study	21 (75.0)
Discontinued study	7 (25.0)
Death	3 (10.7)
Withdrawal by parent or guardian	3 (10.7)
Physician decision	1 (3.6)

*Efficacy is defined as prevention of clinically significant CMV infection through week 14 (~100 days) post-transplant and through week 24 (~6 months) post-transplant.

TABLE 2. Baseline Demographic and Clinical Characteristics (All Participants as Treated)

Parameter	Age Group 1 (N = 28)
Median (range) age, years	13.5 (12–17)
Median (range) body weight, kg	53.8 (28.7–95.0)
Sex, n (%)	
Male	15 (53.6)
Female	13 (46.4)
Race, n (%)	
White	15 (53.6)
Asian	6 (21.4)
Black or African-American	3 (10.7)
Mixed	4 (14.3)
Ethnicity, n (%)	
Hispanic or Latino	9 (32.1)
Not Hispanic or Latino	14 (50.0)
Not reported	4 (14.3)
Unknown	1 (3.6)
Region, n (%)	
Europe and Middle East	9 (32.1)
Asia-Pacific	8 (28.6)
North America	6 (21.4)
Latin America	5 (17.9)
Immunosuppressive regimen, n (%)	
CsA*	19 (67.9)
Tacrolimus†	9 (32.1)
Other‡	0 (0.0)
CMV DNA on day 1 of study treatment, n (%)	
Detected	3 (10.7)
Not detected	25 (89.3)
Primary reason for transplant	
Acute lymphocytic leukemia	1 (3.6)
Acute lymphocytic leukemia, recurrent	3 (10.7)
Acute myeloid leukemia	6 (21.4)
Acute myeloid leukemia, recurrent	1 (3.6)
Aplastic anemia	4 (14.3)
B precursor type acute leukemia	2 (7.1)
Bone marrow failure	1 (3.6)
Chronic granulomatous disease	1 (3.6)
Chronic myeloid leukemia	1 (3.6)
Congenital dyskeratosis	1 (3.6)
Gene mutation	1 (3.6)
Immunodeficiency, congenital	1 (3.6)
Myelodysplastic syndrome	1 (3.6)
Myeloid leukemia	1 (3.6)
Non-Hodgkin lymphoma	1 (3.6)
Sickle cell anemia	1 (3.6)
Sickle cell disease	1 (3.6)
Recipient CMV-seropositive, n (%)	28 (100.0)
Donor CMV serostatus, n (%)	
CMV-seropositive	20 (71.4)
CMV-seronegative	8 (28.6)
Donor type, n (%)	
Matched related	6 (21.4)
Mismatched related	9 (32.1)
Matched unrelated	9 (32.1)
Mismatched unrelated	4 (14.3)
Haploidentical donor, n (%)	
Yes	8 (28.6)
No	20 (71.4)
Stem cell source, n (%)	
Peripheral blood	15 (53.6)
Bone marrow	12 (42.9)
Cord blood	1 (3.6)
Conditioning regimen, n (%)	
Myeloablative	25 (89.3)
Reduced intensity	3 (10.7)

*Coadministered with letermovir during the treatment phase with or without other immunosuppressants.

†Regimen containing tacrolimus alone or with any other immunosuppressant except CsA.

‡Regimen containing any immunosuppressant except CsA and tacrolimus.

CMV indicates cytomegalovirus; CsA, cyclosporin A.

© 2024 The Author(s). Published by Wolters Kluwer Health, Inc

29

13.5 years, and 53.6% of participants were male. Three (10.7%) participants had detectable CMV DNA on day 1 of study treatment and were not included in the primary efficacy analysis. The most common conditions necessitating transplant were acute myeloid leukemia [6 participants (21.4%)], aplastic anemia [4 participants (14.3%)] and recurrent acute lymphocytic leukemia [3 participants (10.7%)].

Pharmacokinetics

PBPK and Population PK modeling approaches provided similar exposure in AG1 participants, supporting the dose selection for this group. All AG1 participants who received letermovir orally were administered the adult tablets, except for 1 participant who received the oral granules through a nasogastric tube.

The AG1 PK population included 14 participants who had intensive PK data; 12 were included in the per-protocol population for the final PK analysis. One participant's PK profile was not physiologically plausible for an adolescent administered 480 mg of oral letermovir and was therefore excluded from the PK analysis. One participant was excluded from the analysis due to missing PK samples on intensive PK day.

Of the 12 evaluable participants (body weight 28.7–95.0 kg), 8 received 480 mg QD letermovir without CsA, and 4 received 240 mg QD letermovir with CsA. The PK parameters for letermovir based on noncompartmental analysis are summarized in Table 3. In AG1 Panel A, letermovir exposures at the 480 mg oral dose (n = 5) were comparable with the reference adult exposure range (ie, 16,900–148,000 h × ng/mL). One participant achieved exposure above the upper bound of the adult HCT reference range, but lower than the maximum observed in the clinical program (~328,000 h × ng/mL, with oral administration) (Fig. 1). No letermovir dose modifications were necessary based on the final intensive PK analysis for AG1 Panel A. Letermovir exposures for participants in AG1 Panel B, who received 480 mg IV letermovir (n = 3) or 240 mg IV letermovir with CsA (n = 4), were comparable with the reference adult exposure.

Safety

All participants experienced at least 1 AE during the treatment phase. The most common recorded AEs were vomiting [14 (50%) cases], nausea [12 (42.9%) cases], diarrhea [12 (42.9%) cases], abdominal pain [11 (39.3%) cases] and pyrexia [11 (39.3%) cases]. Individual AEs occurring in ≥5 participants are summarized in Table 4. AEs leading to discontinuation of letermovir were reported in 5 participants. No safety signal was observed as none of the AEs were reported in more than 1 participant (Table, Supplemental Digital Content 3, http://links.lww.com/INF/F346).

The most common AEs considered to be drug-related by the investigators were nausea (14.3%) and drug-drug interactions (with CsA, tacrolimus and voriconazole) (10.3%), which is consistent with the previously reported AE profile for letermovir.[12] The drug-drug interactions have been described in the product label.[13]

Efficacy

Of the 25 efficacy-evaluable participants, there were 5 (20%) "failures" (ie, participants who developed CS-CMVi, prematurely discontinued from the study, or had missing data at the visit window) through week 14 post-transplant, and 6 (24%) failures through week 24 post-transplant (Table, Supplemental Digital Content 4, http://links.lww.com/INF/F347). None of the participants developed documented CMV end-organ disease.

TABLE 3. Pharmacokinetic Parameters for Letermovir in 12 Evaluable Age Group 1 Participants Who Underwent Intensive Pharmacokinetic Sampling

Cohort	CsA	Route	Dose	n	$AUC_{0\text{–}24}$ (h × ng/mL) GM (GCV, %)	C_{max}* (ng/mL) GM (GCV, %)	T_{max} (h) Median (min, max)	$t½$† (h) GM (GCV, %)
1A	No	PO	480 mg	5	80,300 (74.9)	7,410 (70.1)	5.85 (2.38, 8.00)	5.48 (26.3)
1B	No	IV	480 mg	3‡	114,000 (37.8)	30,600 (16.4)	1.07 (1.00, 1.15)	6.21 (39.8)
	Yes	IV	240 mg	4§,¶	78,900 (54.8)	13,600 (48.2)	1.20 (1.00, 2.85)	8.27 (40.0)

*C_{max} is the concentration at the end of the 1-hour infusion (C_{EOI}) for participants who received IV.
†For 3 participants in AG1 Panel A, half-life is calculated using 1 terminal PK sampling time point after T_{max}.
‡In AG1 Panel B, 1 participant (at 480 mg dose) had C_{EOI} samples collected outside the collection window. C_{EOI} for these samples was predicted by using the log-linear model and the same was considered for the analysis.
§In AG1 Panel B, 1 participant (at 240 mg dose) had infusion duration >1-hour, which may have some (not a significant) effect on C_{EOI} but not on AUC.
¶In AG1 Panel B, 1 participant (at 240 mg dose) had a longer infusion duration (~2.75 hours vs. 1-hour). Hence this participant was excluded from C_{EOI} summary statistics, but included in the summary AUC calculation.
$AUC_{0\text{–}24}$ indicates area under the curve from administration to 24 hours postdose; C_{max}, maximum plasma concentration; CsA, cyclosporin A; GCV, geometric coefficient of variation; GM, geometric mean; IV, intravenous; max, maximum; min, minimum; PK, pharmacokinetic; PO, oral; QD, once daily; $t½$, half-life; T_{max}, time to maximum plasma concentration.

© 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

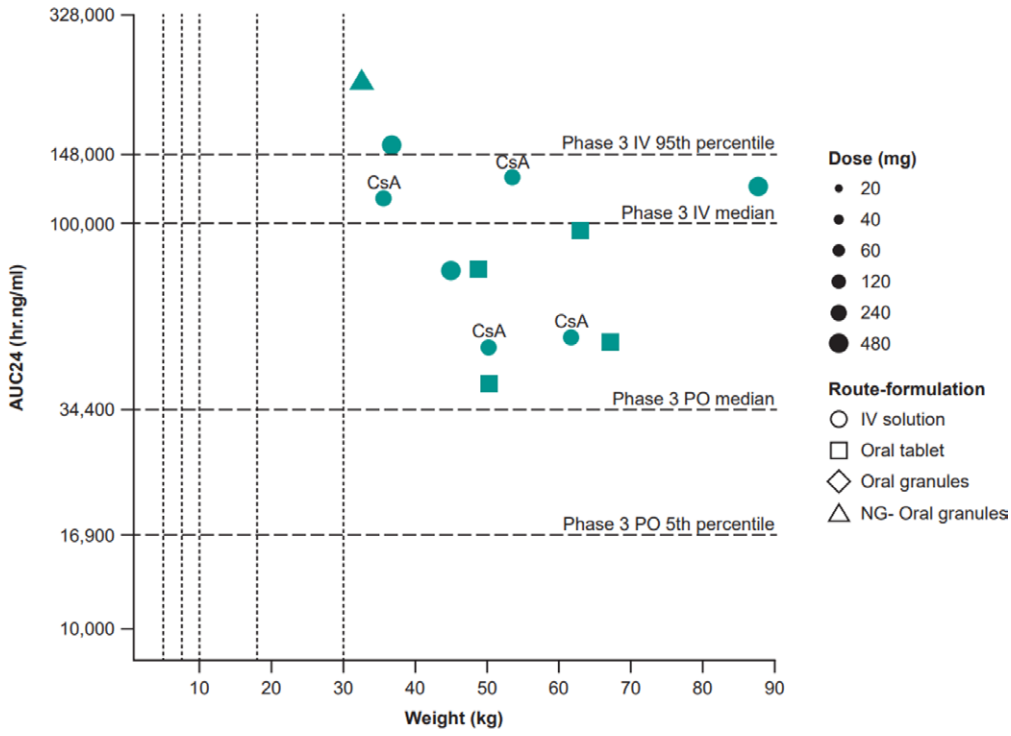


FIGURE 1. Individual letermovir exposures for all evaluable age group 1 participants who underwent intensive pharmacokinetic sampling. AUC_{0-24} indicates area under the concentration–time curve from administration to 24 hours postdose (logarithmic scale); CsA, cyclosporin A; IV, intravenous; NG, nasogastric tube; PO, oral; phase 1 PO maximum, highest AUC_{0-24} observed in letermovir program.

TABLE 4. Participants With Adverse Events During Treatment Phase (Incidence ≥5 Participants; All Participants as Treated*)

Participants, n (%)	Age Group 1 (N = 28)
With ≥1 AE†	28 (100)
Gastrointestinal disorders	27 (96.4)
Vomiting	14 (50.0)
Nausea	12 (42.9)
Diarrhea	12 (42.9)
Abdominal pain	11 (39.3)
Stomatitis	8 (28.6)
General disorders and administration site conditions	16 (57.1)
Pyrexia	11 (39.3)
Immune system disorders	15 (53.6)
Graft-versus-host disease	10 (35.7)
Renal and urinary disorders	14 (50.0)
Dysuria	6 (21.4)
Nervous system disorders	13 (46.4)
Headache	6 (21.4)
Respiratory, thoracic, and mediastinal disorders	13 (46.4)
Oropharyngeal pain	5 (17.9)
Skin and subcutaneous tissue disorders	12 (42.9)
Pruritus	6 (21.4)
Vascular disorders	10 (35.7)
Hypertension	7 (25.0)
Blood and lymphatic system disorders	8 (28.6)
Thrombocytopenia	5 (17.9)

*Primary safety population, defined as all allocated participants who received ≥1 dose of study intervention.

†AEs were reported using the medical dictionary for regulatory activities (MedDRA) Version 24.1. Each participant was counted once for each system organ class or specific AE.

AE indicates adverse event.

DISCUSSION

The results obtained in adolescent (12 < 18 years of age) allo-HCT recipients enrolled in the pediatric phase 2b dose-finding study (NCT03940586) of letermovir indicate that administration of adult doses of letermovir for CMV prophylaxis post-transplant in adolescent participants resulted in exposures within the prespecified bounds of the adult HCT exposure range.

Selection of the 480 mg (240 mg when coadministered with CsA) dose of letermovir for use in adolescent participants was guided by population PK and PBPK models developed based on concentration data obtained in clinical trials in adults.[16] PK exposures in adolescents observed in this study confirm the appropriateness of these modeled dose predictions and lend support to their continued use for dose prediction in the younger age groups of the study. Moreover, given that the pathogenesis of CMV and mechanism of action of letermovir in pediatric patients are not anticipated to be fundamentally different from adults, achievement of letermovir exposures in adolescent HCT recipients like exposures observed in adult HCT recipients is expected to result in similar efficacy and safety in the 2 populations. This is supported by safety and efficacy results observed to date, notwithstanding the limited number of study participants discussed here.

No new major safety concerns were reported with letermovir use in adolescent HCT recipients in this study. The AE profile was like that seen in adult participants in the pivotal trial evaluating letermovir prophylaxis in adult HCT recipients, with no evidence of myelotoxicity, hepatotoxicity or nephrotoxicity.[12]

In the pivotal trial, efficacy as evaluated by incidence of treatment failure (ie, CS-CMVi or early discontinuation or missing data imputed as a primary endpoint case) was 37.5% among letermovir recipients versus 60.6% among placebo recipients ($P < 0.001$) at

© 2024 The Author(s). Published by Wolters Kluwer Health, Inc

week 24 post-transplant.[12] Efficacy of letermovir in the prevention of CS-CMVi in adolescents through week 24 post-transplant in the current study (ie, failure rate of 24.0%) was comparable to that in adults from the pivotal trial.[12]

This study provides limited safety and efficacy data because it was primarily designed for selecting doses. The results here support using 480 mg QD (240 mg if coadministered with CsA) as the letermovir dosing regimen for CMV prophylaxis in adolescent allo-HCT recipients.

ACKNOWLEDGMENTS

V.L.T., B.H., L.C., J.B.M., C.F., M.P., K.M. and C.B. designed the study. All authors analyzed and interpreted the data, reviewed the draft critically for important intellectual content, approved of the version to be published, and agreed to be accountable for all aspects of the work. The authors are grateful to all study participants, investigators, study site personnel, and contributors. Medical writing assistance, under the direction of the authors, was provided by CMC AFFINITY, a division of IPG Health Medical Communications, in accordance with Good Publication Practice (GPP 2022) guidelines. This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA.

REFERENCES

1. Center for International Blood and Marrow Transplant Research. *HRSA Transplant Activity Report: Number of HCTs performed in the United States and reported to CIBMTR, by year and age group, 2016–2020*. 2022. Available at: https://bloodstemcell.hrsa.gov/data/donation-and-transplantation-statistics/transplant-activity-report. Accessed May 17, 2022.
2. Castagnola E, Cappelli B, Erba D, et al. Cytomegalovirus infection after bone marrow transplantation in children. *Hum Immunol*. 2004;65:416–422.
3. Bateman CM, Kesson A, Powys M, et al. Cytomegalovirus infections in children with primary and secondary immune deficiencies. *Viruses*. 2021;13:2001.
4. Ljungman P, Hakki M, Boeckh M. Cytomegalovirus in hematopoietic stem cell transplant recipients. *Hematol Oncol Clin North Am*. 2011;25:151–169.
5. Rastogi S, Ricci A, Jin Z, et al. Clinical and economic impact of cytomegalovirus infection among children undergoing allogeneic hematopoietic cell transplantation. *Biol Blood Marrow Transplant*. 2019;25:1253–1259.
6. Hiwarkar P, Gaspar HB, Gilmour K, et al. Impact of viral reactivations in the era of pre-emptive antiviral drug therapy following allogeneic haematopoietic SCT in paediatric recipients. *Bone Marrow Transplant*. 2013;48:803–808.
7. Green ML, Leisenring W, Xie H, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. *Lancet Haematol*. 2016;3:e119–e127.
8. Schmidt-Hieber M, Labopin M, Beelen D, et al. CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT. *Blood*. 2013;122:3359–3364.
9. Ljungman P, Schmitt M, Marty FM, et al. A mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. *Clin Infect Dis*. 2020;70:1525–1533.
10. El Helou G, Razonable RR. Letermovir for the prevention of cytomegalovirus infection and disease in transplant recipients: an evidence-based review. *Infect Drug Resist*. 2019;12:1481–1491.
11. Hakki M. Moving past ganciclovir and foscarnet: advances in CMV therapy. *Curr Hematol Malig Rep*. 2020;15:90–102.
12. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. *N Engl J Med*. 2017;377:2433–2444.
13. Merck & Co., Inc., Rahway, NJ, USA. Prevymis™ prescribing information. 2020. Available at: https://www.merck.com/product/usa/pi_circulars/p/prevymis/prevymis_pi.pdf. Accessed May 27, 2023.
14. European Medicines Agency (EMA). PREVYMIS summary of product characteristics. 2018. Available at: https://www.ema.europa.eu/en/documents/product-information/prevymis-epar-product-information_en.pdf. Accessed September 1, 2023.
15. Menzel K, Kuo Y, Chen D, et al. Developing a mechanistic understanding of the nonlinear pharmacokinetics of letermovir and prospective drug interaction with everolimus using physiological-based pharmacokinetic modeling. *Clin Transl Sci*. 2023;16:1039–1048.
16. Prohn M, Viberg A, Zhang D, et al. Population pharmacokinetics of letermovir following oral and intravenous administration in healthy subjects and allogeneic hematopoietic cell transplantation recipients. *CPT Pharmacometrics Syst Pharmacol*. 2021;10:255–267.

© 2024 The Author(s). Published by Wolters Kluwer Health, Inc.

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

| Pharmacology | Full-Length Text

Cytomegalovirus prophylaxis with letermovir in pediatric (birth to <18 years of age) hematopoietic cell transplant recipients: pharmacokinetics, efficacy, and safety results of a Phase 2b study

Andreas H. Groll,[1] Lara Danziger-Isakov,[2] Aharon Gefen,[3,4] Christopher J. Fraser,[5] Johannes H. Schulte,[6] Bella Bielorai,[7,8] Nicole A. Karras,[9] David Bueno,[10] Peter J. Shaw,[11] Natalya Broyde,[12] Barbara Haber,[12] Christopher L. Gilbert,[12] Mayankbhai Patel,[12] Jacqueline B. McCrea,[12] Cyrus Badshah[12]

AUTHOR AFFILIATIONS See affiliation list on p. 11.

ABSTRACT Letermovir, a cytomegalovirus (CMV) terminase complex inhibitor, was first approved for prophylaxis of CMV infection and disease in adult CMV-seropositive allogeneic hematopoietic cell transplant (HCT) recipients (R+). This study evaluated the pharmacokinetics (PK), efficacy, and safety of letermovir in pediatric R+ allogeneic HCT recipients. In this Phase 2b, single-arm, open-label study, 65 participants were enrolled sequentially in three age groups (AG; AG1, 12 to <18 years; AG2, 2 to <12 years; and AG3, birth to <2 years). PK was evaluated in an initial cohort in each AG using intensive PK data to confirm or modify dosing before enrolling the remaining participants. Adult HCT population PK (PopPK) data were used to establish the exposure reference range. The adult letermovir dose evaluated in AG1 and AG2 participants achieved exposures generally within the adult HCT reference range. In AG3, the initial cohort (letermovir with cyclosporin A) achieved exposures trending lower than the median exposure target; the letermovir dose was increased for the remaining participants. Efficacy and safety in pediatric participants were generally consistent with adult HCT data. A pediatric HCT PopPK model was developed to determine dose recommendations to be included in patient prescribing information. The doses evaluated achieved exposures generally within the adult HCT reference range. At exposures achieved, letermovir was efficacious and safe in preventing clinically significant CMV infection in pediatric allogeneic HCT recipients. The observed concentration data informed a pediatric PopPK model to optimize final letermovir dose recommendations in this population.

CLINICAL TRIALS This study is registered with ClinicalTrials.gov as NCT03940586.

KEYWORDS pharmacokinetics, letermovir, cytomegalovirus, hematopoietic cell transplantation, pediatric

Cytomegalovirus (CMV) is a common viral pathogen associated with considerable morbidity and mortality in recipients of allogeneic hematopoietic cell transplant (HCT), with CMV-seropositive recipients (R+) being at the highest risk of CMV reactivation (1). In Europe in 2021, ~20% of recipients of allogeneic HCTs were pediatric patients, with over 4,000 patients aged <18 years receiving an HCT that year (2). More than 12,000 HCTs, or approximately 10% of total HCTs, in the United States were performed in pediatric patients (aged <18 years) during 2016–2020 (3). Approximately one-quarter of pediatric allogeneic HCT recipients develop CMV infection (i.e., CMV viremia) (4). There were no approved antiviral agents available for CMV prophylaxis in pediatric allogeneic

Editor Miguel Angel Martinez, IrsiCaixa Institut de Recerca de la Sida, Barcelona, Spain

Address correspondence to Andreas H. Groll, andreas.groll@ukmuenster.de.

D.B. has participated in advisory boards for Alexion and served on speakers' bureau of Jazz Pharmaceuticals. L.D.-I. has received research support from AiCuris, Ansun BioPharma, Astellas, MSD, and Pfizer, and is a consultant for Astellas, MSD, and Takeda. C.J.F. has participated in advisory boards for Amgen, Jazz Pharmaceuticals, and Link Healthcare. A.H.G. has participated in advisory boards for Novartis and Sanofi. A.H.G. has received research support from Gilead Sciences, MSD, and Pfizer; is a consultant for Amplyx, Astellas, Basilea, F2G, Gilead Sciences, MSD, and Pfizer; and served on the speakers' bureau of Astellas, Basilea, F2G, Gilead Sciences, MSD, and Pfizer. N.B., B.H., C.L.G., M.P., J.B.M., and C.B. are current employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, and may own stock and/or stock options in Merck & Co., Inc., Rahway, NJ, USA. The other authors declare no conflict of interest.

See the funding table on p. 12.

Received 1 April 2025
Accepted 2 July 2025
Published 18 August 2025

Copyright © 2025 Groll et al. This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International license.

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

HCT recipients when the current study was initiated. Therefore, there was a substantial unmet need for a safe and effective agent for CMV prophylaxis in this population.

Letermovir, a CMV DNA terminase inhibitor, is approved for the prophylaxis of CMV infection and disease in adult R+ allogeneic HCT recipients in over 60 countries, including the United States, the European Union, and Japan (5). Results of a Phase 3 placebo-controlled study (P001, NCT02137772) conducted in adult R+ allogeneic HCT recipients demonstrated that letermovir was generally safe, well tolerated, and efficacious in the prevention of clinically significant CMV infection (CS-CMVi; defined as initiation of anti-CMV pre-emptive therapy [PET] based on documented CMV viremia and/or the onset of CMV end-organ disease) (6). In adult HCT recipients (P001), exposure-response analyses indicated efficacy within the entire range of exposures achieved with letermovir 480 mg once daily, adjusted to 240 mg once daily with concomitant cyclosporin A (CsA). The pathogenesis of CMV infection (viremia) and disease, and the mechanism of action of letermovir, are not anticipated to differ in pediatric patients compared with adults. Therefore, letermovir pediatric exposures within the range of exposures achieved in adult HCT recipients are expected to provide comparable efficacy and safety in the pediatric population. The steady-state area under the concentration-time curve from 0 to 24 h post-dose (AUC0–24) in adults following oral and intravenous (IV) letermovir 480 mg (without CsA) was defined as the pediatric HCT exposure target (reference exposure range, 16,900 to 148,000 h × ng/mL).

The objectives of this study were to evaluate the pharmacokinetics (PK), efficacy, and safety of letermovir in pediatric R+ allogeneic HCT recipients. The PK data from this study were used to assess plasma exposures following the doses evaluated and to develop a pediatric HCT population PK (PopPK) model to derive the final dose recommendations for approval in the pediatric HCT population (7).

MATERIALS AND METHODS

Study design and participants

This Phase 2b (P030, NCT03940586), open-label, single-arm study assessed PK, efficacy, and safety of letermovir for CMV prophylaxis in pediatric participants from birth to <18 years of age at risk of developing CMV infection and/or disease following an allogeneic HCT. The study design is summarized in Fig. 1a. All study participants received letermovir within 28 days post-HCT through Week 14 post-HCT. Thereafter, participants were followed through Week 24 post-HCT for efficacy, and through Week 48 post-HCT for safety and tolerability. Intensive and sparse PK sampling were performed to characterize letermovir PK in pediatric HCT recipients (Fig. 1a).

There were three interim PK analyses planned to confirm dosing. Interim analysis 1 for an initial cohort of participants for age group (AG) 1 Panel A (aged 12 to <18 years, $n = 6$) was used to determine the optimum dosing for oral letermovir in the absence of CsA. The final dose selected in AG1 Panel A simultaneously triggered enrollment of AG1 Panel B and AG2 Panel A. Similarly, with interim analysis 2, AG2 Panel A (aged 2 to <7 years, $n = 3$; and aged 7 to <12 years, $n = 3$) PK was evaluated to determine the optimum oral letermovir dosing (without concomitant CsA). The final dose selection in AG2 Panel A simultaneously triggered enrollment of AG2 Panel B and AG3 (aged birth to <2 years; initial cohort, $n = 3$). Interim analysis 3 informed dosing for the remaining cohort of AG3 ($n = 5$). All AG3 participants (initial cohort, $n = 3$ and remaining participants, $n = 5$) were dosed with oral or IV letermovir, with or without CsA coadministration, prior to PK evaluation (Fig. 1b).

Interim analysis data for AG1 were previously reported and demonstrated that administration of letermovir 480 mg once daily (240 mg once daily with concomitant CsA) in adolescents resulted in exposures within the prespecified bounds of the adult HCT exposure range, as well as an efficacy and safety profile similar to adults (8). The study was subsequently completed on 25 August 2023, and final analyses of the data for the entire study population are presented here.

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

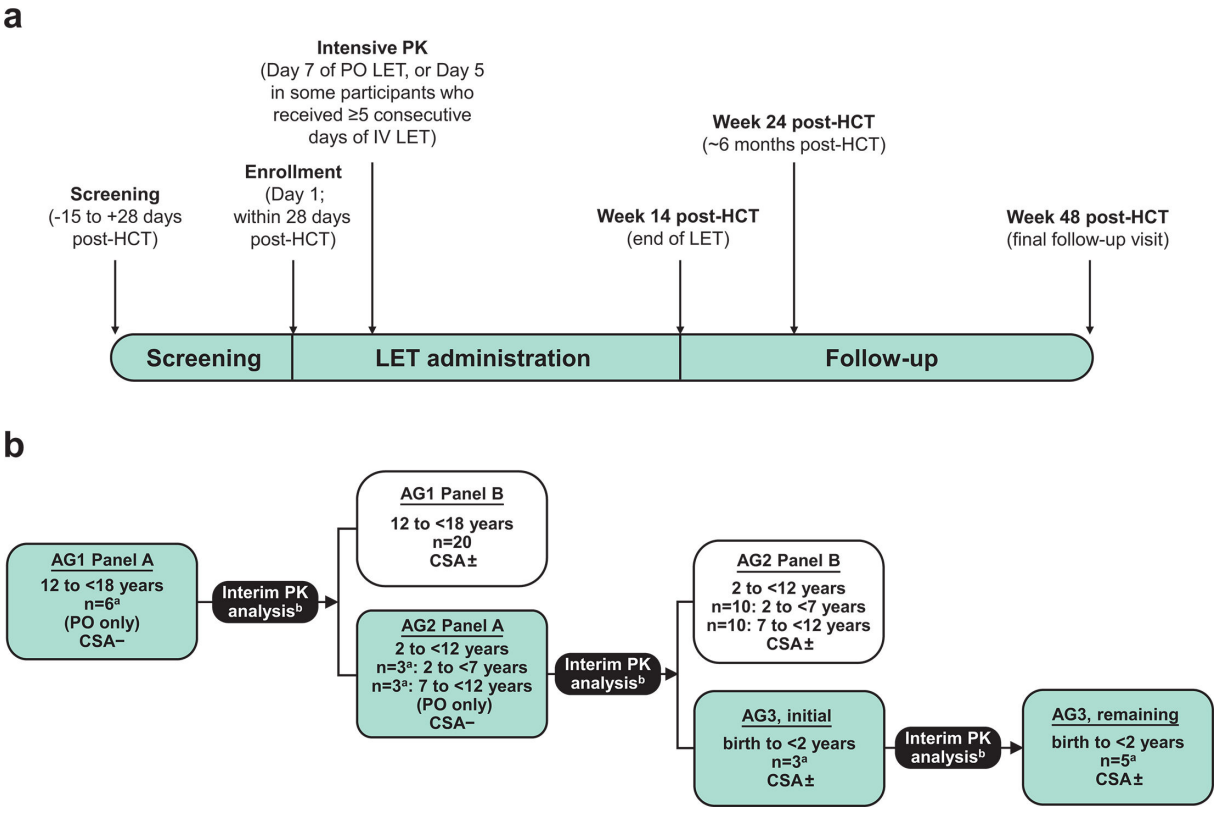


FIG 1 (a) Study design and (b) sequential pharmacokinetic (PK) evaluation of age groups. AG, age group; CSA±, may receive concomitant cyclosporin A; CSA–, cannot receive concomitant cyclosporin A; HCT, hematopoietic cell transplant; IV, intravenous; LET, letermovir; PO, oral. Intensive PK sampling was performed pre-dose and 1, 2.5, 8, and 24 h post-dose. Sparse PK sampling took place at Weeks 2, 4, 6, 8, 10, 12, and 14 post-HCT during the treatment phase. [a]Number of PK-evaluable participants. [b]Interim PK analysis occurred at three time points: when all evaluable participants had completed intensive PK sampling in AG1 Panel A, when all evaluable participants had completed intensive PK sampling in AG2 Panel A, and when the first three evaluable participants had completed intensive PK sampling in AG3.

Eligible participants were recipients of a first allogeneic HCT (bone marrow, peripheral blood stem cell, or cord blood) within 28 days prior to enrollment and had undetectable CMV DNA from a plasma or whole blood sample collected within 5 days prior to enrollment. AG1 participants had to be documented with a CMV R+ status within 90 days prior to enrollment; AG2/3 participants had to be documented as CMV R+ within 90 days prior to enrollment and/or the donor had to be CMV-seropositive within 1 year prior to enrollment. Given the relatively small number of HCTs performed in pediatric patients and the lower CMV seroprevalence in younger individuals (3, 4), restricting enrollment to only include participants with CMV R+ status in this study would have been challenging, particularly in the youngest AGs. These considerations were taken into account when designing the study to enable broad enrollment across the subpopulation of HCT recipients. Key exclusion criteria included CMV end-organ disease within 6 months prior to enrollment, prior allogeneic HCT, and evidence of CMV viremia at any time between informed consent or HCT procedure (whichever was earlier) until enrollment. Full eligibility criteria are provided in the Supplementary Material (Tables S1 and S2).

Participants' legally acceptable representative(s) provided written informed consent. The study was reviewed and approved by the appropriate institutional review board or independent ethics committee at each center. This study was conducted in accordance with local and/or national regulations (including all applicable protection laws and regulations), the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice, and the ethical principles that have their origin in the Declaration of Helsinki regarding independent ethics committee

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

review, informed consent, and the protection of human participants in biomedical research.

Letermovir dose selection and administration

Initial dose selection was guided by both physiologically based PK and PopPK models. The pre-study initial dosing selections were based on simulations using an allometrically scaled adult HCT PopPK model. The participants in AG1 received the recommended daily adult dose of 480 mg letermovir (adjusted to 240 mg with concomitant CsA administration, if needed, in Panel B) through Week 14 post-HCT (without weight limits). The remaining initial dose selections for AG2 and AG3 were based on weight-band dosing. Dose modifications based on the interim analyses are described in the results (Table S3).

Participants received letermovir from the day of enrollment through Week 14 post-HCT (Fig. 1a). All Panel A participants in AG1 and AG2 received oral letermovir, with no CsA, from Day 1 through Day 7, after which they could receive letermovir by oral or IV administration. AG1/2 Panel B participants and AG3 participants received either oral or IV letermovir with or without concomitant CsA. Oral letermovir administration was preferred, with IV administration provided to participants who could not tolerate oral intake (e.g., due to nausea and vomiting, mucositis, or a malabsorptive condition). For oral administration, AG1 participants received either the currently marketed oral tablets or a newly developed oral granule formulation (or "oral pellets"), which were administered mixed with soft food or via a gastric or nasogastric tube; AG2 and AG3 study participants received only the oral granule formulation.

PK exposure targets

The steady-state median target range for AUC0–24, predicted in adult HCT recipients from the Phase 3 PopPK model following administration of letermovir 480 mg orally or IV once daily without CsA, was 34,400–100,000 h × ng/mL (9). The lower and upper bounds of the adult HCT exposure range were 16,900 h × ng/mL (5th AUC0–24 percentile following letermovir 480 mg orally) and 148,000 h × ng/mL (95th AUC0–24 percentile following letermovir 480 mg IV), respectively.

Objectives and end points

The primary objective of the study was to evaluate letermovir PK in pediatric participants grouped by standard age cohorts. PK end points were assessed in the per-protocol population (defined as the subset of participants who comply with the protocol sufficiently to ensure that these data are likely to exhibit the effects of the study drug, according to the underlying scientific model). The primary measure of PK exposure was the AUC0–24 for determination of letermovir exposure. This parameter was used to match pediatric exposure to the adult HCT reference range and is the focus of the results.

Efficacy was a secondary objective evaluated in all participants who received at least one dose of study drug and had no detectable CMV DNA on Day 1 when the study drug was initiated (primary efficacy population). The efficacy end points were the proportion of participants with CS-CMVi (1) through Week 14 and (2) through Week 24 post-HCT. Efficacy was assessed through Week 14, the period of the highest risk of CMV reactivation (1). Participants were followed for an additional 10 weeks, through Week 24, to assess rebound CMV infection after cessation of prophylaxis. CS-CMVi was defined as the initiation of anti-CMV PET based on documented CMV viremia and the participant's clinical condition, and/or the onset of CMV end-organ disease. Documented viremia was defined as any detectable CMV viral DNA (including polymerase chain reaction results above or below the lower limit of quantification) using local laboratory testing. The primary missing data approach for the primary efficacy analyses was the non-completer = failure (NC = F) approach. Under this approach, not only were participants who developed CS-CMVi (true failures) counted as failures, but participants who prematurely discontinued from the study or who had missing outcome data were also imputed as failures. An alternative missing data approach, the Data as Observed (DAO) approach,

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

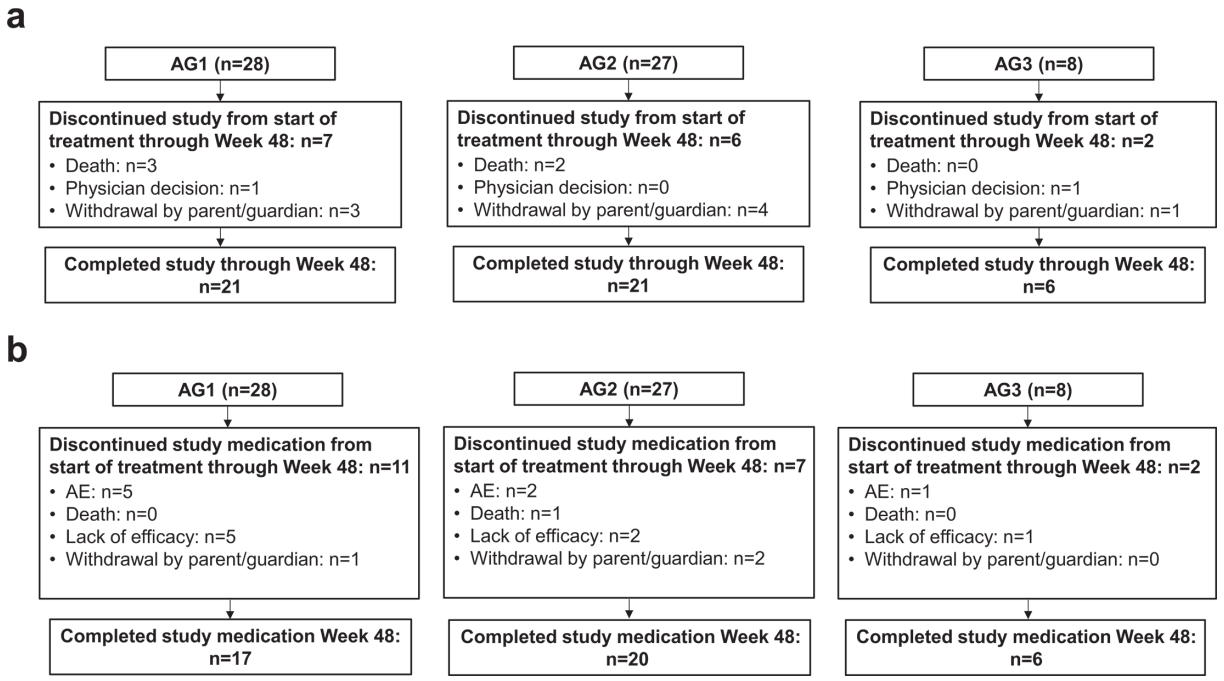


FIG 2 Participant disposition (all randomized and treated participants): (a) status for trial and (b) status for study medication in trial. AE, adverse event; AG, age group.

was also used for the efficacy analyses. With this approach, participants who discontinued prematurely or had missing outcome data (i.e., imputed failures) were excluded from the analysis. The DAO approach thus accounts for the incidence of CS-CMVi (i.e., true failure rate) only.

Safety and tolerability were assessed by clinical review of relevant parameters, including adverse events (AEs), prospectively collected during the study. All AEs were collected through 28 days following the last dose of the study drug (treatment phase). Thereafter, only drug-related serious AEs (SAEs) and SAEs leading to death were collected through Week 48 post-HCT. The primary safety population consisted of all participants who received at least one dose of the study drug.

To assess genotypic resistance, CMV DNA sequence analysis was performed using next-generation sequencing on samples from participants with CS-CMVi. Letermovir resistance was assessed by genotypic analysis of the CMV terminase complex genes (UL56, UL89, and UL51) with detectable CMV DNA.

Statistical analysis

There was no formal hypothesis testing in this study. A noncompartmental analysis was used for the primary PK parameters of interest, which was AUC0–24 derived from the intensive PK sampling on Day 7. The interim noncompartmental PK analyses occurred at three intervals: (i) when all evaluable participants completed intensive PK sampling in AG1 Panel A; (ii) when all evaluable participants completed intensive PK sampling in AG2 Panel A; and (iii) when the first three evaluable participants completed intensive PK sampling in AG3. The final noncompartmental PK analyses were performed on the PK population who underwent intensive PK sampling. Individual AUC0–24 values were plotted by dose and weight. Additional PK parameters, including but not limited to C_{max}, T_{max}, and $T_{1/2}$, were estimated as well, although they are not presented in this paper as AUC0–24 was the primary parameter determining dose selection.

For efficacy analyses, the estimated proportion of participants with CS-CMVi through Weeks 14 and 24 post-HCT, 95% CIs were calculated based on the exact binomial method of Clopper and Pearson (10). For safety analyses, the proportions of participants within

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

different categories of AEs were summarized, with 95% CIs estimated by the Clopper-Pearson method (10).

RESULTS

Participants

The study was initiated on 8 August 2019, and completed on 25 August 2023. Among 65 participants <18 years of age enrolled in the study, 28 participants were 12 to <18 years of age, 29 participants were 2 to <12 years of age, and 8 participants were <2 years of age (Fig. 2a). Sixty-three participants (96.9%) received at least one dose of letermovir, and 48 (73.8%) completed treatment (Fig. 2a). The most common reasons for early discontinuation of letermovir were AEs (12.7%) and lack of efficacy (i.e., due to CS-CMVi; 12.7%) (Fig. 2b).

Participant demographics and baseline clinical characteristics are shown in Table 1. Approximately 70% of participants were male, and the median age was 11.0 years (range, 0–17). The most common indications for HCT were acute myeloid leukemia (11 [17.5%] cases), aplastic anemia (6 [9.5%] cases), and chronic granulomatous disease (4 [6.3%] cases) (Table S4). Seven (11.1%) participants had detectable CMV viremia on Day 1 of treatment and were not included in the primary efficacy analysis.

PK

The PK analyses were performed on a subset (n = 36) of the PK population who underwent intensive PK sampling and did not have any missing PK samples on intensive

TABLE 1 Baseline demographic and clinical characteristics (all participants as treated)[a]

Parameter	AG1 (n = 28)	AG2 (n = 27)	AG3 (n = 8)	Total (N = 63)
Sex, *n* (%)				
Male	15 (53.6)	22 (81.5)	7 (87.5)	44 (69.8)
Female	13 (46.4)	5 (18.5)	1 (12.5)	19 (30.2)
Age (years)				
Mean (SD)	14.1 (1.5)	6.6 (3.2)	0.7 (0.3)	9.1 (5.3)
Median (range)	13.5 (12–17)	7.0 (2–11)	0.7 (0–1)	11.0 (0–17)
Race, *n* (%)				
Asian	6 (21.4)	3 (11.1)	0	9 (14.3)
Black or African American	3 (10.7)	0	0	3 (4.8)
Multiple	4 (14.3)	2 (7.4)	1 (12.5)	7 (11.1)
White	15 (53.6)	22 (81.5)	7 (87.5)	44 (69.8)
Stem cell source, *n* (%)				
Peripheral blood	15 (53.6)	16 (59.3)	4 (50.0)	35 (55.6)
Bone marrow	12 (42.9)	10 (37.0)	3 (37.5)	25 (39.7)
Cord blood	1 (3.6)	1 (3.7)	1 (12.5)	3 (4.8)
Conditioning regimen used, *n* (%)				
Myeloablative	25 (89.3)	24 (88.9)	6 (75.0)	55 (87.3)
Reduced intensity conditioning	3 (10.7)	1 (3.7)	2 (25.0)	6 (9.5)
Non-myeloablative	0	2 (7.4)	0	2 (3.2)
Days from transplantation to randomization				
Mean (SD)	9.9 (8.38)	9.0 (8.59)	6.5 (4.07)	9.1 (8.03)
Median (range)	7.5 (1.0–28.0)	5.0 (1.0–27.0)	7.5 (1.0–11.0)	7.0 (1.0–28.0)
Donor/recipient CMV serostatus, *n* (%)				
D+/R+	20 (71.4)	18 (66.7)	0	38 (60.3)
D−/R+	8 (28.6)	6 (22.2)	4 (50.0)	18 (28.6)
D+/R−	0	3 (11.1)	4 (50.0)	7 (11.1)

[a]AG, age group; CMV, cytomegalovirus; D+, CMV-seropositive donor; D−, CMV-seronegative donor; R+, CMV-seropositive recipient; R−, CMV-seronegative recipient; SD, standard deviation.

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

PK sampling days. The intensive and sparse PK data for each AG (total n = 60) were included in the pediatric HCT PopPK analysis, which was used to optimize the final dose recommendations. The pediatric PopPK analysis will be described in a separate publication.

Of the 12 PK-evaluable participants in AG1, 8 received letermovir 480 mg orally or IV once daily without CsA, and 4 received letermovir 240 mg IV once daily with CsA (Fig. 3). Participants in AG1 Panel A achieved letermovir exposures comparable with the reference adult exposure, with one participant (480 mg, oral) achieving a higher exposure than the adult reference range, but lower than the maximum observed in the Phase 1 letermovir program (upper limit of 328,000 h × ng/mL). No dose modifications were necessary in AG1 Panel A based on interim PK analysis. All participants in AG1 Panel B achieved letermovir exposures comparable with the reference adult exposure (Fig. 3).

Of the 16 PK-evaluable participants in AG2, 6 received letermovir 240 mg orally or IV once daily without CsA, 4 received letermovir 120 mg orally or IV once daily without CsA, 1 received letermovir 60 mg IV once daily without CsA, 1 received letermovir 120 mg IV once daily with CsA, and 4 received letermovir 60 mg IV once daily with CsA (Fig. 3). Similar to AG1, participants in AG2 Panel A, all of whom received oral letermovir without concomitant CsA, experienced letermovir exposures comparable with the reference adult exposure. No dose modifications based on the interim PK analysis were necessary in AG2 Panel B. In AG2 Panel B, eight of the participants who received IV letermovir were within the reference adult exposure range, and the remaining two participants, who received IV letermovir with CsA, had exposures lower than the reference adult exposure (Fig. 3).

Of the eight PK-evaluable participants in AG3, one received letermovir 60 mg orally once daily without CsA, one received letermovir 40 mg IV once daily without CsA, two received letermovir 60 mg orally or IV once daily with CsA, three received letermovir 40 mg orally once daily with CsA, and one received letermovir 20 mg IV once daily with CsA (Fig. 3). Letermovir exposures for the first three AG3 participants, all of whom received concomitant CsA, were lower than the target median adult exposure (Fig. 3). The letermovir dose was increased for the remaining five participants (body weight <10 kg) (Table S3). The resulting letermovir exposures were comparable with the reference adult exposures (Fig. 3).

Efficacy

Of the 56 participants evaluable for efficacy (i.e., received at least one dose of study drug and had undetectable viremia on Day 1) using the NC = F approach, there were 11 (19.6%) failures (true and imputed) through Week 14 post-HCT and 14 (25.0%) failures through Week 24 post-HCT (Table 2). The proportion of participants for whom treatment failed was similar across the three AGs at both time points, and there were no cases of CMV end-organ disease at either time point.

The true failure rate (incidence of CS-CMVi only) as evaluated using the DAO approach for missing data were 8.2% (4/49) and 12.5% (6/48) at Weeks 14 and 24, respectively (Table S5).

Safety

There were 63 participants in the safety population (i.e., those who received at least one dose of study drug). Overall, the AE profile was comparable across the three AGs in the broad categories of AEs during the treatment phase (Table S6). The most common AEs reported were vomiting (37 [58.7%] cases), pyrexia (27 [42.9%] cases), diarrhea (24 [38.1%] cases), graft-versus-host disease (GVHD; 24 [38.1%] cases), nausea (18 [28.6%] cases), and abdominal pain (18 [28.6%] cases) (Table 3). Among these, the most common drug-related AEs were gastrointestinal disorders, including vomiting (11 [17.5%] cases) and nausea (2 [3.2%] cases) (Table S7).

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

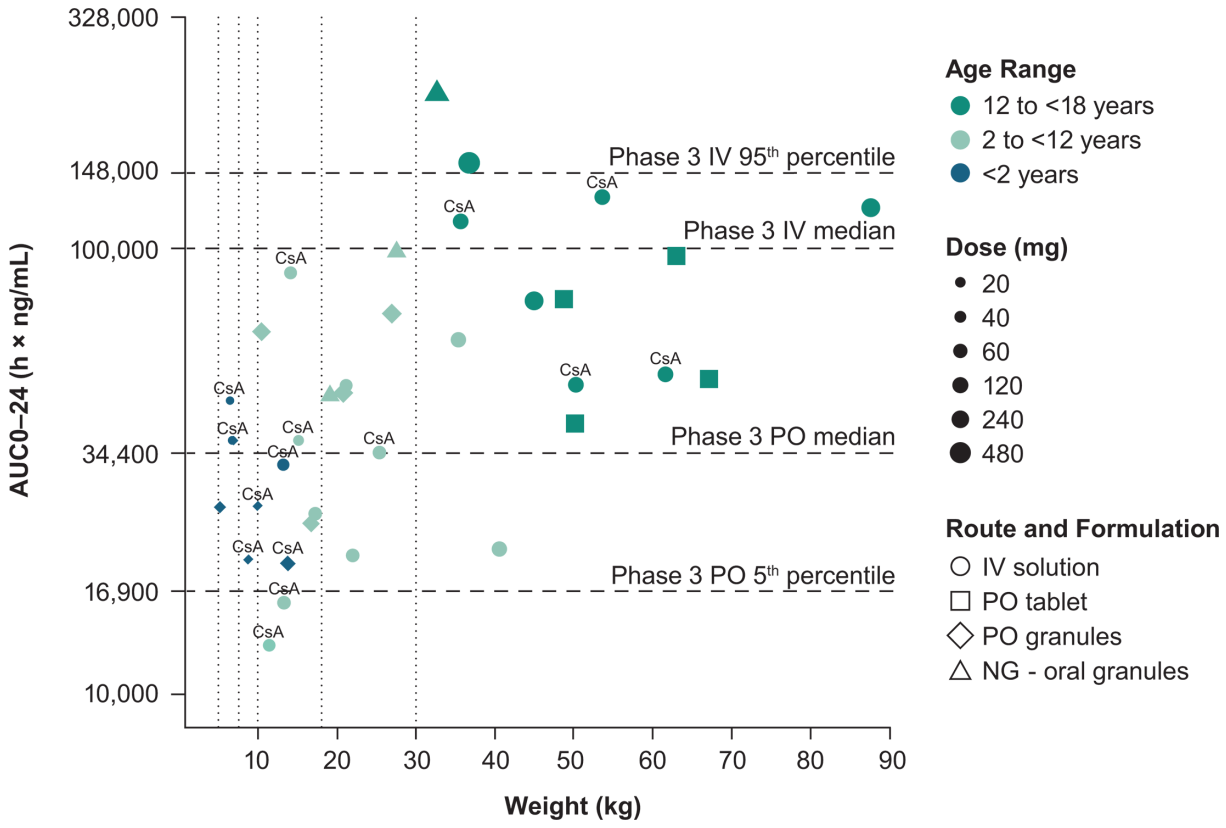


FIG 3 Individual letermovir exposures for all participants who underwent intensive PK sampling compared with reference adult values (n = 36). AG, age group; AUC0–24, area under the concentration-time curve for the dosing interval (0–24 h) (logarithmic scale); CsA, cyclosporin A; IV, intravenous; NG, nasogastric; PK, pharmacokinetic; PO, oral; PopPK, population PK. CsA above the symbol indicates CsA was coadministered with the letermovir dose. Vertical dotted lines show the dosing weight-band boundaries for 2 to < 12 years (AG2) and birth to < 2 years (AG3); there are no dosing weight boundaries for 12 to < 18 years (AG1). The upper and lower bounds of the adult reference exposure range were prespecified based on the Phase 3 PopPK model (9).

Thirty-five (55.6%) participants experienced at least one SAE (Table S6). The most commonly reported SAEs were pyrexia (7.9%) and GVHD (4.8%). Only two participants had SAEs that were considered by investigators to be drug-related (one case each of atrial fibrillation and increased blood bilirubin). Both SAEs were multifactorial in origin, such that other etiologies could not be ruled out, and both resolved.

There were four deaths reported during the treatment phase that were considered to be due to AEs. The causes of death included *Candida* infection and multiple organ dysfunction syndrome (n = 1), post-HCT lymphoproliferative disorder and hepatosplenic candidiasis (n = 1), recurrent acute myeloid leukemia (n = 1), and septic shock (n = 1). None of the deaths were considered related to the study drug by the investigators.

Viral resistance

Resistance genotyping was attempted on samples collected from 12 participants with viremia. Of these, 10 participants had evaluable sequence data available for analysis (AG1, n = 4; AG2, n = 4; and AG3, n = 2). In two participants, known letermovir resistance-associated amino acid substitutions were detected in pUL56 at an allele frequency above the validated assay cutoff of 5%. One was an AG1 participant who had an R369S substitution detected on Day 54 of the study. The other, an AG3 participant who was positive for CMV DNAemia on Day 1, had a C325W substitution detected on Day 129 of the study. Among the 10 participants with evaluable data, no known letermovir resistance-associated substitutions were observed in the pUL51 or pUL89 terminase subunits.

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

TABLE 2 Proportion of participants with CS-CMVi through Weeks 14 and 24 post-HCT (NC=F approach, primary efficacy population)[a,b]

Parameter, *n* (%)	AG1 (*n* = 25)	AG2 (*n* = 24)	AG3 (*n* = 7)	Total (*N* = 56)
Through Week 14 post-HCT				
Failures[c]	5 (20.0)	4 (16.7)	2 (28.6)	11 (19.6)
CS-CMVi[d] through visit window	2 (8.0)	1 (4.2)	1 (14.3)	4 (7.1)
Initiation of PET based on documented CMV viremia	2 (8.0)	1 (4.2)	1 (14.3)	4 (7.1)
CMV end-organ disease	0	0	0	0
Discontinued from study before visit window	2 (8.0)	3 (12.5)	1 (14.3)	6 (10.7)
Missing outcome in visit window	1 (4.0)	0	0	1 (1.8)
Through Week 24 post-HCT				
Failures[c]	6 (24.0)	6 (25.0)	2 (28.6)	14 (25.0)
CS-CMVi[d] through visit window	2 (8.0)	3 (12.5)	1 (14.3)	6 (10.7)
Initiation of PET based on documented CMV viremia	2 (8.0)	3 (12.5)	1 (14.3)	6 (10.7)
CMV end-organ disease	0	0	0	0
Discontinued from study before visit window	4 (16.0)	3 (12.5)	1 (14.3)	8 (14.3)
Missing outcome in visit window	0	0	0	0

[a]AG, age group; CMV, cytomegalovirus; CS-CMVi, clinically significant CMV infection; HCT, hematopoietic cell transplant; NC = F, non-completer = failure; PET, pre-emptive therapy.
[b]Primary efficacy population, defined as all participants who received ≥1 dose of study intervention and had no detectable CMV viral DNA on Day 1 of treatment.
[c]Categories of failure are mutually exclusive and listed in hierarchical order. With the NC = F approach, failure was defined as all participants who developed CS-CMVi, prematurely discontinued from the study, or had a missing outcome through the post-HCT visit window.
[d]Defined as proven or probable CMV end-organ disease, or initiation of PET based on documented CMV viremia and the participant's clinical condition.

DISCUSSION

Pediatric allogeneic HCT recipients are at risk of CMV infection or reactivation (1, 4), and there is a significant need for an antiviral agent for CMV prophylaxis in this population (4). As the pathogenesis and manifestations of CMV infection and disease are similar in adult and pediatric patients (11), the initial dose selections and dose recommendations of letermovir were based on achieving comparable exposures anticipated to result in similar efficacy and safety in both populations. The primary objective of this study was to evaluate the PK of letermovir in pediatric HCT recipients from birth to <18 years of age to inform proposed pediatric dosing of letermovir. Another objective of the study was to generate additional data to provide substantial evidence for the safe and effective use of letermovir in this population. Viral resistance was also assessed in this study.

The doses used in this study were based on simulations using an allometric scaling of an adult HCT PopPK model to approximate letermovir exposures in pediatric participants to the adult HCT reference exposure range. There were no letermovir dose modifications to the initial dose selections for AG1 and AG2. For AG3, the youngest participants, letermovir exposures for the first three participants (who received letermovir with CsA) were trending lower than the target median adult exposure at the interim analysis. In the remaining five AG3 participants, the letermovir dose was increased for participants weighing <10 kg. The letermovir exposures in pediatric participants for the doses evaluated in the study were generally within the adult HCT recipient reference exposure range.

The final dose recommendations for the pediatric HCT population were based on using the PK data from this study in a pediatric HCT PopPK model, which will be the subject of a separate publication. The predicted letermovir exposures, based upon the final pediatric HCT PopPK model, informed and supported the dose recommendations of the recent pediatric approval (7). The weight-band dosing of letermovir for participants <12 years of age is largely consistent with the doses evaluated in this study with the addition of combining some weight bands across ages.

The efficacy of letermovir in preventing CS-CMVi in this study was consistent with the efficacy demonstrated in the pivotal Phase 3 adult study. With the NC = F approach used to account for missing data, 19.6% of study participants had failed at Week 14 post-HCT, compared with 19.1% in the adult study at the same time point. The corresponding

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

TABLE 3 Participants with AEs through Week 14 post-HCT (incidence ≥20% in one or more AG; safety population; treatment phase)[a,b]

n (%)	AG1 (*n* = 28)	AG2 (*n* = 27)	AG3 (*n* = 8)	Total (*N* = 63)
With ≥1 AE[c]	28 (100)	27 (100)	8 (100)	63 (100)
Gastrointestinal disorders	27 (96.4)	27 (100)	5 (62.5)	59 (93.7)
Vomiting	14 (50.0)	20 (74.1)	3 (37.5)	37 (58.7)
Nausea	12 (42.9)	6 (22.2)	0	18 (28.6)
Diarrhea	12 (42.9)	12 (44.4)	0	24 (38.1)
Abdominal pain	11 (39.3)	6 (22.2)	1 (12.5)	18 (28.6)
Stomatitis	8 (28.6)	9 (33.3)	0	17 (27.0)
Infections and infestations	21 (75.0)	18 (66.7)	5 (62.5)	44 (69.8)
Device-related infection	1 (3.6)	3 (11.1)	2 (25.0)	6 (9.5)
Epstein-Barr virus infection reactivation	2 (7.1)	0	2 (25.0)	4 (6.3)
General disorders and administration site conditions	16 (57.1)	18 (66.7)	4 (50.0)	38 (60.3)
Pyrexia	11 (39.3)	13 (48.1)	3 (37.5)	27 (42.9)
Immune system disorders	15 (53.6)	13 (48.1)	4 (50.0)	32 (50.8)
Graft-versus-host disease	10 (35.7)	11 (40.7)	3 (37.5)	24 (38.1)
Skin and subcutaneous tissue disorders	12 (42.9)	17 (63.0)	2 (25.0)	31 (49.2)
Pruritus	6 (21.4)	3 (11.1)	0	9 (14.3)
Metabolism and nutritional disorders	12 (42.9)	14 (51.9)	4 (50.0)	30 (47.6)
Decreased appetite	3 (10.7)	8 (29.6)	0	11 (17.5)
Blood and lymphatic system disorders	8 (28.6)	15 (55.6)	1 (12.5)	24 (38.1)
Thrombocytopenia	5 (17.9)	9 (33.3)	0	14 (22.2)
Neutropenia	2 (7.1)	8 (29.6)	1 (12.5)	11 (17.5)
Anemia	1 (3.6)	7 (25.9)	0	8 (12.7)
Vascular disorders	10 (35.7)	11 (40.7)	2 (25.0)	23 (36.5)
Hypertension	7 (25.0)	9 (33.3)	0	16 (25.4)
Renal and urinary disorders	14 (50.0)	8 (29.6)	0	22 (34.9)
Dysuria	6 (21.4)	3 (11.1)	0	9 (14.3)
Nervous system disorders	13 (46.4)	5 (18.5)	1 (12.5)	19 (30.2)
Headache	6 (21.4)	3 (11.1)	0	9 (14.3)

[a]AE, adverse event; AG, age group; HCT, hematopoietic cell transplant.
[b]Safety population, defined as all participants who received ≥1 dose of study drug.
[c]AEs were reported using the Medical Dictionary for Regulatory Activities Version 25.1. Each participant was counted once for each system organ class or specific AE.

rates at Week 24 post-HCT were 25.0% and 37.5% in pediatric and adult participants, respectively (6).

It should be noted that the NC = F approach for estimating failure rates is a conservative approach, where the failure rate includes not only individuals who develop CS-CMVi (true failures), but also those who discontinue the study prematurely or where data are missing (imputed failures). The true failure rate with the DAO approach was substantially lower (8.2% and 12.5% at Weeks 14 and 24 post-HCT, respectively).

It should also be noted that a subset of participants from AG2 and AG3 were CMV-seronegative recipients with a CMV-seropositive donor (D+/R−) at baseline (to facilitate study enrollment of the younger AGs given the relatively small number of HCTs performed in pediatric patients and lower CMV seroprevalence observed globally in younger individuals [3, 4]). As D+/R− allogeneic HCT recipients have a lower risk of

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

developing CS-CMVi (~30% risk [12]), this would be a potential caveat when comparing failure rates in this study with the adult data.

Letermovir was generally safe and well tolerated in this study, with a safety profile similar to that seen in the adult Phase 3 HCT study. Gastrointestinal-related AEs were the most common treatment-emergent AEs, and treatment discontinuation due to drug-related AEs was rare (3.2%; Table S6). No treatment-related deaths were reported. Thus, letermovir has a favorable toxicity profile compared with other anti-CMV agents (such as ganciclovir, foscarnet, and cidofovir); most notably, letermovir shows no evidence of hematologic toxicity in the allogeneic HCT setting (1, 6, 13).

There are several well-recognized approaches to providing substantial evidence for the safe and effective use of a drug in a pediatric population that often involve leveraging available data in adults. This concept is referred to as pediatric extrapolation (14, 15), and it is an accepted means to facilitate pediatric drug approval without necessitating large pediatric Phase 3 trials. Pediatric extrapolation of efficacy is considered to be appropriate when it can be assumed that the course of the disease and the expected response to a drug would be sufficiently similar in the pediatric and reference populations.

For the purpose of pediatric extrapolation, robust safety and efficacy data were available from a large multicenter trial in adults demonstrating a clinically meaningful and statistically significant effect on CS-CMVi prevention, as well as a mortality benefit (6). Confirmation of these results in a pediatric population in a second large trial with a traditional design (i.e., large sample size, double-blind with a placebo comparator) was unnecessary and would have been impracticable given the difficulties of patient recruitment for pediatric trials and the length of time needed to complete them (16). A traditional trial design would also have presented significant ethical concerns as no additional benefits would have been demonstrated, and there would have been substantial delays in the availability of a much-needed intervention in this vulnerable patient population.

The PK data obtained in this study were used in a pediatric HCT PopPK model to predict exposures for this population and support proposed dose recommendations, along with additional safety and efficacy data supporting pediatric extrapolation, for submission to regulatory authorities. The first regulatory approval for use of letermovir in pediatric R+ HCT recipients for CMV prophylaxis was obtained in August 2024. Final dose recommendations are provided in the patient prescribing information (Table S8).

In conclusion, at the doses used and the letermovir exposures achieved in this study, letermovir is generally safe and effective in preventing CS-CMVi in pediatric HCT recipients.

ACKNOWLEDGMENTS

The authors are grateful to all study participants, investigators, site personnel, and contributors. Funding was provided by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA. Medical writing assistance, under the direction of the authors, was provided by Jane Chung, PharmD, of CMC Affinity, a division of IPG Health Medical Communications, in accordance with Good Publication Practice (GPP 2022) guidelines. This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc, Rahway, NJ, USA.

AUTHOR AFFILIATIONS

[1]University Children's Hospital Münster, Münster, Germany
[2]Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio, USA
[3]Ruth Rappaport Children's Hospital, Rambam Health Care Campus, Haifa, Israel
[4]Faculty of Medicine, Technion Israel Institute of Technology, Haifa, Israel
[5]Queensland Children's Hospital, Brisbane, Queensland, Australia

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

[6]Charité Universitätsmedizin Berlin, Berlin, Germany
[7]Sheba Medical Center, Tel HaShomer, Israel
[8]Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel
[9]City of Hope Cancer Center, Duarte, California, USA
[10]Hospital Infantil Universitario La Paz, Madrid, Spain
[11]Royal Alexandra Hospital for Children, Westmead, New South Wales, Australia
[12]Merck & Co., Inc., Rahway, New Jersey, USA

AUTHOR ORCIDs

Andreas H. Groll http://orcid.org/0000-0003-1188-393X

FUNDING

Funder	Grant(s)	Author(s)
Merck Sharp & Dohme LLC	NA	Cyrus Badshah

DATA AVAILABILITY

The data sharing policy, including restrictions, of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, is available at https://externaldatasharing-msd.com/. Requests for access to the clinical study data can be submitted via email to the Data Access mailbox (dataaccess@msd.com).

ADDITIONAL FILES

The following material is available online.

Supplemental Material

Supplemental tables (AAC00420-25-s0001.pdf). Tables S1 to S8.

REFERENCES

1. Cui J, Zhao K, Sun Y, Wen R, Zhang X, Li X, Long B. 2022. Diagnosis and treatment for the early stage of cytomegalovirus infection during hematopoietic stem cell transplantation. Front Immunol 13:971156. https://doi.org/10.3389/fimmu.2022.971156
2. Passweg JR, Baldomero H, Ciceri F, Corbacioglu S, de la Cámara R, Dolstra H, Glass B, Greco R, McLornan DP, Neven B, de Latour RP, Perić Z, Ruggeri A, Snowden JA, Sureda A. 2023. Hematopoietic cell transplantation and cellular therapies in Europe 2021. The second year of the SARS-CoV-2 pandemic. a report from the EBMT activity survey. Bone Marrow Transplant 58:647–658. https://doi.org/10.1038/s41409-023-01943-3
3. Center for International Blood and Marrow Transplant Research. 2022. HRSA transplant activity report: number of HCTs performed in the United States and reported to CIBMTR, by year and age group, 2016–2020
4. Bateman CM, Kesson A, Powys M, Wong M, Blyth E. 2021. Cytomegalovirus infections in children with primary and secondary immune deficiencies. Viruses 13:2001. https://doi.org/10.3390/v13102001
5. Kim ES. 2018. Letermovir: first global approval. Drugs (Abingdon Engl) 78:147–152. https://doi.org/10.1007/s40265-017-0860-8
6. Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, Haider S, Ullmann AJ, Katayama Y, Brown J, Mullane KM, Boeckh M, Blumberg EA, Einsele H, Snydman DR, Kanda Y, DiNubile MJ, Teal VL, Wan H, Murata Y, Kartsonis NA, Leavitt RY, Badshah C. 2017. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med 377:2433–2444. https://doi.org/10.1056/NEJMoa1706640
7. US Food and Drug Administration. 2024. Prevymis (letermovir) prescribing information
8. Groll AH, Schulte JH, Antmen AB, Fraser CJ, Teal VL, Haber B, Caro L, McCrea JB, Fancourt C, Patel M, Menzel K, Badshah C. 2024. Pharmacokinetics, safety, and efficacy of letermovir for cytomegalovirus prophylaxis in adolescent hematopoietic cell transplantation recipients. Pediatr Infect Dis J 43:203–208. https://doi.org/10.1097/INF.0000000000004208
9. Prohn M, Viberg A, Zhang D, Dykstra K, Davis C, Macha S, Sabato P, de Alwis D, Iwamoto M, Fancourt C, Cho CR. 2021. Population pharmacokinetics of letermovir following oral and intravenous administration in healthy participants and allogeneic hematopoietic cell transplantation recipients. CPT Pharmacometrics Syst Pharmacol 10:255–267. https://doi.org/10.1002/psp4.12593
10. Clopper CJ, Pearson ES. 1934. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika 26:404–413. https://doi.org/10.1093/biomet/26.4.404
11. Castagnola E, Cappelli B, Erba D, Rabagliati A, Lanino E, Dini G. 2004. Cytomegalovirus infection after bone marrow transplantation in children. Hum Immunol 65:416–422. https://doi.org/10.1016/j.humimm.2004.02.013
12. Ljungman P, Hakki M, Boeckh M. 2011. Cytomegalovirus in hematopoietic stem cell transplant recipients. Hematol Oncol Clin North Am 25:151–169. https://doi.org/10.1016/j.hoc.2010.11.011
13. Chemaly RF, Ullmann AJ, Stoelben S, Richard MP, Bornhäuser M, Groth C, Einsele H, Silverman M, Mullane KM, Brown J, Nowak H, Kölling K, Stobernack HP, Lischka P, Zimmermann H, Rübsamen-Schaeff H, Champlin RE, Ehninger G, AIC246 Study Team. 2014. Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation. N Engl J Med 370:1781–1789. https://doi.org/10.1056/NEJMoa1309533
14. US Food and Drug Administration. 2022. General clinical pharmacology considerations for pediatric studies of drugs, including biological products - guidance for industry. Center for Drug Evaluation and Research. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/general-clinical-pharmacology-considerations-pediatric-studies-drugs-including-biological-products
15. European Medicines Agency. 2017. ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e11r1-guideline-clinical-investigation-medicinal-products-pediatric-population-revision-1-addendum_en.pdf

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

16. Bi Y, Liu J, Li L, Yu J, Bhattaram A, Bewernitz M, Li RJ, Liu C, Earp J, Ma L, Zhuang L, Yang Y, Zhang X, Zhu H, Wang Y. 2019. Role of model-informed drug development in pediatric drug development, regulatory evaluation, and labeling. J Clin Pharmacol 59 Suppl 1:S104–S111. https://doi.org/10.1002/jcph.1478

Downloaded from https://journals.asm.org/journal/aac on 02 March 2026 by 186.154.32.33.

Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Letermovir for CMV prophylaxis in very high-risk pediatric hematopoietic stem cell transplantation recipients for inborn errors of immunity.

Thibaut César (tcesar@chu-grenoble.fr)
Hospital Necker for Sick Children: Hopital universitaire Necker-Enfants malades https://orcid.org/0009-0009-0103-2892
Minh Patrick Le
Roman Klifa
Martin Castelle
Benjamin Fournier
Romain Lévy
Marwa Chbihi
Virginie Courteille
Despina Moshous
Stéphane Blanche
Mickaël Alligon
Marianne Leruez-Ville
Gilles Peytavin
Pierre Frange
Benedicte Neven
https://orcid.org/0000-0001-8941-0935

Research Article

Keywords: Letermovir, CMV prophylaxis, Hematopoietic stem cell transplant, Pediatrics, Inborn errors of immunity, Pharmacokinetics

Posted Date: August 22nd, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3252427/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Version of Record: A version of this preprint was published at Journal of Clinical Immunology on December 20th, 2023. See the published version at https://doi.org/10.1007/s10875-023-01617-1.

47

Abstract

The burden of CMV infection and disease is important in pediatric hematopoietic stem cell transplantation (HSCT), notably in the subgroup of patients with inborn errors of immunity (IEIs). Letermovir (LMV) is now a standard of care for CMV prophylaxis in adult sero-positive (R+) recipients, but is not yet labeled for children. Published pediatric studies are still scarce. We report a monocentric real-life use of LMV in 36 HSCT pediatric recipients with IEIs considered at high-risk of CMV infection including 14 patients between 2 and 12 months of age. A homogenous dosage proportional to the body surface area was used. Pharmacokinetic (PK) was performed in 8 patients with a median of 6 years of age (range 0,6;15). The cumulative incidence of clinically significant CMV infections (CS-CMVi) and the overall survival of patients under LMV were compared to a very similar historical cohort under (val)aciclovir prophylaxis. LMV tolerance was good. As compared to the historical cohort, the incidence of CS-CMVi was significantly lower in LMV group (5 out of 36 transplants (13.9%) versus 28 of the 62 HSCT (45.2%)) ($p = 0.002$). Plasma LMV exposures did not significantly differ with those reported in adult patients. In this high-risk pediatric HSCT cohort transplanted for IEIs, CMV prophylaxis with LMV at a homogenous dosage was well tolerated and effective in preventing CS-CMVi compared with a historical cohort.

Introduction

Human cytomegalovirus (CMV) infection and disease remain clinically significant complications in recipients of hematopoietic stem cell transplantation (HSCT) [1–2]. Despite close monitoring with a regular sensitive polymerase chain-reaction (PCR) and preemptive strategy, CMV sero-positive recipients (R+) and those with any degree of CMV reactivation after HSCT are associated with an increased risk of overall mortality after transplant through direct and indirect effects, such as increased incidence of opportunistic infections, association between CMV and graft versus host disease (GVHD) [3]. Moreover, anti-CMV drugs such as (val)ganciclovir, foscarnet or cidofovir available for the preemptive treament have significant side effects making their use challenging in the post-HSCT period. Thus, the development of safe and effective antiviral drugs for CMV prophylaxis is a major goal in HSCT.

Letermovir (LMV) is an antiviral agent with a unique mechanism of action through inhibition of the CMV-terminase complex [4–5]. LMV pharmacokinetics (PK) in adult HSCT recipients is well described with a two-compartment model with linear elimination and absorption, following administration of 480 mg once daily orally or intravenously (dose reduced to 240 mg/day in case of cyclosporin (CSA) comedication) [6–7]. LMV was shown to be well tolerated and highly efficient to prevent clinically significant CMV infections (CS-CMVi) in adult R + in a phase 3 randomized double-blind trial [8] and has become the standard of care for prophylaxis of CMV infection/disease in adult R + recipients through day 100 post-transplant. Moreover, LMV prophylaxis may be effective in reducing mortality beyond day 200 among adult allo-HSCT recipients. [9] While most of the studies so far focused on R + recipients, seronegative patients with a seropositive donor (D+/R-), a frequent scenario in pediatric transplants, are also at risk of CMV infection/disease and the impact of LMV in such cases still needs to be confirmed.

Published experiences in children remain still scarce with only 7 small series (of maximum 17 cases), with patients mostly in late childhood or adolescence [10–18]. There is no data in infants and in patients with inborn errors of immunity (IEI). The latter group of patients are highly vulnerable to CMV infection and disease [19–20].

We report in this monocentric, real-life study, the tolerance, efficacy and preliminary PK data of LMV for CMV prophylaxis in very high-risk pediatric HSCT recipients transplanted for IEIs.

Methods & patients

Since November 2020, recipients of HSCT transplanted for IEIs at Necker Hospital (Paris, France) and considered to be at high-risk of CMV infection/disease received LMV prophylaxis. These patients could be i) R + or D+/R- transplanted with a mismatched related donor (MMRD), a mismatched unrelated donor (MMUD) or a matched unrelated donor (MUD) and free of recent episode of CS-CMVi (= primary prophylaxis); or ii) regardless on donor compatibility, recipients having experienced CS-CMVi either within 3 weeks before HCST or earlier in case of profound immunosuppression in the bridging period to transplant (= secondary prophylaxis). LMV was initiated no later than on D0 or, in case of secondary prophylaxis, as soon as CMV PCR reached the lower limit of quantification. A daily dose in milligrams was given once daily based on body surface area (BSA): BSAx480/1.73 (reduced to BSAx240/1.73 in case of CSA comedication). LMV was initiated intravenously and given orally without dose modification as soon as the patient could swallow, either with the existing tablets if the dosage was appropriate, or with reconstituted capsules of LMV provided by the hospital pharmacy. Capsules were opened and content diluted before oral administration.

CMV PCR was quantified in whole blood weekly until M3 then every 2 other weeks until M6, using the same CMV R gene assay (Argene BioMerieux®) bearing a lower limit of detection (LLOD) and a lower limit of quantification (LLOQ) of 2,6 and 2,8 $\log_{10}$ IU/ml respectively. CS-CMVi was defined as CMV disease or CMV DNAemia leading to preemptive treatment [21]. In the case of CS-CMVi, LMV was stopped and could be later reinitiated after resolution of the episode and the interruption of the preemptive/curative treatment. The duration of LMV treatment was based on immune reconstitution data.

Results were compared with an historical cohort consisting of 59 consecutive recipients of 62 transplants performed for IEIs between January 2017 and December 2019 in the same pediatric unit and fulfilling the same inclusion criteria as the LMV cohort. Patients in the historical group received antiviral prophylaxis with acyclovir 500 mg/m^2 every 8h intravenously followed by valacyclovir 6.7 mg/kg three times daily. Viral monitoring and definition of CS-CMVi were similar for both cohorts.

PK studies were performed in a sub-set of patients. Blood samples were collected at T0, T1 (end of the infusion), T2 (i.e. 2 hours after the start of the infusion), T6 and T10 a few days after LMV initiation. LMV plasma concentrations were determined using ultra high-performance liquid chromatography coupled

with tandem mass spectrometry (UPLC-MS/MS, Waters Xevo®, Milford, MA, USA) [22]. PK data were analyzed using Monolix Suite 2023R1 (Lixoft, France).

The outcomes were the tolerance, the efficacy of LMV prophylaxis and the evaluation of the PK in children. LMV tolerance was assessed by the number of reported adverse events imputable to the drug. Number, percentage and cumulative incidence of CS-CMVi and CMV disease were compared between the 2 groups. The maximum CMV PCR values, type and duration of curative treatment received by each group were also compared. Overall survival and causes of death were analyzed.

Categorical and continuous variables were compared by Chi-square or Fisher exact tests where relevant and by Mann-Whitney test, respectively. The baseline of all survival analyses was the age at HSCT. The survival without CS-CMVi and the 6-months overall survival were estimated with the Kaplan-Meier method, accommodating competing risks, and compared with the Cox model. Death from any cause, receiving another HSCT and discontinuation of LMV treatment were considered as competing risks. In the LMV group, patients were at risk only if they had already started their treatment. All analyses were performed using R software version 3.6.1 (→ Core Team, Vienna, Austria). Due to the pediatric age of the patients, LMV was prescribed outside the EMA marketing authorization but followed the French legislation. The study was in accordance with the Helsinki Declaration and approved by the local ethical committee (IRB registration n°00011928).

Results

Between November 2020 and November 2022, LMV was initiated in 31 patients, recipients of 36 transplants at a median of D0 (range: D-52 to D + 48). In 24 and 12 transplants, LMV was used as primary prophylaxis and secondary prophylaxis, respectively (see Table S1 for details on the secondary prophylaxis subgroup).

The characteristics of the historical cohort and the LMV cohort are given in Table 1 and showed no statistically significant differences in terms of age at transplant, donor compatibility, presence of CMV DNAemia in the 3 weeks prior to HSCT, intensity of conditioning, use of serotherapy, T-depletion of the graft and occurrence of GVHD. Distribution of IEIs differed between the 2 groups with slightly more T-cell immune deficiencies in the historical cohort and more primary hemophagocytic lymphohistiocytosis and phagocyte defects in the LMV cohort.

Table 1
Characteristics of the patients.

	Historical Group 62 HSCT (in 59 patients)	Letermovir Group 36 HSCT (in 31 patients)	p-value
Age – yr			
Median [IQR25-75%] (range)	4 [0.7;10.4] (0.2;17.3)	4.7 [0.6;7.6] (0.2;19.2)	0.991
Age < 1 – no. (%)	21 (33.9%)	14 (38.9%)	0.617
Male sex – no. (%)	40 (64.5%)	22 (61.1%)	0.736
Reason for HSCT – no. (%)			0.042
SCID	14 (22.6%)	5 (13.9%)	
CID	26 (41.9%)	12 (33.3%)	
HLH	5 (8.1%)	6 (16.7%)	
PIRD	6 (9.7%)	0 (0%)	
Phagocyte defects	11 (17.7%)	11 (30.6%)	
Agammaglobulinemia	0 (0%)	2 (5.6%)	
Number of HSCT – no. (%)			0.148
1st HSCT	58 (93.5%)	30 (83.3%)	
2nd HSCT	4 (6.5%)	5 (13.9%)	
3rd HSCT	0 (0%)	1 (2.8%)	
HLA matching and donor type – no. (%)			0.695
Matched unrelated	15 (24.2%)	8 (22.2%)	
Matched related	7 (11.3%)	5 (13.9%)	
Mismatched related	38 (61.3%)	20 (55.6%)	
Mismatched unrelated	2 (3.2%)	3 (8.3%)	
Stem cell source – no. (%)			0.046
Bone marrow	57 (91.9%)	28 (77.8%)	

SCID: severe combined immune deficiency, CID: combined immune deficiency, HLH: hemophagocytic lymphohistiocytosis, PIRD: primary immune regulatory disorder, HSCT: hematopoietic stem cell transplantation, GVHD: graft versus host disease. Categorical and continuous variables were compared by Chi-square or Fisher exact tests where relevant and by Mann-Whitney test, respectively.

51

	Historical Group 62 HSCT (in 59 patients)	Letermovir Group 36 HSCT (in 31 patients)	p-value
Peripheral blood	5 (8.1%)	8 (22.2%)	
CMV serological status – no. (%)			0.852
D-/R+	6 (9.7%)	2 (5.6%)	
D+/R+	36 (58.1%)	22 (61.1%)	
D+/R-	20 (32.3%)	12 (33.3%)	
CMV DNAemia within 3 weeks before HSCT – no. (%)	14 (22.6%)	9 (25%)	0.785
Myeloablative conditioning regimen – no. (%)	52 (85.2%)	31 (86.1%)	0.907
Antithymocyte globulin use – no. (%)	20 (32.3%)	9 (25%)	0.448
Alemtuzumab use – no. (%)	36 (58.1%)	24 (66.7%)	0.399
Ex vivo T-cell depletion – no. (%)	8 (12.9%)	7 (19.4%)	0.386
GVHD prophylaxis – no. (%)	60 (96.8%)	31 (86.1%)	0.096
Acute GVHD of grade 2 or more – no. (%)	19 (30.6%)	9 (25%)	0.551

SCID: severe combined immune deficiency, CID: combined immune deficiency, HLH: hemophagocytic lymphohistiocytosis, PIRD: primary immune regulatory disorder, HSCT: hematopoietic stem cell transplantation, GVHD: graft versus host disease. Categorical and continuous variables were compared by Chi-square or Fisher exact tests where relevant and by Mann-Whitney test, respectively.

Tolerance of LMV was good with only 2 patients presenting nausea and iterative vomiting concomitant to oral intake of the drug, leading to its premature discontinuation at D70 in one. No other adverse event attributable to LMV was noticed.

As compared to the historical cohort, the incidence of CS-CMVi was significantly lower in LMV group (5 out of 36 transplants (13.9%) versus 28 of the 62 HSCT (45.2%) (p = 0.002)) (Table 2). Details of the CMV viral load, sequences of antiviral treatment and characteristics of the 5 patients who experienced LMV failure are shown in Fig. 1. They did not differ from the other patients in terms of baseline characteristics. In 2 of these 5 patients, the CMV viral loads were transiently detected below the LLOQ. The 5 CS-CMVi under LMV occurred at a median of 7 days (range: 4–14) after HSCT. The maximal viral load in the LMV cohort (median 3.7 $\log_{10}$ UI/l, range not quantifiable; 3.8) was significantly lower than in the historical cohort (median 4.2 $\log_{10}$ UI/l, range 3.1; 6.5) (p = 0.025). No CMV disease occurred in the LMV cohort, compared to 4/62 (6.5%) in the historical group (p = 0.293). The durations of curative/preemptive treatment with anti CMV drugs were similar between the 2 groups. The survival without CS-CMVi was

significantly higher in the LMV group (84%, 95% CI 65; 93) than in the control group (55%, 95% CI 41; 66) (p = 0.009) (Fig. 2A). Two patients in the LMV group (5.6%) died (respectively of adenovirus infection and veno-occlusive disease (VOD) at 38 and 30 days post HSCT) as compared to 16 in the historical cohort (25.8%) (infectious causes n = 13, graft failure n = 1 and toxicities n = 2) (median 58 days post HSCT, range 5; 212). Among patients who died in the latter group, 8 (50%) experienced a CS-CMVi including 3 CMV disease (CMV colitis and CMV pneumonia in 1 patient each and CMV pneumonia, colitis, meningitis and retinitis in one). As shown in Fig. 2B, six-month overall survival (OS) was 93% (95% CI 85; 100) and 75% (95% CI 64; 87) for the LMV and the historical groups respectively (p = 0.0266).

Table 2
Efficacy endpoints.

	Control Group **62 HSCT** **(in 59 patients)**	**Letermovir Group** **36 HSCT** **(in 31 patients)**	**p-value**
Clinically significant CMV infection – no. (%)	28 (45.2%)	5 (13.9%)	0.002
Maximal CMV PCR value – median [IQR25-75%] (range) log UI/l	4.2 [3.7;4.8] (3.1;6.5)	3.7 [2.8;3.8] (NQ;3.8)	0.025
CMV disease – no. (%)	4 (6.5%)	0 (0%)	0.293
Preemptive/curative treatment used			0.001
Ganciclovir – no. (%)	9 (32.1%)	0 (0%)	
Foscavir – no. (%)	16 (57.1%)	1 (20%)	
Ganciclovir and Foscavir – no. (%)	1 (3.6%)	4 (80%)	
Brincidofovir – no. (%)	2 (7.1%)	0 (0%)	
Treatment duration – median [IQR25-75%] (range)	20.5 [14;28] (6;216)	21 [14;41] (7;64)	0.84
All-cause mortality – no. (%)	16 (25.8%)	2 (5.6%)	0.014

HSCT: hematopoietic stem cell transplantation, NQ: not quantifiable. Categorical and continuous variables were compared by Chi-square or Fisher exact tests where relevant and by Mann-Whitney test, respectively.

Three CS-CMVi among 24 HSCT (12.5%) occurred in the primary prophylaxis subgroup compared with 2 CS-CMVi out of 12 HSCT (17%) in the secondary prophylaxis subgroup (NS) (Table S2).

Among the LMV group, the emergence of mutation of resistance to LMV could not be documented in the 5 children who experienced CS-CMVi (too low CMV DNAemia (n = 3), no available blood sample (n = 2)). After treatment of CS-CMVi, LMV was resumed after the negativation of the CMV PCR due to the low level

of immune reconstitution. There was no recrudescence of the CMV DNAemia in 4 of them while in the last case (see patient 2 in Fig. 1), a second CS-CMVi occurred 1 week after the resume of LVM, followed rapidly by the patient's death due to VOD. At the most recent follow up, LMV was terminated in all but 1 patient, at a median of D155 post-HSCT (range: 47–349) and a median count of CD4 T-cells of 278/µl (range: 8-1000). Eight patients (28.6%) experienced transient low level CMV replications, left untreated in all cases because of the sufficient immune reconstitution level.

Drug monitoring with PK data were available in 8 patients (62 samples) who received intravenous LMV, including 2 infants. Their characteristics are presented in Table S3. In our setting, a two-compartment model best fitted the PK of intravenous LMV. Gender, age (considering adolescent group (12–18 years old) as reference) and the co-administration of CSA were identified as co-variates impacting LMV clearance. The PK parameters are available in Table S4. From the data at steady-state in these 8 children, the median AUC_{0-24h} was 50.9 mg.h/L (IQR25-75% 35.4–84.4) and C24h was 0.2 mg/L (IQR25-75% 0.1–0.6).

Discussion

This monocentric real-life study in a high-risk pediatric population showed that LMV was effective and well tolerated to prevent CS-CMVi. As compared to an historical cohort bearing very similar characteristics, a decreased incidence of CS-CMVi and overall mortality was documented.

While LMV has become the standard of care to prevent CS-CMVi in adult R+, the experience in children is limited. The results of the on-going prospective study aiming to evaluate PK, efficacy and tolerability of LMV at pediatric age are not yet available. Seven small series (including 2 to 17 patients) and few cases reports have been published so far [10–18] accumulating less than 70 recipients mostly transplanted for malignant diseases. Half of these reported patients were adolescent (12 years or older), the youngest being 3.5 years old. LMV dosing was heterogeneous. The patient cohort included in this study is unique in various ways. Beyond the fact that it is, to our knowledge, the largest pediatric cohort reported to date, these patients are also the youngest, the LMV dosage given was homogeneous, and preliminary PK data were generated. The median age of the 36 recipients was 4.6 years; 14 were less than 12 months old and the youngest was merely 2 months of age. All were transplanted for IEIs and were at high-risk of CMV infection/diseases with at least one risk factor previously shown to expose to these events (such as R+, active CMV infection early pre-transplant, use of mismatched donor, T-depletion of the graft, use of serotherapy, occurrence of GVHD). This profile justified the extension of the inclusion criteria beyond R + to D+/R- and patients with recent CS-CMVi before HSCT regardless of donor compatibility.

The initial dosage we used in our series was based on adult recommendations proportionally to body surface area. The dosage was modified in the case of co-medication with CSA, as recommended in adults. Plasma LMV exposures did not significantly differ from those reported in adult patients [6], also in the 2 infants for which PK was available.

Tolerance of LMV was generally good and consistent with what is described in the adult population [2, 8, 23–24]. In accordance with the tolerance assessment, no elevated plasma exposure of LMV was reported. As expected [6], we reported an increased clearance of LMV in the younger groups (both 0–2 and 2–12 years of age) compared to the adolescent group. Also, we reported a mild decrease of LMV clearance when CSA was co-administered, since the latter compound is a mild inhibitor of pump efflux transporters [7]. Surprisingly, gender seems to have a relevant impact on LMV clearance. The small number of patients with available PK data in our cohort is a limitation and does not allow firm conclusions about the dosage we used, but these promising preliminary data encourage to study it in a prospective way and to test the bioequivalence of the oral formulation for children.

Compared to our historical cohort that showed incidence of CS-CMVi in line with previous series [19, 25, 26], a lower cumulative incidence (13.9%) of CS-CMVi was observed in subjects receiving LMV prophylaxis, and no CMV disease occurred. Risk factors of developing CMV infection/disease were very similar between the LMV and historical cohorts. The only difference lies in the distribution of underlying IEIs (more HLH and phagocytes defects in the LMV group and more T cell deficiencies in the historical one). Despite this limitation, the significant difference of CS-CMVi between the 2 groups argues for the efficacy of LMV in CMV prophylaxis in our population of patients with IEIs. We did not observe any significant difference between the outcomes in primary or secondary prophylaxis subgroups, and patients in the latter subgroup were at very high-risk regarding CMV infection because, either highly immunosuppressed in the pre-transplant period, or still very early after transplant. Thus, in our cohort, LMV seemed to be also promising as a secondary prophylaxis after a treated CMV infection episode, as a bridge to HSCT and/or immune reconstitution.

The efficacy of LMV to prevent CS-CMVi is in line with the result of the phase 3 randomized controlled double-blind trial performed in adults [8] although the difference between the study populations, the design, the inclusion criteria and the duration of treatment prevent direct comparison of the results.

Among the 5 patients we documented with CS-CMVi, 2 presented transient low CMV DNAemia. The clinical significance of the viral load in these 2 patients is questionable and one could consider this to be a blip rather than a clinically relevant CMV replication. The limited experience in this population of patients and the fear of selecting mutations associated to LMV resistance prevented us from considering these values as clinically irrelevant. It also raises the question of formal criteria for defining and managing blips occurring while on LMV. Relying on CMV viral load kinetics might be a good option. Two distinct positive CMV PCR values with a significant increase might enable to distinguish the relevant patients for treatment, as suggested [27].

Beyond the benefit on the occurrence of CS-CMVi, we also documented a significant improvement of overall survival in the LMV cohort as compared to the historical cohort, with a lower all-cause mortality consistent with the data in adult patients [8, 28]. This benefit, although promising, may rely on other factors than CMV prophylaxis and needs to be confirmed in future larger pediatric prospective studies.

The occurrence of a LMV resistant strain is an important preoccupation [29], and could not be documented in the 3 patients that had a CS-CMVi with a prolonged DNAemia. This is a limitation of our study, in particular in patient 2 who presented a second CS-CMVi under LMV prophylaxis, which could suggest the emergence of a resistant strain.

Duration of LMV treatment in adult R + is currently recommended until D100. Extension up to D200 to prevent late CS-CMVi has been recently shown to be safe and efficient in adults [30] and is currently under evaluation by the FDA. Due to the patients' characteristics we treated with high risk of CMV reactivation, the long-lasting experience of our team in monitoring immune reconstitution after HSCT, LMV prophylaxis was stopped based on CD4 + T cell counts with a threshold of 200/µL CD4 T cells independently of post HSCT timing. Despite frequent transient CMV reactivation after LMV weaning, none was clinically relevant. A strategy based on a monitoring of CMV-specific T-cells is also under investigation and seems promising [31, 32]. Further studies will be needed to document the best timing and best parameters for monitoring treatment duration.

In conclusion, in this high-risk pediatric HSCT cohort transplanted for IEIs, CMV prophylaxis with LMV at a homogenous dosage was well tolerated and effective in preventing CS-CMVi compared with a historical cohort. This study included notably young children, 14 of them being 2 to 12 months old. Further studies are needed in order to corroborate our results, validate the LMV indications, the pediatric dosage and PK, and determine the best parameters to monitor treatment duration.

Declarations

Funding:

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Competing interest:

P.F. has received honoraria and travel grants from MSD France, ViiV Healthcare, Janssen Cilag, Gilead Sciences, Takeda and AiCuris for participation in advisory boards, educational programs, and conferences.

G.P. has received honoraria and travel grants from MSD France, ViiV Healthcare, Gilead Sciences and Takeda for participation in advisory boards, educational programs, and conferences.

The other authors have no relevant financial or non-financial interests to disclose.

Authors' contribution:

Thibaut César, Minh P Le, Roman Klifa, Stéphane Blanche, Pierre Frange, Gilles Peytavin and Bénédicte Neven designed the study. Thibaut César, Minh P Le, Virginie Courteille and Bénédicte Neven collected the

data. Thibaut César, Minh P Le, Pierre Frange and Bénédicte Neven analyzed the data. Mickaël Alligon performed the statistical analysis. Thibaut César, Roman Klifa, Martin Castelle, Benjamin Fournier, Romain Lévy, Marwa Chbihi, Despina Moshous and Bénédicte Neven took care of the patients. Marianne Leruez-Ville and Pierre Frange were responsible for the virologic screening. Minh P Le and Gilles Peytavin performed the pharmacokinetic studies. Thibaut César, Bénédicte Neven and Minh P Le wrote the manuscript, which was reviewed, edited, and approved by all co-authors.

Data availability

The datasets generated during the current study are available from the corresponding author on reasonable request.

Ethics approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Research Ethics Committee of Assistance Publique-Hopitaux de Paris (CERAPHP) (Date 06/06/2023 / IRB registration No 00011928).

Consent to participate

Informed consent was obtained from all individual participants included in the study, or from their parents or legal guardian.

Consent to publish

Informed consent was obtained from all individual participants included in the study, or from their parents or legal guardian.

References

1. Ljungman P, et al. Donor cytomegalovirus status influences the outcome of allogeneic stem cell transplant: a study by the European group for blood and marrow transplantation. Clin Infect Dis Off Publ Infect Dis Soc Am. Aug. 2014;59(4):473–81. 10.1093/cid/ciu364.
2. Helou GE, Razonable RR. Letermovir for the prevention of cytomegalovirus infection and disease in transplant recipients: an evidence-based review. Infect Drug Resist. 2019;12:1481–91. 10.2147/IDR.S180908.
3. Green ML et al. 'CMV Viral Load and Mortality after Hematopoietic Cell Transplantation: A Cohort Study in the Era of Preemptive Therapy', *Lancet Haematol.*, vol. 3, no. 3, pp. e119–e127, Mar. 2016, doi: 10.1016/S2352-3026(15)00289-6.
4. Lischka P et al. 'In Vitro and In Vivo Activities of the Novel Anticytomegalovirus Compound AIC246', *Antimicrob. Agents Chemother.*, vol. 54, no. 3, pp. 1290–1297, Mar. 2010, doi: 10.1128/AAC.01596-09.

57

5. Goldner T, Hewlett G, Ettischer N, Ruebsamen-Schaeff H, Zimmermann H, Lischka P. 'The Novel Anticytomegalovirus Compound AIC246 (Letermovir) Inhibits Human Cytomegalovirus Replication through a Specific Antiviral Mechanism That Involves the Viral Terminase ', *J. Virol.*, vol. 85, no. 20, pp. 10884–10893, Oct. 2011, doi: 10.1128/JVI.05265-11.
6. Prohn M et al. 'Population pharmacokinetics of letermovir following oral and intravenous administration in healthy participants and allogeneic hematopoietic cell transplantation recipients', *CPT Pharmacomet. Syst. Pharmacol.*, vol. 10, no. 3, pp. 255–267, Mar. 2021, doi: 10.1002/psp4.12593.
7. Merck & Co. Inc., 'Prevymis™ prescribing information.' 2019. Accessed: Feb. 12, 2020. [Online]. Available: https://www.merck.com/product/usa/pi_circulars/p/prevymis/ prevymis_pi.pdf.
8. Marty FM et al. 'Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation', *N. Engl. J. Med.*, vol. 377, no. 25, pp. 2433–2444, Dec. 2017, doi: 10.1056/NEJMoa1706640.
9. Vyas A, Raval AD, Kamat S, LaPlante K, Tang Y, Chemaly RF. Real-World Outcomes Associated With Letermovir Use for Cytomegalovirus Primary Prophylaxis in Allogeneic Hematopoietic Cell Transplant Recipients: A Systematic Review and Meta-analysis of Observational Studies. Open Forum Infect Dis. Dec. 2022;10(1):ofac687. 10.1093/ofid/ofac687.
10. Kuhn A et al. 'Letermovir as Cytomegalovirus Prophylaxis in a Pediatric Cohort: A Retrospective Analysis', *Transplant. Cell. Ther.*, vol. 29, no. 1, p. 62.e1-62.e4, Jan. 2023, doi: 10.1016/j.jtct.2022.10.005.
11. Richert-Przygonska M et al. 'Letermovir Prophylaxis for Cytomegalovirus Infection in Children After Hematopoietic Cell Transplantation', *Anticancer Res.*, vol. 42, no. 7, pp. 3607–3612, Jul. 2022, doi: 10.21873/anticanres.15848.
12. Cheng C-N, Li S-S, Yeh Y-H, Shen C-F, Chen J-S. 'Letermovir prophylaxis for cytomegalovirus reactivation in children who underwent hematopoietic stem cell transplantation: A single-institute experience in Taiwan', *J. Microbiol. Immunol. Infect. Wei Mian Yu Gan Ran Za Zhi*, vol. 55, no. 2, pp. 323–327, Apr. 2022, doi: 10.1016/j.jmii.2022.01.002.
13. Styczyński J, et al. Use of letermovir in off-label indications: Infectious Diseases Working Party of European Society of Blood and Marrow Transplantation retrospective study. Bone Marrow Transplant. May 2021;56(5):1171–9. 10.1038/s41409-020-01166-w.
14. Körholz KF et al. 'Letermovir for Prophylaxis and Pre-emptive Therapy of Cytomegalovirus Infection in Paediatric Allogeneic Haematopoietic Cell Transplant Patients', *Paediatr. Drugs*, vol. 25, no. 2, pp. 225–232, Mar. 2023, doi: 10.1007/s40272-022-00547-6.
15. Strenger V et al. 'Letermovir in paediatric HSCT recipients', *J. Antimicrob. Chemother.*, vol. 74, no. 9, pp. 2820–2821, Sep. 2019, doi: 10.1093/jac/dkz218.
16. Pérez Marín M et al. 'Compassionate Use of Letermovir in a 2-Year-Old Immunocompromised Child With Resistant Cytomegalovirus Disease', *J. Pediatr. Infect. Dis. Soc.*, vol. 9, no. 1, pp. 96–99, Feb. 2020, doi: 10.1093/jpids/piz033.

17. Daukshus NP et al. 'Letermovir for Cytomegalovirus Prevention in Adolescent Patients Following Hematopoietic Cell Transplantation', *J. Pediatr. Infect. Dis. Soc.*, vol. 11, no. 7, pp. 337–340, Apr. 2022, doi: 10.1093/jpids/piac017.
18. Chiereghin A, et al. Off-Label Use of Letermovir as Preemptive Anti-Cytomegalovirus Therapy in a Pediatric Allogeneic Peripheral Blood Stem Cell Transplant. Infect Drug Resist. 2021;14:1185–90. 10.2147/IDR.S296927.
19. Bateman CM, Kesson A, Powys M, Wong M, Blyth E. 'Cytomegalovirus Infections in Children with Primary and Secondary Immune Deficiencies', *Viruses*, vol. 13, no. 10, p. 2001, Oct. 2021, doi: 10.3390/v13102001.
20. Rosal T, et al. Impact of cytomegalovirus infection prior to hematopoietic stem cell transplantation in children with inborn errors of immunity. Eur J Pediatr. 2022;181(11):3889–98. 10.1007/s00431-022-04614-5.
21. Ljungman P, et al. Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials: Table 1. Clin Infect Dis. Jan. 2017;64(1):87–91. 10.1093/cid/ciw668.
22. Belabbas T, Yamada T, Tsuchiya Y, Suetsugu K, Egashira N, Ieiri I. Development and Full Validation of a Bioanalytical Method for Quantifying Letermovir in Human Plasma Using Ultra-Performance Liquid Chromatography Coupled with Mass Spectrometry. Chem Pharm Bull (Tokyo). 2021;69(7):646–51. 10.1248/cpb.c21-00142.
23. Kropeit D, von Richter O, Stobernack H-P, Rübsamen-Schaeff H, Zimmermann H. Pharmacokinetics and Safety of Letermovir Coadministered With Cyclosporine A or Tacrolimus in Healthy Subjects. Clin Pharmacol Drug Dev. 2018;7(1):9–21. 10.1002/cpdd.388.
24. Asari K, et al. Pharmacokinetics, Safety, and Tolerability of Letermovir Following Single- and Multiple-Dose Administration in Healthy Japanese Subjects. Clin Pharmacol Drug Dev. 2022;11(8):938–48. 10.1002/cpdd.1081.
25. Rastogi S, et al. Clinical and Economic Impact of Cytomegalovirus Infection among Children Undergoing Allogeneic Hematopoietic Cell Transplantation. Biol Blood Marrow Transplant. Jun. 2019;25(6):1253–9. 10.1016/j.bbmt.2018.11.028.
26. Laberko A et al. 'Mismatched related vs matched unrelated donors in TCRαβ/CD19-depleted HSCT for primary immunodeficiencies', *Blood*, vol. 134, no. 20, pp. 1755–1763, Nov. 2019, doi: 10.1182/blood.2019001757.
27. Huntley D, et al. Features of Cytomegalovirus DNAemia Blips in Allogeneic Hematopoietic Stem Cell Transplant Recipients: Implications for Optimization of Preemptive Antiviral Therapy Strategies. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. May 2020;26(5):972–7. 10.1016/j.bbmt.2020.01.015.
28. 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. Off. Publ. Infect. Dis. Soc. Am.*, vol. 70, no. 8, pp. 1525–1533, Apr. 2020, doi: 10.1093/cid/ciz490.

29. Chou S. A third component of the human cytomegalovirus terminase complex is involved in letermovir resistance. Antiviral Res. Dec. 2017;148:1–4. 10.1016/j.antiviral.2017.10.019.
30. Merck, Sharp, Dohme LLC. 'Extension of Letermovir (LET) From Day 100 to Day 200 Post-transplant for the Prevention of Cytomegalovirus (CMV) Infection in Hematopoietic Stem Cell Transplant (HSCT) Participants (MK-8228-040)'. ClinicalTrials.gov Identifier: NCT03930615.
31. Zamora D et al. 'Cytomegalovirus-specific T-cell reconstitution following letermovir prophylaxis after hematopoietic cell transplantation', *Blood*, vol. 138, no. 1, pp. 34–43, Jul. 2021, doi: 10.1182/blood.2020009396.
32. Zavaglio F, et al. Human Cytomegalovirus (HCMV) - specific T-cell response after letermovir prophylaxis is predictive for subsequent HCMV reactivation in haematopoietic stem cell transplant recipients. J Clin Virol. Aug. 2023;165:105519. 10.1016/j.jcv.2023.105519.

Figures

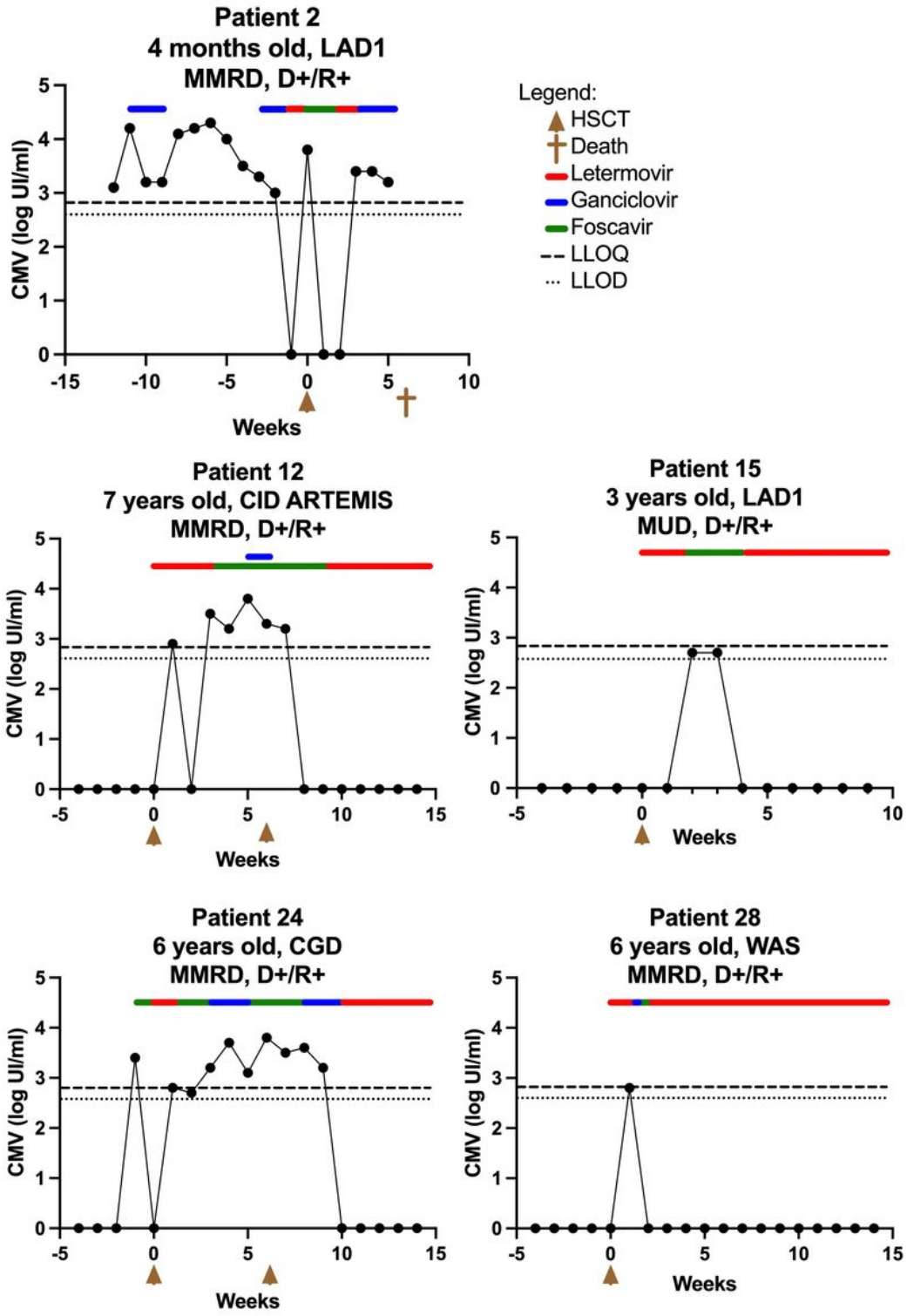


Figure 1

Representation of the virological follow-up of the 5 patients experiencing viral failure while on letermovir prophylaxis. Blood CMV DNAemia was expressed in $\log_{10}$ UI/ml.

HSCT: hematopoietic stem cell transplant, LLOQ: lower limit of quantification (2,8 log UI/ml), LLOD: lower limit of detection (2,6 $\log_{10}$ UI/ml), LAD1: leucocyte adhesion deficiency type 1, CID: combined immune

deficiency, CGD: chronic granulomatous disease, WAS: Wiskott Aldrich Syndrome

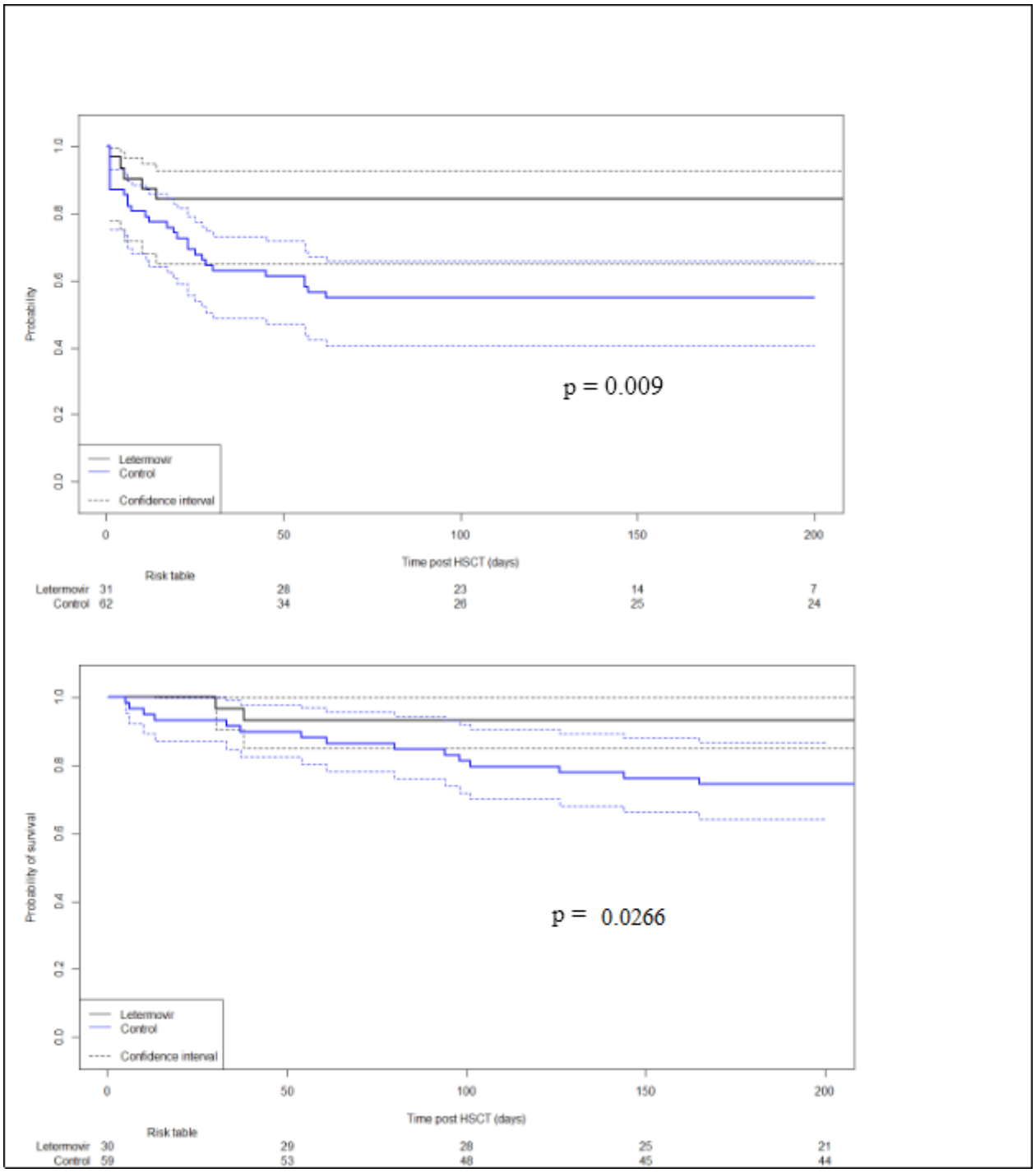


Figure 2

Survival analysis.

(A) Survival without clinically significant CMV infection. Note that 7 patients in the control group were currently treated for a clinically significant CMV infection the day of HSCT and count for an event at day 1. The clinically significant CMV infection at day 1 for the letermovir group concerned the patient 2, treated from 7 days before HSCT. The 5 patients absent of the letermovir group at D0 started the

treatment later, after the resolution of their CMV infection. (B) 6-months overall survival. The survivals were estimated with the Kaplan-Meier method, accommodating competing risks for (A), and compared with the Cox model.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- TableS1S4.docx

63

ANTICANCER RESEARCH *42*: 3607-3612 (2022)
doi:10.21873/anticanres.15848

Letermovir Prophylaxis for Cytomegalovirus Infection in Children After Hematopoietic Cell Transplantation

MONIKA RICHERT-PRZYGONSKA[1*], KAMILA JAREMEK[1*], ROBERT DEBSKI[1], JOANNA KONIECZEK[1], MONIKA LECKA[1], MAGDALENA DZIEDZIC[1], TOMASZ BOGIEL[2], JAN STYCZYNSKI[1] and KRZYSZTOF CZYZEWSKI[1]

[1]*Department of Pediatric Hematology and Oncology, Collegium Medicum, Nicolaus Copernicus University, Antoni Jurasz University Hospital, Bydgoszcz, Poland;*
[2]*Department of Microbiology, Collegium Medicum, Nicolaus Copernicus University, Antoni Jurasz University Hospital, Bydgoszcz, Poland*

Abstract. *Background/Aim: Cytomegalovirus (CMV) infection is one of the major causes of morbidity following hematopoietic cell transplantation (HCT). Allogeneic HCT (allo-HCT) recipients are at the highest risk of clinically significant CMV reactivation. While letermovir has been approved for prophylactic use in CMV seropositive adults, reports on pediatric data are very limited. The objective of the study was to examine the use of letermovir for prophylaxis from CMV infection in children undergoing allo-HCT in a single center. Patients and Methods: This retrospective matched-pair analysis study included 39 CMV-seropositive pediatric patients undergoing allo-HCT receiving letermovir as a primary prophylaxis for CMV infection on a compassionate-use basis (LMV group, n=13) or not (control group, n=26). There were no differences in basic characteristics between the analyzed groups. Among patients of the study group, 12 received primary prophylaxis with letermovir from day +1 after HCT. One patient, previously treated with ganciclovir received secondary prophylaxis from day +18. Results: Prophylactic dose of letermovir was adjusted to cyclosporine co-administration, varied in between 120-480 mg, and given orally, once daily. No CMV reactivation was observed during administration of letermovir. Cumulative incidence of CMV reactivation was significantly higher for the control group not receiving prophylaxis. Of the 13 patients of the study group, three died; however, deaths were not attributable to CMV infection. We did not observe any toxicities related to letermovir. Conclusion: Our data support letermovir prophylaxis efficacy and safety in pediatric patients after allo-HCT. Compared with the historical group, prophylactic use of letermovir decreased the number of CMV reactivations in children.*

Cytomegalovirus (CMV) infection following hematopoietic cell transplantation (HCT) is one of the major causes of morbidity in immunocompromised hosts (1-3). Over the last few decades anti-CMV preemptive therapy based on detection of CMV DNA in plasma is the standard of care (4). The use of antiviral agents reduces the incidence of CMV disease; however, it does not prevent early CMV reactivation, which is associated with lower overall survival. Moreover, CMV viral load has been identified as a surrogate clinical endpoint, which is associated with an increased risk of overall mortality and non-relapse mortality during the first year after HCT (5).

CMV-seropositive allogeneic HCT recipients are at the highest risk of clinically significant CMV reactivation. The risk factors for reactivation include: haploidentical transplantation, CMV-seronegative donors or HLA mismatch, steroids, immunosuppressive therapy for graft versus host disease (GVHD) (1, 3, 6-8).

Depending on the patient risk factors, clinically significant CMV infection (CS-CMVi) onset is being defined as virus isolation or detection of viral proteins in any tissue or body fluid sample. CMV disease is diagnosed considering a combination of clinical symptoms with CMV tissue sampling, DNAemia or documented immunochemistry recognition (9). The most common clinical manifestation of CMV infection in HCT recipients is pneumonia, hepatitis, gastroenteritis, retinitis or encephalitis. Furthermore, in these

*These Authors contributed equally to this study.

Correspondence to: Monika Richert-Przygońska (ORCID: 0000-0001-8197-5499), MD, PhD, Department of Pediatric Hematology and Oncology, Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Toruń, ul. Skłodowskiej-Curie 9, 85-094 Bydgoszcz, Poland. Tel: +48 525854860, Fax: +48 525854087, e-mail: monika_richert@yahoo.com

Key Words: Cytomegalovirus, children, letermovir, prophylaxis, transplantation.

patients indirect CMV effects increase the risk of secondary bacterial or fungal infections or the risk of GVHD development (10).

Among currently available antiviral agents with anti-CMV potential, letermovir is approved by the Food and Drug Agency (FDA) and European Medicine Agency (EMA) for CMV prophylaxis in CMV-seropositive adult patients undergoing HCT procedure. With its unique mechanism of action, letermovir binds to components of the terminase complex inhibiting replication of the CMV, effectively preventing CMV viremia in transplant recipients (1, 11-14). As described in previous adult randomized studies, letermovir significantly reduces the risk of CS-CMVi and was proven to be safe and well-tolerated (1, 4, 10). Yet, published pediatric data are limited to only few studies (15-18) and study protocols for children were not published. So far, the use of letermovir in pediatrics is off-label based.

The objective of our study was to retrospectively analyze the use of letermovir given off-label as a primary or secondary prophylaxis in children undergoing HCT in a single center.

Patients and Methods

Design of the study. This retrospective matched-pair study included 39 CMV- seropositive pediatric patients who underwent allogeneic HCT and received letermovir as a primary prophylaxis for CMV infection on a compassionate-use basis (LMV group, n=13) or not (control group, n=26). The patients in the study group were matched and compared to a historical population treated and followed at the same hospital (1:2). The matching analysis took into account CMV serology status of recipient and donor, diagnosis, conditioning and type of transplantation.

Patients. There were no differences in basic characteristics between the analyzed groups with respect to diagnosis (p=0.632), sex (male/female, 6/7 *vs*. 14/12, p=0.741), age (median, 13.2 *vs*. 12.5, p=0.233). Patient characteristics are presented in Table I.

Transplant/conditioning characteristics. In both groups, the majority of patients received myeloablative conditioning appropriate for diagnosis (69.2% *vs*. 65.4%). Patients with acute leukemias were treated with either TBI/VP (total body irradiation, vepeside), BuMel (busulfan, melfalan), FluMel (fludarabine, melfalan) or TreoFluThio (treosulfan, fludarabine, thiotepa). Lymphoma patients received either TBI/VP or TreoFlu and severe aplastic anemia patients were treated with FluCy+ATG (fludarabine, cyclophosphamide, anti-thymocyte globulin) regimens. The stem cell source was peripheral blood in 10/13 patients in the study group, and 20/26 patients in the control group. There were no differences in donor characteristics in between groups (p=0.909), 10 patients were transplanted from matched family donor (MFD), 28 were transplanted from matched unrelated donor (MUD), and one donor was haploidentical. We noted statistically significant differences in GVHD prophylaxis in between the groups (p<0.001). In the control group, GVHD prophylaxis was cyclosporine-based for all patients (n=26; 100%), while in the study group, 53.8% of patients received cyclosporine-based treatment and 46.2% were treated with post-transplant cyclophosphamide (PTCy). We did not notice any differences regarding acute GVHD development or delayed engraftment between groups (Table II).

Table I. *Patient characteristics*.

Variable	LMV	Controls	*p*-Value
Number of patients	13	26	
Sex (Male/Female)	6/7	14/12	0.741
Age (median, range) (years)	13.2 (7.1-16.9)	12.5 (4.6-16.7)	0.233
Diagnosis			0.632
Leukemia	8	16	
Aplastic anemia	3	7	
Lymphoma	2	2	
Primary immunodeficiency	0	1	
Conditioning (myeloablative)	9 (69.2%)	17 (65.4%)	0.813
Donor			0.909
MFD	4	6	
MUD	8	20	
Haploidentical	1	0	
CMV recipient positive	13	26	1.000
CMV donor positive	8 (61.5%)	20 (76.9%)	0.635
GVHD prophylaxis			<0.001
CsA-based	7 (53.8%)	26 (100%)	
PTCy-based	6 (46.2%)	0	

CMV: Cytomegalovirus; GVHD: graft *versus* host disease; CsA: cyclosporine; PTCy: post-transplant cyclophosphamide; LMV: letermovir; MFD: matched family donor; MUD: matched unrelated donor.

Criteria of inclusion. All patients in each group were CMV-seropositive before HCT and 12/13 in the study group received letermovir as primary prophylaxis. One patient diagnosed with acute lymphoblastic leukemia relapse was treated with gancyclovir due to CMV DNAemia (2,440 IU/ml) documented before HCT procedure. Once the viral load was negative, the patient started secondary prophylaxis with letermovir after transplantation.

Letermovir administration. Letermovir prophylaxis was administered orally once daily starting from day +1 after HCT, except for one patient on secondary prophylaxis, who started on day +18. Dose was adjusted to cyclosporine co-administration and calculated according to patient body weight and data available from the literature (19, 20).

Antimicrobial prophylaxis. Standard prophylactic and supportive therapy were used in all patients. Depending on conditioning regimen, patients received cefuroxime axetil, ciprofloxacin, micafungin, posaconazole, acyclovir and trimethoprim/sulfamethoxazole as antimicrobial prophylaxis.

CMV monitoring. Patients were screened for CMV DNA on weekly basis until day +100 after transplantation. Later, PCR testing was performed every 2-4 weeks. Viremia was monitored by standardized PCR with the use of PCR Cobas z480 device (Roche, Basel, Switzerland).

Definitions. We defined CMV reactivation when the virus, its antigens (proteins) or genetic material were identified in any tissue or body

fluid. Clinically significant CMV infection (CS-CMVi) was defined as viremia that required the use of antiviral therapy. While CMV disease was defined as proven disease with clinical symptoms, confirmed by new findings on imaging, combined with CMV viremia or positive results of histopathology, immunochemistry, or DNA hybridization techniques.

Bioethical issues. This retrospective study was performed as part of the project of management of viral infections after HST (Local Bioethical Committee agreement 696/2017). All patients/parents gave their consent for the use of letermovir.

Statistical analysis. The Mann-Whitney *U*-test was used for non-categorical comparisons and Chi-square test for categorical comparisons. Cumulative incidence of CMV infections was calculated using the competing risk analysis from the first day of letermovir administration. Death was considered as a competing event. A *p*-value <0.05 was considered as statistically significant.

Results

Letermovir administration. Letermovir prophylaxis was started at day +1 for primary prophylaxis (n=12) and at day +18 for secondary prophylaxis (n=1). Letermovir was administered for a median of 12 weeks, with a shortest and maximum time of treatment of 8 and 21 weeks, respectively. Prophylactic dose of letermovir was adjusted to cyclosporine co-administration and calculated by body weight and varied between 120-480 mg. In our study group, 8/13 of patients (61.5%) received 240 mg, 3/13 of patients received 120 mg, and 2/13 received 480 mg of letermovir orally once daily.

Letermovir efficacy. No CMV reactivation was observed during administration of letermovir in our study group. In weekly screening, based on molecular PCR testing (CMV DNA), we noted transient CMV DNAemia in 2 patients in the study group. None of the patients from the study group developed break through CMV disease on letermovir therapy and during follow-up period, regardless GVHD prophylactic treatment (Table II). In the control group, 16/26 patients (61.5%) developed CMV reactivation and 2/26 patients (7.7%) were diagnosed for CMV disease: 1 developed CMV encephalitis and 1 was diagnosed for multiorgan CMV disease (retinitis, typhlitis and pneumonia). Cumulative incidence of CMV reactivation was significantly higher for the historical group ($p<0.001$) (Figure 1). Follow-up period was significantly longer in the control group (median, >18 months *vs*. 4 months, $p<0.001$). During the follow up period, 3/13 patients died in the study group, and 10/26 died in the control group, and survival was comparable in both groups (66.9% *vs*. 51.5%, $p=0.343$). In patients receiving letermovir, deaths were not attributable to CMV; 1 patient died because of disease progression, 1 of GVHD with pulmonary manifestation, and 1 of septic shock complications. In the control group, we noted 2 deaths caused by active CMV infection: 1 with clinical manifestation of encephalitis and 1 with severe pneumonia and typhlitis, while the other deaths were due to relapse/progression (n=5), sepsis with multiorgan failure (n=2) or GVHD (n=1).

Table II. *Transplant outcomes*.

Variable	LMV	Controls	*p*-Value
Granulocyte engraftment	12 (92.3%)	25 (96.1%)	0.999
ANC >0.5 g/l (days after HCT) (median, range)	19 (15-24)	19 (12-25)	0.213
Platelet engraftment	11 (84.6%)	25 (96.1%)	0.253
PLT >20 g/l (days after HCT) (median, range)	15 (8-30)	16 (9-42)	0.452
Acute GVHD ≥2	6 (46.2%)	8 (30.8%)	0.351
CMV reactivation (overall)	0/13	16 (61.5%)	<0.001
CMV reactivation (CsA-based GVHD prophylaxis)	0/7	16 (61.5%)	0.007
CMV disease	0/13	2 (7.7%)	0.311
Follow-up	4 (2-13)	>18	<0.001
Relapse	1 (7.7%)	7 (26.9%)	0.166
Death	3 (23.1%)	10 (38.5%)	0.343
Death CMV-attributed	0/13	2 (7.7%)	0.543

ANC: Absolute neutrophil count; HCT: hematopoietic cell transplantation; PLT: platelet count; GVHD: graft *versus* host disease; CsA: cyclosporine; CMV: cytomegalovirus; LMV: letermovir.

Toxicity. We did not notice any delay in hematological reconstitution in the study group. No differences regarding granulocyte engraftment (92.3% *vs*. 96.1%; $p=0.999$) or platelet engraftment (84.6% *vs*. 96.1%; $p=0.253$) were found. No serious hepatotoxicity, nephrotoxicity or letermovir intolerance was described.

Discussion

In this report, we showed that administration of letermovir as a primary prophylaxis for CMV infection in children resulted in a significant decrease in CMV reactivation. Even more, in the group of 13 CMV-positive pediatric recipients, no patient reactivated CMV neither during letermovir administration nor during subsequent follow-up. Overall, our data present the excellent efficacy of letermovir in, so far, the largest pediatric analysis and obviously confirms previously published results in adults (1, 2, 10, 21, 22). Among the entire analyzed group, no breakthrough CMV infection or disease was observed. Furthermore, in the study group, we did not notice any toxicity, which could be attributable to CMV infection.

Letermovir dose administered in the pediatric group ranged between 120-480 mg, depending on concomitant cyclosporine use and calculations according to body weight. Despite off-label use of letermovir, without existing dose recommendation and therapy duration, we did not report any toxicities. In

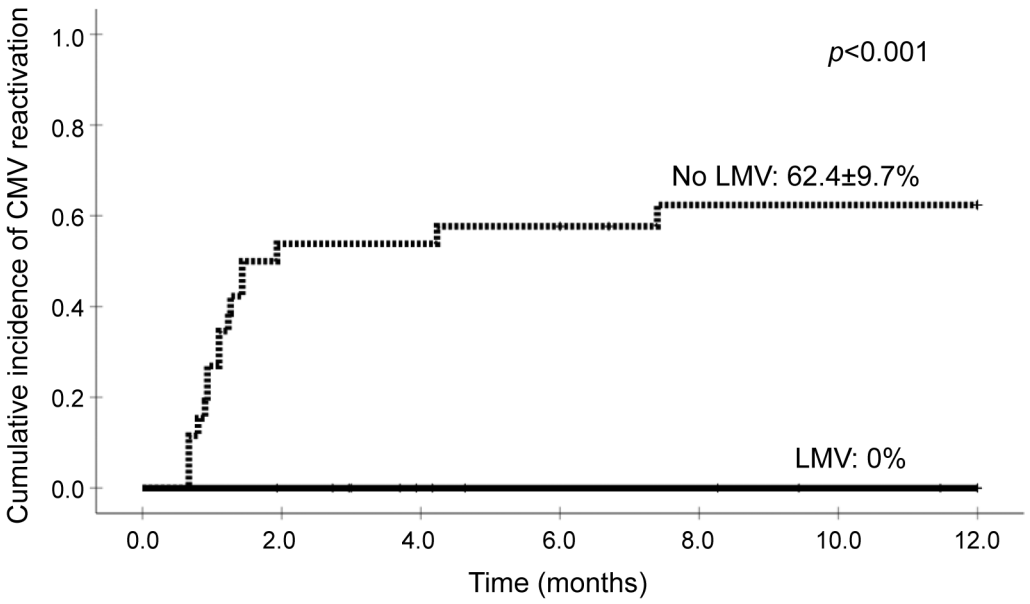


Figure 1. *Cumulative incidence of CMV reactivation.*

addition, no evidence of myelotoxicity or engraftment failure was noted. Median time of white blood cell (absolute neutrophil count >0.5 g/l) and platelets (>20 g/l) recovery was 19 days and 15 days, respectively, after HCT, and those parameters were comparable with the control group.

For comparison, we analyzed CMV reactivations in the historical group of patients which appeared in children treated with cyclosporine for GVHD prophylaxis. Analyzing the potential risk of post-transplant CMV reactivation (HLA mismatch, haploidentical donor, GVHD of grade 2 or higher or the use of *ex vivo* T-cell-depleted grafts) (1), we did not find significant differences in between the groups.

Letermovir prevented CMV reactivation in all our CMV-seropositive pediatric patients, regardless of GVHD prophylaxis. It has been reported that the use of PTCy can influence the rate of CMV viremia (23, 24). However, in our study the preventive effect of letermovir was significant also in this subgroup of patients when compared to the historical group (Table II).

There are some limitations to the study, including the small patient numbers and relatively short post-LMV follow-up. The retrospective nature is a consequence of off-label use of the drug.

In conclusion, incidence of CMV reactivation and disease was highly decreased in the group of CMV-seropositive children receiving prophylaxis with letermovir in comparison to the historic control group not receiving prophylaxis. No deaths were attributable to CMV infection in the letermovir group. Our data support the high efficacy and safety of letermovir prophylaxis in pediatric patients after allo-HCT. Further studies in children are ongoing.

Conflicts of Interest

KC participated in meetings organized by MSD. JS has received lecture fee and participated in meetings organized by MSD.

Authors' Contributions

MRP, KC, JS- study design, MRP, KJ- data analysis, MRP, KJ, KC, JS- manuscript writing, MRP, KJ, RD, JK, ML, MD, TB, KC, JS- provision of important clinical data, MRP, KJ, RD, JK, ML, MD, KC, JS- data check-up and MRP, KJ, RD, JK, ML, MD, TB, KC, JS- final approval of the manuscript.

Acknowledgements

The Authors thank all physicians and nurses for their excellent work.

References

1 Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, Haider S, Ullmann AJ, Katayama Y, Brown J, Mullane KM, Boeckh M, Blumberg EA, Einsele H, Snydman DR, Kanda Y, DiNubile MJ, Teal VL, Wan H, Murata Y, Kartsonis NA, Leavitt RY and Badshah C: Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med *377(25)*: 2433-2444, 2017. PMID: 29211658. DOI: 10.1056/NEJMoa1706640

2 Lin A, Maloy M, Su Y, Bhatt V, DeRespiris L, Griffin M, Lau C, Proli A, Barker J, Shaffer B, Giralt SA, Jakubowski AA, Papadopoulos EB, Papanicolaou GA, Seo SK and Perales MA: Letermovir for primary and secondary cytomegalovirus prevention in allogeneic hematopoietic cell transplant recipients: Real-world experience. Transpl Infect Dis *21(6)*: e13187, 2019. PMID: 31585500. DOI: 10.1111/tid.13187

3 El Helou G and Razonable RR: Letermovir for the prevention of cytomegalovirus infection and disease in transplant recipients: an evidence-based review. Infect Drug Resist *12*: 1481-1491, 2019. PMID: 31239725. DOI: 10.2147/IDR.S180908

4 Ljungman P, Schmitt M, Marty FM, Maertens J, Chemaly RF, Kartsonis NA, Butterton JR, Wan H, Teal VL, Sarratt K, Murata Y, Leavitt RY and Badshah C: A mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. Clin Infect Dis *70(8)*: 1525-1533, 2020. PMID: 31179485. DOI: 10.1093/cid/ciz490

5 Green ML, Leisenring W, Xie H, Mast TC, Cui Y, Sandmaier BM, Sorror ML, Goyal S, Özkök S, Yi J, Sahoo F, Kimball LE, Jerome KR, Marks MA and Boeckh M: Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. Lancet Haematol *3(3)*: e119-e127, 2016. PMID: 26947200. DOI: 10.1016/S2352-3026(15)00289-6

6 Schmidt-Hieber M, Labopin M, Beelen D, Volin L, Ehninger G, Finke J, Socié G, Schwerdtfeger R, Kröger N, Ganser A, Niederwieser D, Polge E, Blau IW and Mohty M: CMV serostatus still has an important prognostic impact in de novo acute leukemia patients after allogeneic stem cell transplantation: a report from the Acute Leukemia Working Party of EBMT. Blood *122(19)*: 3359-3364, 2013. PMID: 24037724. DOI: 10.1182/blood-2013-05-499830

7 Ljungman P, Brand R, Hoek J, de la Camara R, Cordonnier C, Einsele H, Styczynski J, Ward KN, Cesaro S and Infectious Diseases Working Party of the European Group for Blood and Marrow Transplantation: Donor cytomegalovirus status influences the outcome of allogeneic stem cell transplant: a study by the European group for blood and marrow transplantation. Clin Infect Dis *59(4)*: 473-481, 2014. PMID: 24850801. DOI: 10.1093/cid/ciu364

8 Dziedzic M, Sadowska-Krawczenko I and Styczynski J: Risk factors for cytomegalovirus infection after allogeneic hematopoietic cell transplantation in malignancies: Proposal for classification. Anticancer Res *37(12)*: 6551-6556, 2017. PMID: 29187429. DOI: 10.21873/anticanres.12111

9 Ljungman P, Boeckh M, Hirsch HH, Josephson F, Lundgren J, Nichols G, Pikis A, Razonable RR, Miller V, Griffiths PD and Disease Definitions Working Group of the Cytomegalovirus Drug Development Forum: Definitions of cytomegalovirus infection and disease in transplant patients for use in clinical trials. Clin Infect Dis *64(1)*: 87-91, 2017. PMID: 27682069. DOI: 10.1093/cid/ciw668

10 Marty FM, Ljungman PT, Chemaly RF, Wan H, Teal VL, Butterton JR, Yeh WW, Leavitt RY and Badshah CS: Outcomes of patients with detectable CMV DNA at randomization in the phase III trial of letermovir for the prevention of CMV infection in allogeneic hematopoietic cell transplantation. Am J Transplant *20(6)*: 1703-1711, 2020. PMID: 31883426. DOI: 10.1111/ajt.15764

11 Chemaly RF, Ullmann AJ, Stoelben S, Richard MP, Bornhäuser M, Groth C, Einsele H, Silverman M, Mullane KM, Brown J, Nowak H, Kölling K, Stobernack HP, Lischka P, Zimmermann H, Rübsamen-Schaeff H, Champlin RE, Ehninger G and AIC246 Study Team: Letermovir for cytomegalovirus prophylaxis in hematopoietic-cell transplantation. N Engl J Med *370(19)*: 1781-1789, 2014. PMID: 24806159. DOI: 10.1056/NEJMoa1309533

12 Chen K, Cheng MP, Hammond SP, Einsele H and Marty FM: Antiviral prophylaxis for cytomegalovirus infection in allogeneic hematopoietic cell transplantation. Blood Adv *2(16)*: 2159-2175, 2018. PMID: 30154125. DOI: 10.1182/bloodadvances.2018016493

13 Goldner T, Hewlett G, Ettischer N, Ruebsamen-Schaeff H, Zimmermann H and Lischka P: The novel anticytomegalovirus compound AIC246 (Letermovir) inhibits human cytomegalovirus replication through a specific antiviral mechanism that involves the viral terminase. J Virol *85(20)*: 10884-10893, 2011. PMID: 21752907. DOI: 10.1128/JVI.05265-11

14 Studer U, Khanna N, Leuzinger K, Hirsch HH, Heim D, Lengerke C, Tsakiris DA, Halter J, Gerull S, Passweg J, Medinger M and Gwerder M: Incidence of CMV replication and the role of letermovir primary/secondary prophylaxis in the early phase after allogeneic hematopoietic stem cell transplantation - a single centre study. Anticancer Res *40(10)*: 5909-5917, 2020. PMID: 32988922. DOI: 10.21873/anticanres.14611

15 Strenger V, Sperl D, Kubesch K, Donnerer J, Schwinger W, Zach K, Lackner H and Benesch M: Letermovir in paediatric HSCT recipients. J Antimicrob Chemother *74(9)*: 2820-2821, 2019. PMID: 31139834. DOI: 10.1093/jac/dkz218

16 Kilgore JT, Becken B, Varga MG, Parikh S, Prasad V, Lugo D and Chang YC: Use of letermovir for salvage therapy for resistant cytomegalovirus in a pediatric hematopoietic stem cell transplant recipient. J Pediatric Infect Dis Soc *9(4)*: 486-489, 2020. PMID: 31362308. DOI: 10.1093/jpids/piz050

17 Pérez Marín M, Decosterd LA, Andre P, Buclin T, Mercier T, Murray K, Rizzi M, Meylan P, Jaton-Ogay K, Opota O, Gengler C, Perez MH, Natterer J and Asner SA: Compassionate use of letermovir in a 2-year-old immunocompromised child with resistant cytomegalovirus disease. J Pediatric Infect Dis Soc *9(1)*: 96-99, 2020. PMID: 31183500. DOI: 10.1093/jpids/piz033

18 P Daukshus N, Cirincione A, Siver M, Mathew S, Kunvarjee B, Chan A, Boelens JJ, Seo SK, Papanicolaou GA and Kernan NA: Letermovir for cytomegalovirus prevention in adolescent patients following hematopoietic cell transplantation. J Pediatric Infect Dis Soc: piac017, 2022. PMID: 35472147. DOI: 10.1093/jpids/piac017

19 Styczyński J, Tridello G, Xhaard A, Medinger M, Mielke S, Taskinen M, Blijlevens N, Rodriguez MAB, Solano C, Nikolousis E, Biffi A, Groll AH, Junghanss C, Tsirigotis P, Lioure B, Šrámek J, Holler E, Galaverna F, Fagioli F, Knelange N, Wendel L, Gil L, de la Camara R, Mikulska M and Ljungman P: Use of letermovir in off-label indications: Infectious Diseases Working Party of European Society of Blood and Marrow Transplantation retrospective study. Bone Marrow Transplant *56(5)*: 1171-1179, 2021. PMID: 33288863. DOI: 10.1038/s41409-020-01166-w

20 Styczynski J: Prophylaxis vs preemptive therapy in prevention of cmv infection: New insight on prophylactic strategy after allogeneic hematopoietic cell transplantation. Acta Haematol Pol *51(1)*: 17-23, 2020. DOI: 10.2478/ahp-2020-0005

21 Chong PP, Teiber D, Prokesch BC, Arasaratnam RJ, Peltz M, Drazner MH and Garg S: Letermovir successfully used for secondary prophylaxis in a heart transplant recipient with ganciclovir-resistant cytomegalovirus syndrome (UL97

mutation). Transpl Infect Dis *20(5)*: e12965, 2018. PMID: 29989279. DOI: 10.1111/tid.12965

22 Beauvais D, Robin C, Thiebaut A, Alain S, Coiteux V, Ducastelle-Lepretre S, Marçais A, Ceballos P, Xhaard A, Redjoul R, Nguyen S, Brissot E, Joris M, Turlure P, Rubio MT, Chevallier P, Bénard N, Liautard C and Yakoub-Agha I: Effective Letermovir Prophylaxis of CMV infection post allogeneic hematopoietic cell transplantation: Results from the French temporary authorization of use compassionate program. J Clin Virol *148*: 105106, 2022. PMID: 35182958. DOI: 10.1016/j.jcv.2022.105106

23 Terao T, Matsuoka KI, Narita K, Tsushima T, Yuyama S, Kuzume A, Tabata R, Miura D, Takeuchi M and Matsue K: Letermovir administration to prevent cytomegalovirus reactivation is the potential risk of chronic graft-*versus*-host disease in patients who received haploidentical stem-cell transplantation with post-transplant cyclophosphamide. Front Oncol *11*: 666774, 2021. PMID: 33996594. DOI: 10.3389/fonc.2021.666774

24 Bansal R, Gordillo CA, Abramova R, Assal A, Mapara MY, Pereira MR and Reshef R: Extended letermovir administration, beyond day 100, is effective for CMV prophylaxis in patients with graft *versus* host disease. Transpl Infect Dis *23(2)*: e13487, 2021. PMID: 33034124. DOI: 10.1111/tid.13487

Received May 8, 2022
Revised June 8, 2022
Accepted June 9, 2022

Pediatric Drugs (2023) 25:225–232
https://doi.org/10.1007/s40272-022-00547-6

ORIGINAL RESEARCH ARTICLE

Letermovir for Prophylaxis and Pre-emptive Therapy of *Cytomegalovirus* Infection in Paediatric Allogeneic Haematopoietic Cell Transplant Patients

Katharina F. Körholz[1] · Miriam A. Füller[1] · Marc Hennies[2] · Malcolm Holterhus[1] · Susanne Hagedorn[1] · Martina Ahlmann[1] · Heike Thorer[1] · Birgit Burkhardt[1] · Andreas H. Groll[1]

Accepted: 16 November 2022 / Published online: 27 December 2022
© The Author(s) 2022, corrected publication 2023

Abstract

Background Cytomegalovirus (CMV) infection is a frequent event in patients undergoing allogeneic haematopoietic cell transplantation (HCT) and is associated with increased morbidity and mortality due to eventual progress to end-organ disease. Letermovir prophylaxis for CMV infections has become a standard of care in adult HCT recipients due to its efficacy and high tolerability. However, it is not yet approved for paediatric patients.

Objective In a retrospective single-centre observational study we evaluated the use of letermovir for prophylaxis or pre-emptive treatment of cytomegalovirus (CMV) infection in seropositive paediatric HCT recipients receiving the compound outside of clinical trials. The primary endpoint was CMV reactivation requiring a change of medication.

Methods A total of 17 patients (seven female/ten male; median age 12.2 [range 3.5–19] years, median body weight 39.5 [range 15–63] kg; median follow-up time 463.7 [range 41–1022] days) were identified who were started on oral (14) or intravenous (3) followed by oral (2) letermovir shortly after neutrophil engraftment at doses determined on the basis of age, weight, and concomitant cyclosporine use.

Results Five patients had no evidence of viral replication (prophylactic use), while 12 patients had varying extents of viral replication (pre-emptive therapy). A change of therapy was required in one patient due to a sustained increase in CMV viral load, and in two patients, letermovir was stopped without later reactivation after initiation of palliative care for recurrent leukaemia. Of the 14 patients who completed treatment, 3 had evidence of transient viral replication after end of treatment that required no further antiviral treatment. No patients (of 17) discontinued letermovir due to an adverse event.

Conclusion Letermovir was effective in controlling CMV infection in seropositive paediatric allogeneic HCT recipients and was overall well tolerated. Pending completion of the still ongoing paediatric investigation plans, letermovir will be an important adjunct to our options for control of infectious complications in this special population.

Key Points

Letermovir was effective in controlling CMV infection in seropositive paediatric HCT recipients.

Letermovir was well tolerated in paediatric patients.

Katharina F. Körholz and Miriam A. Füller contributed equally.

✉ Andreas H. Groll
andreas.groll@ukmuenster.de

[1] Centre for Bone Marrow Transplantation and Department of Paediatric Haematology/Oncology, University Children's Hospital, Albert-Schweitzer-Campus 1, 48129 Muenster, Germany

[2] Department for Clinical Virology, Institute of Virology, University Hospital Muenster, Muenster, Federal Republic of Germany

1 Introduction

Cytomegalovirus (CMV) infection with evidence of viral replication in blood by polymerase chain reaction (PCR) assays is a frequent event in patients undergoing allogeneic hematopoietic cell transplantation (HCT) [1, 2]. It is associated with increased morbidity and mortality due to eventual progress to end-organ disease, including chorioretinitis, pneumonia, and gastrointestinal disease [3–7]. Cytomegalovirus-seropositivity of the recipient and/or the donor is the most important risk factor for CMV infection in adults [8, 9] and is similarly associated with increased CMV infection rates in paediatric patients [7, 10].

Letermovir is an antiviral compound targeting the viral terminase complex of the cytomegalovirus [11]. Randomised controlled clinical trials in adults have demonstrated that letermovir is well tolerated and significantly reduces CMV infection and mortality in high-risk allogeneic HCT recipients receiving the compound in prophylactic intent when started within 28 days after transplant [12–14]. Since FDA approval for prophylaxis against CMV infections in CMV-seropositive adult HCT recipients in 2017, letermovir prophylaxis has become a standard of care in adult allogeneic HCT recipients who are seropositive and/or have a seropositive donor [13, 15]. Additionally, there is an increased interest in using letermovir in off-label indications, including prophylaxis of CMV-reactivation or pre-emptive therapy in paediatric patients [16]. Pre-emptive treatment with ganciclovir, foscavir or cidofovir has long been the therapy of choice for paediatric patients with CMV infection, but is associated with critically unfavourable and treatment-limiting safety profiles [17]. Therefore, there is an urgent need for the investigation of safer CMV-directed antiviral agents in paediatric patients.

A Phase IIb dose-finding study for prophylactic letermovir use in children and adolescents is ongoing but has not yet been completed or published (NCT03940586) [18]. In this single-centre retrospective study, we assess the effectiveness, safety and tolerance of prophylactic and pre-emptive off-label use of letermovir in paediatric allogeneic HCT patients who were at increased risk of CMV-infection and disease and who were not included in the ongoing clinical trial.

2 Patients and Methods

The study was a single-centre, retrospective, observational cohort study including all CMV-seropositive children, adolescents and young adults aged < 20 years who underwent allogeneic HCT between July 2019 and March 2022 and received letermovir and were not included in the ongoing dose-finding trial of the manufacturer. During that period, a total of 72 children and young adults received allogeneic HCT at our centre, 38 of whom were CMV-seropositive. Written informed consent for off-label drug use, data collection and analysis was obtained within the consent procedure for cancer treatment, HCT and specialised medical care approved by the local institutional review board.

The Centre for Bone Marrow Transplantation of the Department of Paediatric Haematology and Oncology of the University Children's Hospital of Muenster is one of the largest paediatric transplant centres in Germany with 25 to 30 allogeneic transplantations per year for standard indications in malignant and non-malignant conditions without restrictions as to the underlying condition [19]. Conditioning regimens follow the recommendations of the relevant registries and study groups [20, 21] with post-transplant immunosuppression consisting of methotrexate and cyclosporine A in the vast majority of patients, and management of acute or chronic graft-vs-host disease (GVHD) follows the recommendations of the European Society for Blood and Marrow Transplantation (EBMT [22]). Therapeutic drug monitoring is regularly performed for cyclosporine, tacrolimus and sirolimus, and for voriconazole and posaconazole if used. Prior to transplant, both recipient and donor are screened for CMV by CMV immunoassays (Elecsys® CMV IgG and IgM, cobas® e 801 system, Roche, Basel, Switzerland) and polymerase-chain reaction (PCR) investigations (artus CMV QS-RGQ Kit; QIAsymphony RGQ System, Qiagen, Hilden, Germany). Post-transplant, quantitative PCR investigations are performed once weekly, and twice weekly once CMV replication is detected. The centre is accredited by the Joint Accreditation Committee of the International Society for Cellular Therapies and the European Society for Blood and Marrow Transplantation [23].

Letermovir was commenced as prophylaxis in PCR-negative patients or as (per definition) pre-emptive therapy in asymptomatic PCR-positive patients at viral copy thresholds left to the discretion of the responsible attending physician. Dosing was based on age, body weight, and use of cyclosporine and in accordance with the preliminary dosing scheme of the ongoing paediatric dose-finding trial [18]. Patients weighing > 30 kg received adult doses of 480 mg letermovir (orally), patients weighing < 30 kg and > 18 kg received 50% reduced adult doses of letermovir (240 mg), and patients weighing < 18 kg received 25% of the adult dose (120 mg). In patients receiving concomitant cyclosporine (but not tacrolimus or sirolimus), letermovir doses were reduced by 50% in each weight cohort. Intravenous doses of letermovir were similar to oral doses, except for patients aged < 12 years and > 30 kg who received 120 mg letermovir (with and without concomitant cyclosporine).

Letermovir was continued until discontinuation of immunosuppression and stable recovery of the CD4+ lymphocyte count to at least 200 cells/µL in patients with successful suppression of viral replication, and prematurely discontinued in patients with either lack of response as measured by increasing viral replication without predefined threshold and/or signs of CMV disease, or occurrence of adverse events attributed to letermovir at the discretion of the responsible attending physician.

For analysis, the following characteristics were obtained in each patient: sex, age and weight at the time of transplant, underlying disease, CMV serostatus of donor and recipient, type of donor and transplant, day of neutrophil engraftment, CD4+ lymphocyte counts around Day +50, +100, +180, and +360 post-transplant, occurrence and treatment with steroids of GVHD, and duration of follow up. Start and duration of letermovir treatment and reason for stop of treatment; CMV replication in blood at the start of treatment, while on treatment, and at the end of treatment; occurrence of CMV-disease and reactivation of CMV after discontinuation of letermovir treatment; and adverse events attributed to letermovir were also recorded.

The primary endpoint of the descriptive analysis was defined as increases in CMV-copies/CMV-replication (reactivation) during letermovir treatment that prompted a change of antiviral medication. Adverse events resulting in discontinuation of letermovir; the impact of GVHD treatment on CMV replication under letermovir; and the occurrence of CMV-reactivation and -disease after elective discontinuation of letermovir were secondary endpoints of the study.

3 Results

A total of 17 patients (seven girls / ten boys; median [3.5–19 y] age 12.2 years, median [15–63 kg] body weight 39.5 kg) were identified who received letermovir post-transplant due to their high predicted risk to develop CMV infection and disease as assessed by the individual CMV serostatus constellation of donor and recipient (positive/negative, $n = 11$; and positive/positive, $n = 6$). The relevant patient demographics are summarised in Table 1. Nine of the patients underwent allogeneic HCT for high-risk acute leukaemia or non-Hodgkin's lymphoma, and eight for either bone marrow failure syndrome or inherited haemoglobin disorders. The majority of patients received bone marrow from a matched related or unrelated donor with post-transplant immunosuppression with methotrexate and cyclosporine A. Neutrophil engraftment occurred between Day +11 and +26, and six patients developed transient grade I or II GVHD controlled successfully with systemic steroids (Table 1).

Table 1 Demographics of 17 patients receiving letermovir between July 2019 and March 2022 off-label for prophylaxis or pre-emptive treatment

Variable/unit	No. of patients (*n*) or median ±SD	Percent (%) or range
Median age (years)	12.2 ± 5.1	3.5–19
Median weight (kg)	39.5 ± 16.3	15–63
Female sex	7	41.2
Underlying disease		
Malignant haematological disease*	9	52.9
Non-malignant haematological disease**	8	47.1
Cytomegalovirus IgG serostatus		
Donor positive/recipient positive	6	35.3
Donor positive/recipient negative	11	64.7
HLA-matching and donor type		
Matched sibling donor	4	23.5
Matched family donor	1	5.9
Matched unrelated donor	10	58.8
Mismatched unrelated donor	2	11.8
Transplant type		
Bone marrow	16	94.1
Peripheral blood stem cells	1	5.9
Immunosuppression		
Cyclosporin A	15	88.2
Tacrolimus/sirolimus	2	11.8
Neutrophil engraftment day (day post-HCT)	20.6 ± 4.3	11–26
Graft-vs-host disease (GVHD)		
Acute GVHD	6	35.3
Acute GVHD receiving steroids	6	35.3
Chronic GVHD	0	0
Stop of all immunosuppression (day post-HCT) ($n = 14$)	131.4 ± 47.6	72–259

ALL acute lymphoblastic leukaemia, *AML* acute myeloid leukaemia, *GVHD* graft-vs-host disease, *HCT* haematopoietic cell transplantation, IgG immunoglobulin G, *MDS* myelodysplastic syndromes, *NHL* non-Hodgkin lymphoma, *SCD* sickle-cell disease, *VSAA* very severe aplastic anemia

*ALL, 5 pts; AML, 1 pt; NHL, 3 pts; ** bone marrow failure syndromes (e.g., MDS, VSAA), 4 pts; inherited haemoglobin-disorders (e.g., SCD, ß-Thalassemia), 4 pts

Details of treatment with letermovir of the 17 patients are listed in Table 2. A diagram of the descriptive results is depicted in Fig. 2. In most of the patients ($n = 13$), letermovir was started post-neutrophil engraftment at a median of 27.8 days post-transplant. Five patients had no evidence of viral replication, while 12 patients had varying extents of viral replication. Letermovir was administered orally in 14 patients, intravenously in one patient, and intravenously followed by oral administration in the remaining

Table 2 Treatment details of 17 patients receiving letermovir between July 2019 and March 2022 off-label for prophylaxis or pre-emptive treatment

Variable/unit	No. of patients (*n*) or median ±SD	Percent (%) or range
Start of letermovir (day post-HCT)	27.8 ± 10	14–55
Viral replication at start of letermovir		
No	5	29.4
Yes	12	70.6
Route of administration		
Oral	14	82.3
Intravenous	1	5.9
Intravenous followed by oral	2	11.8
Letermovir daily dose		
240 mg	12	70.6
120 mg	4	23.5
60 mg	1	5.9
Treatment outcomes		
Change to other CMV directed treatment	1	5.9
Discontinuation due to intolerance	0	0
Treatment ongoing	0	0
Treatment completed	14	82.4
Transient reactivation after end of treatment	3	17.6
Duration of treatment (days) $n = 14$	139.7 ± 86.3	10–302
Follow-up after completed LTV treatment (days) $n = 14$	362.6 ± 196.4	91–665
Patients replication kinetics during treatment		
Transient increase in CMV viral load	8	47.1
Maximum viral load (1000 IU/mL) $n = 16$ *	4.7 ± 9.1	0–38.8
Patients with acute GVHD and steroid therapy	6	35.3
Transient increase in CMV viral load	3	17.6

CMV cytomegalovirus, *GVHD* graft-vs-host disease, *HCT* haematopoietic cell transplantation, *LTV* letermovir

*Pt 13 excluded due to change to ganciclovir treatment at a max. viral load of 366000 IU/mL

two patients at doses selected on the basis of age, weight, and concomitant cyclosporine use.

In one of the patients (pt. 13), letermovir was prematurely discontinued on Day 10 of treatment due to a sustained increase in the viral load and antiviral therapy was changed to ganciclovir; resistance testing was initiated with inconclusive results due to technical problems with the assay. In two patients (pts 5 and 14), letermovir was stopped without later reactivation on Days 107 and 10 of treatment, respectively, due to recurrent disease and initiation of palliative care. The remaining 14 patients (pts. 1–4, 6–13 and 15–17) received letermovir until recovery of the CD4+ lymphocyte count to >200 cells/µL and durable absence of viral replication, for a median duration of 139.7 days (Table 2). On average, a CD4+ lymphocyte count above 200 cells/µL was reached at Day +180 post-HCT, with a median CD4+ count of 352.3 cell/µL [81–1056 cells/µL].

Figure 1 depicts the course over time of the CMV viral load in plasma in the 17 patients receiving letermovir. In the five patients who were started without prior evidence of replication, only one patient had transient increases in the viral load up to a maximum of 1498 IU/mL. At end of treatment, all of the five patients had no detectable viral load (Fig. 1a). Of the 12 patients with evidence for CMV replication at start of treatment, eight patients experienced a transient increase in CMV-viral load. Ten of the 12 patients had an undetectable viral load at the end of letermovir treatment; one patient was changed to ganciclovir due to absent response to letermovir, and in one patient, letermovir was discontinued due to lymphoma relapse and palliative care (Fig. 1b). Of note, of the six patients who developed grade I/II GVHD and received short-term steroid treatment, three had a transient increase in the viral load to a maximum of 1040, 940 and 1498, IU/mL, respectively, and one had an increase to up to 366,000 IU/mL in the course of 10 days.

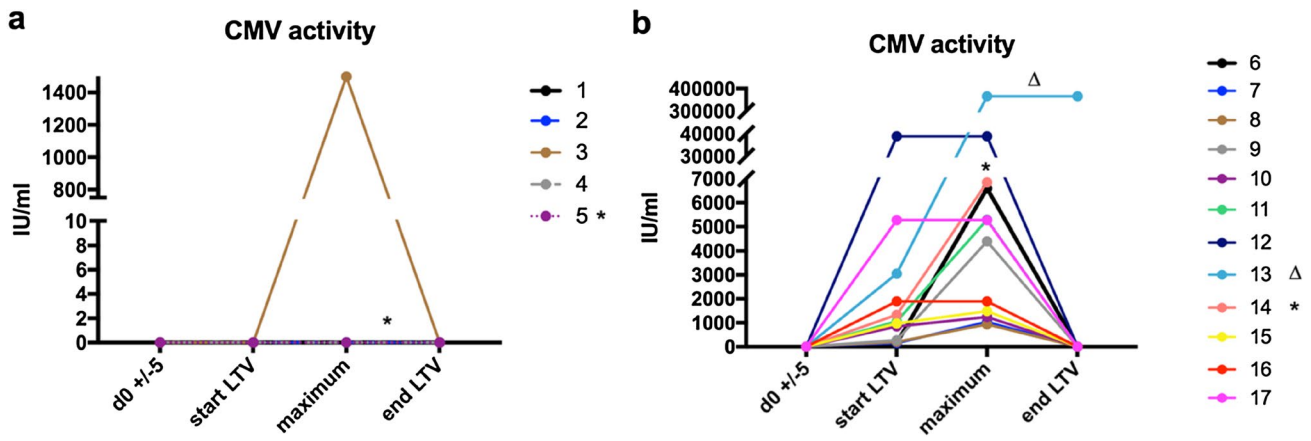


Fig. 1 Course of CMV viral load in plasma over time in 17 patients receiving letermovir between July 2019 and March 2022 off-label for prophylaxis or pre-emptive treatment. In each plot, CMV viral replication at transplant day ± 5 days, at the start of letermovir treatment, at the end of letermovir treatment and in between, the maximum observed value while on letermovir therapy with letermovir is depicted. Each line represents one individual patient. (**a**) CMV viral load in plasma in IU/mL over time in five patients with no evidence of viral replication at the time of start of treatment. * Patient (5) died before end of treatment. (**b**) CMV viral load in plasma in IU/mL over time in 12 patients with evidence of viral replication at the time of start of treatment. * Patient (14) died before end of treatment. Δ Patient (13) was changed to ganciclovir treatment. *CMV* cytomegalovirus, *LTV* letermovir

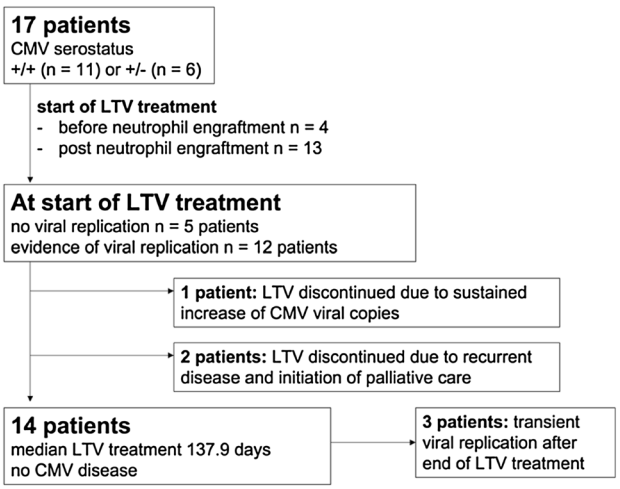


Fig. 2 Diagram depicting the descriptive results concerning viral replication status and LTV treatment status. *CMV* cytomegalovirus, *LTV* letermovir

There was no discontinuation of letermovir due to an adverse event in the 17 patients, and no patient developed CMV disease. Of the 14 patients who completed treatment, after a median follow-up time of 362.6 days after discontinuation, three had evidence of transient viral replication after the end of letermovir treatment that was followed clinically and did not require further antiviral treatment (Fig. 2, Table 2).

4 Discussion

In this single-centre, retrospective, observational cohort study including all paediatric patients at high risk for CMV reactivation who received letermovir outside of the ongoing dose-finding trial as primary prophylaxis ($n = 5$) or early pre-emptive therapy ($n = 12$), letermovir was discontinued prematurely due to a persistently high viral load in one patient who was salvaged with ganciclovir and in two further patients who were transitioned to palliative care for recurrent disease. In 14 patients who completed treatment, transient reactivations after the end of treatment without need for intervention occurred in three patients. Letermovir was overall well-tolerated, and no patients developed treatment-limiting adverse events.

Transient increases in the CMV viral load in plasma were not infrequent while on treatment with letermovir and were observed in 5 of 11 patients (45%) without and in 3 of 6 patients (50%) with acute GVHD receiving steroid treatment. While the occurrence of GVHD is a well-described risk factor for the development of CMV reactivation [13, 24–27], the latter appeared not to have been influenced by the presence of GVHD during letermovir exposure. Supporting the efficacy of letermovir in our study, no breakthrough CMV infections were reported by others in children with off-label prophylactic letermovir treatment [16, 27]. Styczynski et al, in an EBMT-initiated multicentre, retrospective observational study, reported an incidence of CMV breakthrough infections in patients (adults and children) with letermovir prophylaxis of approximately 10% [16]. However, transient increases

in the CMV viral load were not captured in that study. Most patients included in this study (70%) received letermovir per definition as pre-emptive treatment following documented CMV reactivation, and most responded very well to letermovir treatment. There are only few reports for letermovir pre-emptive therapy or secondary prophylaxis in children, which show, however, overall high viral clearance rates [16, 28, 29]. In adult patients, a Phase 2a study was conducted for pre-emptive letermovir treatment in kidney transplant recipients [30] and experiences with letermovir secondary prophylaxis in HSCT recipients have been previously published [16, 31]. However, at the time of the writing of this article, letermovir is approved for prophylaxis of CMV reactivation only [13, 16] and approval of this indication in paediatric patients is pending until completion of the ongoing paediatric dose-finding trial.

We found that letermovir was overall very well tolerated: there were no treatment discontinuations due to adverse events thought to be related to letermovir treatment. This observation is in line with previous reports of letermovir use in paediatric patients, where letermovir provoked common adverse events such as nausea and vomiting [16, 27] or mild liver function impairment [27, 29] but did not result in letermovir discontinuation. With a median treatment duration of 132.6 days, even long-term use of letermovir was well tolerated in our cohort. In one patient, letermovir had to be discontinued due to absent response to letermovir pre-emptive therapy. While resistance testing in our patient was prompted but was unsuccessful due to technical problems with the assay, resistance to letermovir has been linked to mutations in a gene for the viral terminase subunit (UL56) that does not affect susceptibility to ganciclovir treatment [32, 33]. In line with these findings, breakthrough CMV-viremia in our patient could be cleared with ganciclovir treatment.

A limitation of our study is the lack of a comparator group receiving alternative CMV prophylaxis or pre-emptive treatment. Therefore, no statistical analyses regarding efficacy and safety can be derived from the study. To date, there are limited reports of letermovir use in children [16, 27–29, 34, 35] with overall very small sample sizes, underlining the need for more analysis of letermovir prophylaxis or pre-emptive treatment in children.

5 conclusions

In conclusion, the results of this necessarily limited analysis suggest that letermovir is well tolerated even for long-term use and effective in CMV prophylaxis and pre-emptive treatment in paediatric patients with high-risk CMV constellations undergoing allogeneic HCT. The demonstration of effective prevention of CMV infection and disease without haematological or renal adverse events with letermovir [13] is a breakthrough in infectious disease supportive care in allogeneic HCT recipients, which needs to be made available to children and adolescents by appropriate dose-findings studies. In addition, further studies are required to investigate the role of letermovir for pre-emptive treatment of CMV infections.

Declarations

Financial support Open Access funding enabled and organized by Projekt DEAL.

Conflicts of interest AHG has received grants from Gilead, Merck, Sharp & Dohme and Pfizer and has served as consultant to Amplyx, Astellas, Basilea, F2G, Gilead. Merck, Sharp & Dohme, Pfizer, Scynexis, and Mundipharma. KFK, MAF, MTH, MH, SAH, MA, HT and BB have no conflicts to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to participate Written informed consent for off label drug use, data collection and analysis was obtained within the consent procedure for cancer treatment, HCT and specialized medical care approved by the local institutional review board. Informed consent to be included in this analysis was waived as the study did not involve additional procedures to the standardized clinical protocols and all data were treated in an anonymous fashion.

Consent for publication All authors give the publisher the permission to publish the work.

Subjects signed informed consent Not applicable.

Data availability statement The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contribution statement All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Miriam A. Füller, Katharina F. Körholz, and Marc Hennies. Malcolm Holterhus, Susanne Hagedorn, Martina Ahlmann, Heike Thorer and Birgit Burkhardt were in charge of patients treatment and patient data collection. The first draft of the manuscript was written by Katharina F. Körholz and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Open Access This article is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License, which permits any non-commercial use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission

directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by-nc/4.0/.

References

1. Ljungman P, de la Camara R, Robin C, Crocchiolo R, Einsele H, Hill JA, Hubacek P, Navarro D, Cordonnier C, Ward KN. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). Lancet Infect Dis. 2019;19:e260–72. https://doi.org/10.1016/s1473-3099(19)30107-0.
2. Solano C, Vázquez L, Giménez E, de la Cámara R, Albert E, Rovira M, Espigado I, Calvo CM, López-Jiménez J, Suárez-Lledó M, et al. Cytomegalovirus DNAemia and risk of mortality in allogeneic hematopoietic stem cell transplantation: analysis from the Spanish hematopoietic transplantation and cell therapy group. Am J Transplant. 2021;21:258–71. https://doi.org/10.1111/ajt.16147.
3. Teira P, Battiwalla M, Ramanathan M, Barrett AJ, Ahn KW, Chen M, Green JS, Saad A, Antin JH, Savani BN, et al. Early cytomegalovirus reactivation remains associated with increased transplant-related mortality in the current era: a CIBMTR analysis. Blood. 2016;127:2427–38. https://doi.org/10.1182/blood-2015-11-679639.
4. Jang JE, Hyun SY, Kim YD, Yoon SH, Hwang DY, Kim SJ, Kim Y, Kim JS, Cheong JW, Min YH. Risk factors for progression from cytomegalovirus viremia to cytomegalovirus disease after allogeneic hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2012;18:881–6. https://doi.org/10.1016/j.bbmt.2011.10.037.
5. Green ML, Leisenring W, Xie H, Mast TC, Cui Y, Sandmaier BM, Sorror ML, Goyal S, Özkök S, Yi J, et al. Cytomegalovirus viral load and mortality after haemopoietic stem cell transplantation in the era of pre-emptive therapy: a retrospective cohort study. Lancet Haematol. 2016;3:e119-127. https://doi.org/10.1016/s2352-3026(15)00289-6.
6. Ariza-Heredia EJ, Nesher L, Chemaly RF. Cytomegalovirus diseases after hematopoietic stem cell transplantation: a mini-review. Cancer Lett. 2014;342:1–8. https://doi.org/10.1016/j.canlet.2013.09.004.
7. Zöllner SK, Herbrüggen H, Kolve H, Mihailovic N, Schubert F, Reicherts C, Rössig C, Groll AH. Cytomegalovirus retinitis in children and adolescents with acute leukemia following allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis. 2019;21: e13089. https://doi.org/10.1111/tid.13089.
8. George B, Pati N, Gilroy N, Ratnamohan M, Huang G, Kerridge I, Hertzberg M, Gottlieb D, Bradstock K. Pre-transplant cytomegalovirus (CMV) serostatus remains the most important determinant of CMV reactivation after allogeneic hematopoietic stem cell transplantation in the era of surveillance and pre-emptive therapy. Transpl Infect Dis. 2010;12:322–9. https://doi.org/10.1111/j.1399-3062.2010.00504.x.
9. Schmidt-Hieber M, Tridello G, Ljungman P, Mikulska M, Knelange N, Blaise D, Socié G, Volin L, Blijlevens N, Fegueux N, et al. The prognostic impact of the cytomegalovirus serostatus in patients with chronic hematological malignancies after allogeneic hematopoietic stem cell transplantation: a report from the Infectious Diseases Working Party of EBMT. Ann Hematol. 2019;98:1755–63. https://doi.org/10.1007/s00277-019-03669-z.
10. Heston SM, Young RR, Tanaka JS, Jenkins K, Vinesett R, Saccoccio FM, Martin PL, Chao NJ, Kelly MS. Risk factors for CMV viremia and treatment-associated adverse events among pediatric hematopoietic stem cell transplant recipients. Open Forum Infect Dis. 2022;9:639. https://doi.org/10.1093/ofid/ofab639.
11. Goldner T, Hewlett G, Ettischer N, Ruebsamen-Schaeff H, Zimmermann H, Lischka P. The novel anticytomegalovirus compound AIC246 (Letermovir) inhibits human cytomegalovirus replication through a specific antiviral mechanism that involves the viral terminase. J Virol. 2011;85:10884–93. https://doi.org/10.1128/jvi.05265-11.
12. Ljungman P, Schmitt M, Marty FM, Maertens J, Chemaly RF, Kartsonis NA, Butterton JR, Wan H, Teal VL, Sarratt K, et al. A mortality analysis of letermovir prophylaxis for cytomegalovirus (CMV) in CMV-seropositive recipients of allogeneic hematopoietic cell transplantation. Clin Infect Dis. 2020;70:1525–33. https://doi.org/10.1093/cid/ciz490.
13. Marty FM, Ljungman P, Chemaly RF, Maertens J, Dadwal SS, Duarte RF, Haider S, Ullmann AJ, Katayama Y, Brown J, et al. Letermovir prophylaxis for cytomegalovirus in hematopoietic-cell transplantation. N Engl J Med. 2017;377:2433–44. https://doi.org/10.1056/NEJMoa1706640.
14. Marty FM, Ljungman PT, Chemaly RF, Wan H, Teal VL, Butterton JR, Yeh WW, Leavitt RY, Badshah CS. Outcomes of patients with detectable CMV DNA at randomization in the phase III trial of letermovir for the prevention of CMV infection in allogeneic hematopoietic cell transplantation. Am J Transplant. 2020;20:1703–11. https://doi.org/10.1111/ajt.15764.
15. Jakharia N, Howard D, Riedel DJ. CMV infection in hematopoietic stem cell transplantation: prevention and treatment strategies. Curr Treat Options Infect Dis. 2021;13:123–40. https://doi.org/10.1007/s40506-021-00253-w.
16. Styczynski J, Tridello G, Xhaard A, Medinger M, Mielke S, Taskinen M, Blijlevens N, Rodriguez MAB, Solano C, Nikolousis E, et al. Use of letermovir in off-label indications: infectious diseases working party of European society of blood and marrow transplantation retrospective study. Bone Marrow Transplant. 2021;56:1171–9. https://doi.org/10.1038/s41409-020-01166-w.
17. Wattles BA, Kim AJ, Cheerva AC, Lucas KG, Elder JJ. Cytomegalovirus treatment in pediatric hematopoietic stem cell transplant patients. J Pediatr Hematol Oncol. 2017;39:241–8. https://doi.org/10.1097/mph.0000000000000730.
18. Merck Sharp & Dohme LLC: Letermovir treatment in pediatric participants following allogeneic haematopoietic stem cell transplantation (HSCT) (MK-8228-030). Availabe online: https://clinicaltrials.gov/ct2/show/NCT****03940586?term=NCT****03940586&draw=2&rank=1 (accessed on 03/11/2022).
19. Medizinische Klinik A / Klinik für Kinder- und Jugendmedizin - Pädiatrische Hämatologie und Onkologie: UKM Knochenmarktransplantationszentrum. Availabe online: https://www.ukm.de/zentren/knochenmarktransplantationszentrum (accessed on 2022/08/27).
20. Reinken K., GrünEberg I.: Kinderkrebsinfo. Availabe online: https://www.gpoh.de/kinderkrebsinfo/content/diseases/index_eng.html (accessed on 03/11/2022).
21. Dobke J., Grüneberg I.. Kinderblutkrankheiten. Availabe online: https://www.kinderblutkrankheiten.de (accessed on 03/11/2022).
22. The EBMT Handbook: Hematopoietic Stem Cell Transplantation and Cellular Therapies [Internet]. 7th edition., 7th ed.; Enric Carreras, C.D., Mohamad Mohty, Nicolaus Kröger, Ed. Springer Nature, pp. 702. https://doi.org/10.1007/978-3-030-02278-5.
23. Joint Accreditation Committee of the International Society for Cell & Gene Therapies; JACIE. Availabe online: https://www.ebmt.org/jacie-accreditation (accessed on 2022/10/27).
24. Meyers JD, Flournoy N, Thomas ED. Risk factors for cytomegalovirus infection after human marrow transplantation. J Infect Dis. 1986;153:478–88. https://doi.org/10.1093/infdis/153.3.478.
25. Jaing TH, Chang TY, Chen SH, Wen YC, Yu TJ, Lee CF, Yang CP, Tsay PK. Factors associated with cytomegalovirus infection

in children undergoing allogeneic hematopoietic stem-cell transplantation. Medicine (Baltimore). 2019;98: e14172. https://doi.org/10.1097/md.0000000000014172.
26. Marty FM, Bryar J, Browne SK, Schwarzberg T, Ho VT, Bassett IV, Koreth J, Alyea EP, Soiffer RJ, Cutler CS, et al. Sirolimus-based graft-versus-host disease prophylaxis protects against cytomegalovirus reactivation after allogeneic hematopoietic stem cell transplantation: a cohort analysis. Blood. 2007;110:490–500. https://doi.org/10.1182/blood-2007-01-069294.
27. Cheng CN, Li SS, Yeh YH, Shen CF, Chen JS. Letermovir prophylaxis for cytomegalovirus reactivation in children who underwent hematopoietic stem cell transplantation: a single-institute experience in Taiwan. J Microbiol Immunol Infect. 2022. https://doi.org/10.1016/j.jmii.2022.01.002.
28. Chiereghin A, Belotti T, Borgatti EC, Fraccascia N, Piccirilli G, Fois M, Borghi M, Turello G, Gabrielli L, Masetti R, et al. Off-label use of letermovir as pre-emptive anti-cytomegalovirus therapy in a pediatric allogeneic peripheral blood stem cell transplant. Infect Drug Resist. 2021;14:1185–90. https://doi.org/10.2147/idr.S296927.
29. Strenger V, Sperl D, Kubesch K, Donnerer J, Schwinger W, Zach K, Lackner H, Benesch M. Letermovir in paediatric HSCT recipients. J Antimicrob Chemother. 2019;74:2820–1. https://doi.org/10.1093/jac/dkz218.
30. Stoelben S, Arns W, Renders L, Hummel J, Mühlfeld A, Stangl M, Fischereder M, Gwinner W, Suwelack B, Witzke O, et al. Pre-emptive treatment of Cytomegalovirus infection in kidney transplant recipients with letermovir: results of a Phase 2a study. Transpl Int. 2014;27:77–86. https://doi.org/10.1111/tri.12225.
31. Lin A, Maloy M, Su Y, Bhatt V, DeRespiris L, Griffin M, Lau C, Proli A, Barker J, Shaffer B, et al. Letermovir for primary and secondary cytomegalovirus prevention in allogeneic hematopoietic cell transplant recipients: real-world experience. Transpl Infect Dis. 2019;21: e13187. https://doi.org/10.1111/tid.13187.
32. Chou S. Rapid in vitro evolution of human cytomegalovirus UL56 mutations that confer letermovir resistance. Antimicrob Agents Chemother. 2015;59:6588–93. https://doi.org/10.1128/aac.01623-15.
33. Lischka P, Michel D, Zimmermann H. Characterization of cytomegalovirus breakthrough events in a phase 2 prophylaxis trial of letermovir (AIC246, MK 8228). J Infect Dis. 2016;213:23–30. https://doi.org/10.1093/infdis/jiv352.
34. Kilgore JT, Becken B, Varga MG, Parikh S, Prasad V, Lugo D, Chang YC. Use of letermovir for salvage therapy for resistant cytomegalovirus in a pediatric hematopoietic stem cell transplant recipient. J Pediatr Infect Dis Soc. 2020;9:486–9. https://doi.org/10.1093/jpids/piz050.
35. Pérez Marín M, Decosterd LA, Andre P, Buclin T, Mercier T, Murray K, Rizzi M, Meylan P, Jaton-Ogay K, Opota O, et al. Compassionate use of letermovir in a 2-year-old immunocompromised child with resistant cytomegalovirus disease. J Pediatric Infect Dis Soc. 2020;9:96–9. https://doi.org/10.1093/jpids/piz033.

Wang X, Jiang C, Liu L, et al. Efficacy and safety of primary letermovir prophylaxis for cytomegalovirus infection in paediatric patients undergoing allogeneic transplantation: a single-centre, retrospective, real-world analysis. *Clinical Hematology International*. 2025;7(1):36-46. doi:10.46989/001c.131683. PMID:40092047

Retrospective study

EFFICACY AND SAFETY OF PRIMARY LETERMOVIR PROPHYLAXIS FOR CYTOMEGALOVIRUS INFECTION IN PAEDIATRIC PATIENTS UNDERGOING ALLOGENEIC TRANSPLANTATION: A SINGLE-CENTRE, RETROSPECTIVE, REAL-WORLD ANALYSIS

Xin Wang[1,2a], Chaoqian Jiang[1,2b], Lipeng Liu[1,2c], Xia Chen[1,2], Yuanyuan Ren[1,2], Yang Wan[1,2], Aoli Zhang[1,2], Xiaoyan Zhang[1,2], Yue Shang[1,2], Yao Zou[1,2], Xiaojuan Chen[1,2], Fang Liu[1,2], Wenyu Yang[1,2], Xiaofan Zhu[1,2d], Ye Guo[1,2e]

[1] Department of Paediatric Hematology, Institute of Hematology & Blood Diseases Hospital, Tianjin, China, [2] Tianjin Institutes of Health Science, Tianjin, China

Keywords: Hematopoietic Stem Cell Transplantation, Paediatrics, Cytomegalovirus, Infectious complications in hematological malignancies, Letermovir

https://doi.org/10.46989/001c.131683

Clinical Hematology International

Vol. 7, Issue 1, 2025

BACKGROUND

Cytomegalovirus (CMV) infection is a common and life-threatening complication following allogeneic haematopoietic stem cell transplantation (allo-HSCT). Letermovir (LET) has been the standard prophylaxis for adult recipients, but studies in children remain limited.

METHODS

We retrospectively analyzed children with or without LET prophylaxis after haploidentical donor (HID) for the Beijing protocol or unrelated cord blood (UCB) transplantation.

RESULTS

Of the 151 patients, 67 received LET, including 35 HID recipients and 32 UCB recipients. During the 180 days after transplantation, we found that the LET group had a lower incidence of clinically significant CMV infection (csCMVi) than the non-LET group (13.4% vs. 56.0%, $P < 0.001$). In the LET group, later LET administration was identified as a risk factor for the occurrence of csCMVi (HR: 1.07, 95% CI: 1.01 - 1.14, P=0.029). Further, the HID subgroup had a lower incidence of csCMVi during follow-up than the UCB subgroup (2.9% vs. 25.0%, P=0.009). In terms of safety, the incidence and severity of adverse events, overall survival, cumulative incidence of relapse, relapse free survival, nonrelapse mortality and graft versus host disease-free, relapse-free survival were similar between the two groups.

CONCLUSION

LET is effective and safe in preventing csCMVi among Chinese children undergoing allo-HSCT. Compared to UCB recipients, children undergoing HID transplantation for the Beijing protocol develop less scCMVi up to 180 days post-HSCT.

a These authors contributed equally to this work

b These authors contributed equally to this work

c These authors contributed equally to this work

d Corresponding author. Xiaofan Zhu, e-mail: xfzhu@ihcams.ac.cn

e Corresponding author. Ye Guo, e-mail: guoye@ihcams.ac.cn

INTRODUCTION

Cytomegalovirus (CMV) infection is a common and life-threatening complication following allogeneic hematopoietic stem cell transplantation (allo-HSCT). It is estimated that 10 to 40% of patients underwent HSCT will develop CMV infection, with a mortality rate as high as 70%. Notably, patients were defined as being a high risk of CMV disease if they received stem cells from unrelated cord blood (UCB) or haploidentical donors (HID), due to their delayed immune reconstitution (IR) and HLA disparity.[1,2]

Letermovir (LET) is a novel exclusive anti-CMV drug that acts by inhibiting the CMV terminase complex and has been successfully confirmed to reduce clinically significant CMV infection (csCMVi) with good tolerability. Since a landmark prospective, randomized, large-scale cohort studies,[3] it has been recommended as the standard prophylaxis for adult seropositive recipients following allo-HSCT by the US Food and Drug Administration (FDA) and the European Conference on Infections in Leukaemia (ECIL 7).[1,3] Subsequently, several studies also unequivocally demonstrated the efficacy and safety of LET in mitigating the risk of CMV disease, particularly among those identified as being at high risk.[4-6] Although the partially published data from the ongoing Phase 2b non-randomized, multicenter, open-label, sequential dose escalation study (NCT03940586; MK-8228-030) indicateed the efficacy and safety of using adult doses of LET in children aged 12-18 years,[7] the use of LET in pediatric patients was still considered off-label, especially in those under the age of 12. Currently, there are several small retrospective cohort studies that have confirmed the efficacy and safety of LET in children,[8-11] but less studies have further explored it in the context of alternative donors.

Here, we retrospectively evaluated the efficacy and safety of primarily prophylactic LET for paediatric patients who underwent UCB or HID transplantation.

MATERIALS AND METHODS

PATIENTS AND STUDY DESIGN

A total of 151 children underwent allo-HSCT between January 2021 and December 2023 at the Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences. Sixty-seven patients who received LET prophylaxis after allo-HSCT were compared retrospectively with eighty-four patients without.

Because infection affects 20% to 30% of CMV-seronegative recipients who have undergone transplantation from CMV-seropositive donors,[12] and the effectiveness of LET in these recipients is specified in the Risk Management Plan mandated by the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan,[13] Our study included these recipients. The primary end point was the incidence of csCMVi within 180 days post-HSCT, which was defined as CMV viremia or the application of preemptive treatment (PET). The secondary end point was the occurrence of adverse events (AEs) and post-transplant outcomes. The median follow-up time for the LET group and the non-LET group was 417 (22-796) and 732.5 (96-1253) days, respectively.

LET PROPHYLAXIS AND CMV MANAGEMENT

The dosages of letermovir were based on body surface area (BSA), specifically BSA/1.73×480mg. The patients who received concomitant cyclosporine (CsA) were administered half a dose of letermovir, BSA/1.73×240mg. According to the medication instructions, we began administering letermovir after allo-HSCT. The median interval from transplantation to LET administration was 10 (1-44) days, and the treatment was continued until day +100 post-transplantation.

We routinely measured the CMV-DNA load in plasma using real-time quantitative polymerase chain reaction (qPCR). This was done twice a week until neutrophil engraftment, then once a week until 100 days post-HSCT, and during subsequent outpatient follow-up visits. CMV DNAemia was defined in accordance with our institu tional guidelines as treatment initiated after CMV-DNA load >125 IU/mL (1000 copies/ml).[14] Due to the bleeding tendency observed in the pediatric patients, the diagnosis of suspected CMV gastrointestinal disease in this study was based on clinical symptoms and CMV DNA in stool samples, without the conduct of histological biopsy. The anti-CMV drugs (intravenous ganciclovir or foscarnet) for PET were selected at the physician 's discretion.

DEFINITIONS

The hematopoietic cell transplantation-specific comorbidity index (HCT-CI) were defined according to Sorror et al.[15] ADs included neutrophil graft failure, any organ impairment and orther infection. Neutrophil engraftment was defined as the first of 3 successive days with an absolute neutrophil count of ⩾500/μl after post-transplantation.[16] The hepatic, renal, and cardiac impairment was according to AST, ALT, Cr, and TnI levels, and their grade referring to the Common Terminology Criteria for Adverse Events (CTCAE - Version 5.0). The overall survival (OS), cumulative incidence of relapse (CIR), relapse free survival (RFS), nonrelapse mortality (NRM), graft versus host disease (GVHD), and GVHDfree, relapse-free survival (GRFS) were assessed as post-transplant outcomes and calculated from the date of HSCT. GRFS events were defined as grade III–IV acute GVHD (aGVHD), moderate to severe chronic GVHD (cGVHD), disease relapse, or death from any cause after HSCT.

STATISTICAL ANALYSES

Continuous variables are expressed using the average (range), while categorical variables are represented using number (percentage). Categorical variables were appropriately evaluated using the Chi-square test, while continuous variables were assessed using the Mann-Whitney U test. A cumulative incidence curve was utilized for comparing cumulative incidence of csCMVi, GVHD, CIR and NRM. The OS, RFS, and GRFS were estimated using the Kaplan-Meier

method and compared with the log-rank test. Cox proportional hazards model was conducted to assess the relationships between clinical factors and csCMVi. A P value greater than 0.05 was considered statistically insignificant when using a two-tailed test. Statistical analyses were performed using R version 4.3.0.

RESULTS

STUDY POPULATION

A total of 151 patients were included, consisting of 67 in the LET group and 84 in the non-LET group. The two groups had well balanced clinical and transplantation characteristics (Table 1). The preexisting disorders included lymphoma and bone marrow failure (BMF), acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), myelodysplastic syndromes (MDS), myelodysplastic/myeloproliferative neoplamsms (MDS/MPN), hybrid acute leukemia (HAL). All HID recipients underwent the Beijing protocol, which included antithymocyte globulin (ATG), and none had received alemtuzumab or undergone ex vivo T-cell depletion

EFFICIENCY ANALYSIS

At the 180 days after transplantation, the cumulative incidence of csCMVi was significantly different between the LET group and the non-LET group (9/67 [13.4%] vs.46/84 [56.0%], P<0.001) (Figure 1A). Further, among patients who reached the primary end point, the LET group had later a later average time of infection onset (day +71 [25-147] vs.+41 [22-115] after transplantation, P=0.306), lower average CMV-DNA peak load (343 [136-811] vs. 1080 [134-7187] IU/ml, P=0.015) and shorter average duration (11 [2-18] vs. 19 [3-53] days, P=0.113) than the non-LET group (Figure 1B&C). In Cox proportional hazards model, LET administration was identified as an independent favourable factor for protecting children from csCMVi (hazard ratio [HR] 0.19, 95% CI 0.09 - 0.40, P<0.001) (Figure 2). A few patients developed suspected CMV infection, affecting the gastrointestinal tract in all cases, with 4/67 (6.0%) in the LET group and 6/84 (7.1%) in the non-LET group. Finally, all successfully treated with antiviral therapy (ganciclovir / foscarnet).

Among the LET group, there were 9 children developed csCMVi. Their clinical features prior to their first csCMVi were presented in Table 2. Their average age was 7.7 years, similar to the average age of the LET group, which was 7.6 years. All pediatric patients were administered Letermovir up to 100 days post-transplantation. Although a few patients experienced csCMVi after discontinuation of LET, they did not resume LET treatment. 6/67 (9.0%) developed breakthrough CMV infection, including 5 receiving UCB transplantation and 1 receiving HID transplantation (P=0.071). Their average time of csCMVi was day +36 (25 - 46) post-HSCT, their average CMV-DNA peak load was 319 (136 - 811) IU/ml, and their average duration of CMVi was 11 (5 - 18) days. After viral clearance, two patients (Pt 4 and Pt 6) developed recurrent csCMVi. Pt 4 developed breakthrough infection again at day +95 post-transplantation, while Pt 6 experienced reactivation at day +123 post-transplantation, which was also the 23 days after LET discontinuation. Besides them, after LET discontinuation, other three patients (Pt 7, Pt 8 and Pt 9) receiving UCB transplantation also developed csCMVi. The cumulative curve showed HID subgroup had significantly lower incidence of csCMVi than UCB subgroup (P=0.009, Figure 1D). The multivariable analysis suggested the late initiatial time of LET administration was risk for the occurence of csCMVi (HR 1.07, 95% CI 1.01 - 1.14, P=0.029) (Figure 2). All pediatric patients who developed GVHD were administered steroid-based immunosuppressive therapy, with gradual dose reduction upon symptomatic improvement. Among those who experienced GVHD, the incidence of csCMVi was also significantly lower in the LET group compared to the non-LET group (30/61, 49.2% versus 8/51, 15.7%, P < 0.001).

SAFETY ANALYSIS

There was no discontinuation due to toxicity was observed in our study. There was no engraftment failure observed in the LET group and the non-LET group, and the average time to neutrophil engraftment was 16 (10 - 34) days and 16 (9 - 28) days in patients with and without LET prophylaxis, respectively (P=0.490). For transplantation-related complication, although the LET group had a higher incidence of Epstein-Barr virus (EBV) infection compared to the non-LET group (9/67 [13.4%] vs.5/84 [6.0%], P=0.196), their subsequent incidence of post-transplantation lymphoproliferative disorder (PTLD) were similar (2/67 [3.0%] vs.2/84 [2.4%], P=1, Table 3). Besides, our data indicated that both groups exhibited comparable frequencies and severity of GVHD (Figure 1E&F), organ damage, and other infections (Figure 1G). The median aGVHD was 30 days and 27 days for the LET and non-LET groups, respectively (p = 0.061, Figure 1E). The median time to onset of aGVHD was 30 days and 27 days for the LET and non-LET groups, respectively (p = 0.061).

The main post-HSCT outcomes are summarized in Table 3. The causes of death among the 11 children included relapse, non-CMV severe infection and transplantation-associated thrombotic microangiopathy (TA-TMA). In each of the LET and non-LET groups, the 1-year OS of 89.6% and 95.2% (p = 0.220), CIR of 16.7% and 8.1% (p = 0.321), RFS of 83.6% and 90.5% (p = 0.261), NRM of 6.3% and 3.2% (p = 0.648) and GRFS of 59.7% and 72.6% (p = 0.071), respectively, were observed (Table 3). There were also no statistically significant differences in OS, CIR, RFS, NRM, and GRFS between the two groups in the cumulative incidence curves. The median GRFS for the LET group was 175 days, the median GRFS for the non-LET group was not reached.

DISCUSSION

The study retrospectively analyzed the efficacy and safety of LET prophylaxis in children undergoing HID and UCB transplantation. In addition, we focused on its efficacy in

Table 1. Baseline characteristics of the all paediatric patients.

	LET Group	Non-LET Group	P.value
n	67	84	
Sex			1
Female	24 (35.8)	31 (36.9)	
Male	43 (64.2)	53 (63.1)	
Age, years			0.194
mean (range)	7.6 (1-17)	8.4 (1-19)	
BMI			0.837
mean (SD)	17.72 (3.75)	17.72 (3.99)	
CMV antibody combination			0.207
Donor+/Recipient+	27 (40.3)	44 (52.4)	
Donor+/Recipient-	14 (20.9)	10 (11.9)	
Donor-/Recipient+	26 (38.8)	30 (35.7)	
Primary reason for transplantation			1
Benign disease	18 (26.9)	23 (27.4)	
Malignant disease	49 (73.1)	61 (72.6)	
HCT-CI			0.132
0	54 (80.6)	75 (89.3)	
≥1	13 (19.4)	9 (10.7)	
Stem cell source			0.288
cord blood	32 (47.8)	33 (39.3)	
peripheral blood	25 (37.3)	30 (35.7)	
bone marrow+peripheral blood	10 (14.9)	21 (25.0)	
Conditioning regimen			1
MAC	49 (73.1)	62 (73.8)	
RIC/NMAC	18 (26.9)	22 (26.2)	
Drugs used for GVHD prophylaxis			0.967
Cyclosporin based	62 (92.5)	79 (94.0)	
Tacrolimus based	5 (7.5)	5 (6.0)	
Type of donor			0.379
UCB	32 (47.8)	33 (39.3)	
HID	35 (52.2)	51 (60.7)	
ABO match graft			0.716
Matched	33 (49.3)	45 (53.6)	
Mismatched	34 (50.7)	39 (46.4)	

[1] LET, Letermovir; BMI, Body Mass Index; CMV, Cytomegalovirus; HCT-CI, Hematopoietic Cell Transplantation-specific Comorbidity Index; MAC, Myeloablative transplantation; RIC/NMAC, Reduced intensity conditioning/Non-MAC; GVHD, graft-versus-host disease; UCB, unrelated cord blood; HID, haploidentical donor; SD: standard deviation.
[2] Values are reported as n (%) of patients, unless indicated otherwise.
[3] P values were calculated using a two-sided Chi-Square Test for categorical variables and a Wilcoxon rank-sum test for continuous variables.

paediatric patients who received transplants from different donor sources.

Among 151 paediatric patients who underwent alternative donor transplantation in our center both before and after the the introduction of LET in China (August 2022), we found that LET was highly effective in preventing CMV infection. Despite the fact that all our study populations were considered high-risk for CMV infection, the reported rates of breakthrough infections (8/39, 20.5%) and the incidence of endpoint events within 180 days post-transplantation (4/41, 9.8%) from previous paediatric studies were comparable to our findings.[8,9] It is noteworthy that both our and previous paediatric studies have reported lower infection rates compared to the phase 3 clinical trial,[3] suggesting that the age of the recipients may be a major factor contributing to this discrepancy. Raheel Iftikhar et al. found that being older than 12 years was an independent risk factor for CMV infection, through analysis of 230 consecutive patients undergoing allo-HSCT.[17] In addition, age-related thymic insufficiency also contributes to differences in CD4+

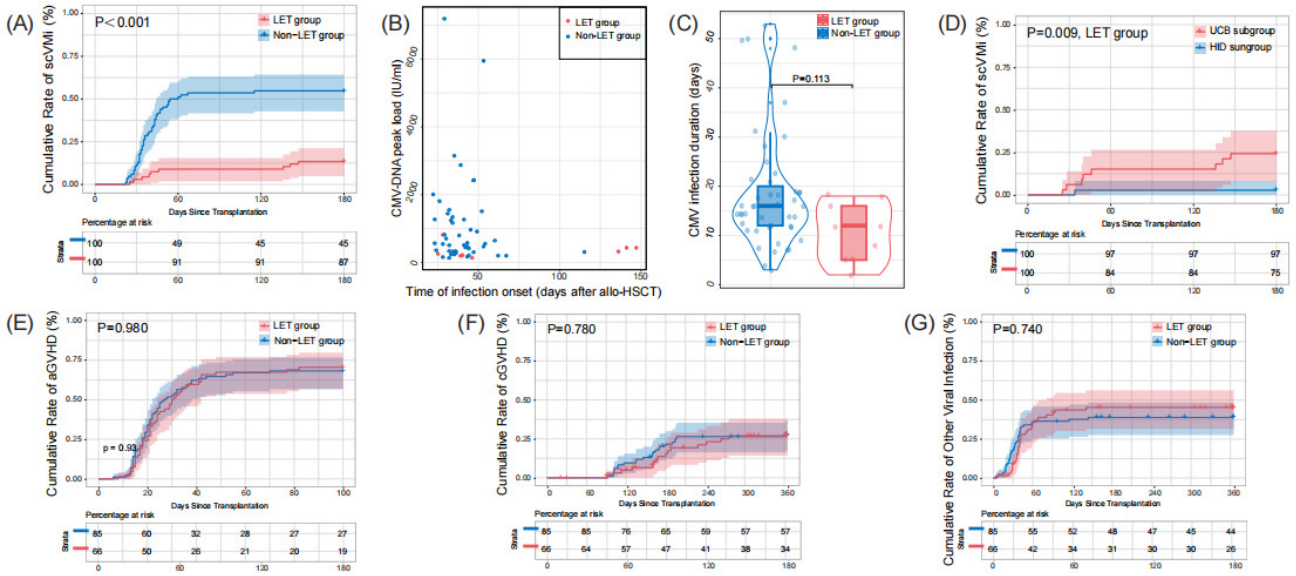


Figure 1. Panel A shows the cumulative incidence of clinically significant Cytomegalovirus infection (csCMVi), stratified by letermovir administration group, through 180 days after allogeneic hematopoietic cell transplantation (allo-HSCT). Panel B and C show the time of csCMVi onset, CMV-DNA peak load and csCMVi duration. Panel D shows the cumulative incidence of csCMVi through 180 days after allo-HSCT, stratified by donor type subgroup. Panel E, F and G show acute graft-versus-host disease (aGVHD), chronic graft-versus-host disease (cGVHD) and orther viral infection probability. All P values are two-sided.

and CD8+ T cells reconstitution patterns between children and adults after transplantation.[18] Besides, the phase 3 clinical trial enrolled only R+ patients, whereas approximately 20% of our study recipients had a negative CMV serostatus, which may partly contribute to the observed difference. Overall, our study highlights the significant efficacy of LET in preventing CMV infection, even in high-risk paediatric patients.

We then conducted a further analysis of the paediatric patients in the LET group. Our study first compared the efficacy of LET in paediatric patients undergoing HID for the Beijing protocol and UCB transplantation. We found that the efficacy of LET in HID recipients for the Beijing protocol exceeded that in UCB recipients. During prophylaxis, 5 out of 6 patients who developed a breakthrough infection received a UCB transplantation. After discontinuation of LET, all 3 cases of late-onset CMV infection were from the UCB subgroup. This may be related to the lower total lymphocyte count in UCB grafts, leading to delayed IR post-transplantation.[19] A retrospective study by Hill et al. of 61 patients who received a UCB transplantation, of whom 21 received LET prophylaxis, also suggested this. After one year of follow-up, they found that the cumulative incidence of CMV infection was almost similar between the group receiving LET prophylaxis and the group not receiving LET prophylaxis.[20] Therefore, long-term monitoring of children undergoing UCB transplantation after discontinuation of LET was indeed necessary. To further optimize the prophylactic strategy, extensive long-term research is essential to investigate the feasibility of extending the duration of LET use in UCB recipients. Most importantly, our results showed that early use of LET after transplantation significantly reduced the risk of CMV infection. This important finding, which has not yet been reported in children, requires further validation and consolidation through larger cohort studies. Such efforts will also help determine the optimal timing of LET administration.

In terms of safety, previous pediatric studies have predominantly determined the dosage of letermovir based on BSA and concurrent CsA use, with all of them validating its favorable efficacy and safety, and our study also adhered to this principle. Nevertheless, age continued to be a crucial factor that cannot be overlooked in pediatric medication. An ongoing Phase 2 clinical trial has divided patients into three age groups to explore optimal dosing strategies.[7] Published data from this trial has indicated that children aged 12-18 could safely receive the same LET dosage as adults, which was consistent with the dosing administered to this age group in our study.

During follow-up, we did not observe any LET-related myelosuppression, organ toxicity or transplant-related complications. The absence of myelosuppression with LET was a prerequisite for its use prior to neutrophil engraftment, thereby ensuring its safety. In line with similar findings in previous studies, the study confirmed that the time to neutrophil engraftment was comparable between patients who received LET and those who did not (P=0.953).[21] Notably, although the EBV infection rate was slightly higher in the LET group compared to the non-LET group, this difference was not statistically significant. In addition, the incidence of PTLD was similar between the two groups. Several recent studies have suggested that LET may increase the risk of EBV infection and PTLD in adults,[22,23] but there are few reports in children.

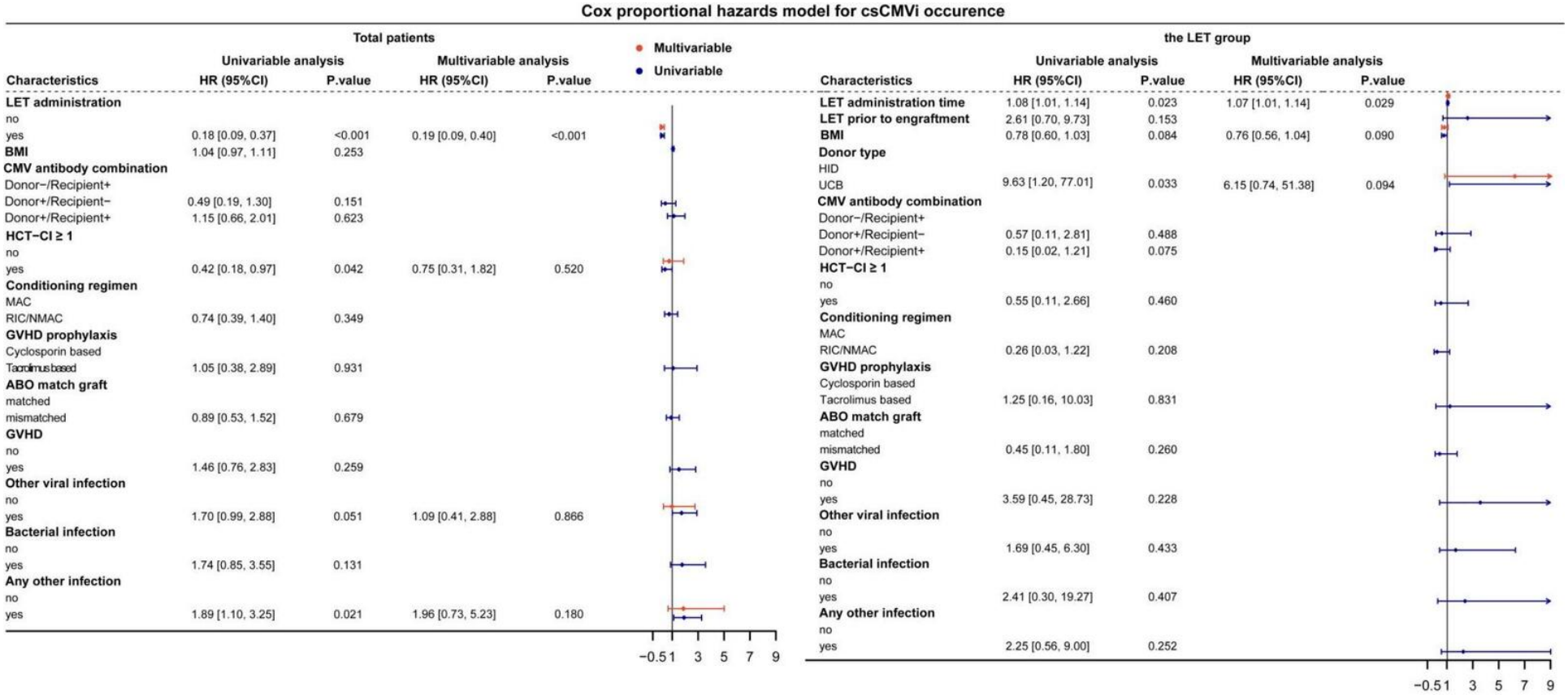


Figure 2. Forest plots showed the impact of clinical factors on the incidence of clinical significant Cytomegalovirus infection (csCMVi) in all patients and the letermovir group.

Clinical factors included the administration of LET, body mass index (BMI), CMV serostatus of recipients, donor type, Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI) score more than one, the conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, ABO match graft, the occurrence of GVHD prior to the csCMVi, and the occurrence of other types of viral, bacterial, or fungal infection prior to the csCMVi. Diamonds represent the hazard ratios, and the horizontal bars extend from the lower limit to the upper limit of the 95% confidence interval.

Table 2. Clinical manifestations before or at primary endpoint in patients within the LET group.

ID	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7	Pt 8	Pt 9
Sex	M	M	F	F	F	M	F	F	M
Age	3	3	2	10	8	14	4	14	11
CMV serostatus	D-/R+	D-/R+	D+/R+	D-/R+	D-/R+	*D+/R-	D-/R+	*D+/R-	D-/R+
Transplant-ation indication	Leukemia	Leukemia	Leukemia	MDS	MDS/ MPN	Leukemia	MDS	Leukemia	Leukemia
Conditioni-ng regimen	MAC	MAC	MAC	MAC	MAC	MAC	MAC	MAC	MAC
Letermovir start time	8	44	23	30	21	2	9	32	2
GVHD prophylaxis	CsA based	CsA based	CsA based	CsA based	CsA based	CsA based	CsA based	CsA based	CsA based
Donor type	UCB	UCB	HID	UCB	UCB	UCB	UCB	UCB	UCB
Neutrophil engraftme-nt	yes	yes	yes	yes	yes	yes	yes	yes	yes
aGVHD grade	-	4	3	1	3	4	2	1	2
cGVHD	-	-	-	-	-	-	-	-	yes
Other infection	bacterial	-	-	-	fungal	BKV	-	-	BKV
Primary end point	day +25	day +28	day +34	day +39	day +40	day +46	day +136	day +141	day +147
Peak CMV DNA load	249 IU/ ml	811 IU/ ml	319 IU/ ml	192 IU/ml	209 IU/ml	136 IU/ ml	315 IU/ml	430 IU/ ml	427 IU/ ml
Therapy									
ganciclovir	yes	yes	yes	yes	yes	yes	yes	yes	yes
foscarnet	-	yes	-	-	yes	-	-	-	-

*CMV-IgG (+) in UCB indicates that the infant was exposed to CMV during the mother's pregnancy, and the CMV IgG antibodies were transferred to the fetus through the mother. Pt: patient; M, Male; F, Female; BMI, Body Mass Index; CMV, Cytomegalovirus; R: recipients; HCT-CI, Hematopoietic Cell Transplantation-specific Comorbidity Index; MAC, Myeloablative transplantation; GVHD, graft-versus-host disease; CsA: Cyclosporin A; UCB, unrelated cord blood; HID, haploidentical donor.

This study was a small-sample, single-center, retrospective real-world study. Additionally, there was no established dosing protocol for LET in children, resulting in a considerable time span for the initiation of LET in the LET group. Furthermore, although most of the patients included in the non-LET group underwent transplantation before the approval of LET (August 2022), a portion of them received allo-HSCT recently without LET prophylaxis. Due to the advent of new antibiotics, diagnostic techniques and so on,[24] the clinical outcomes of patients undergoing transplantation recently have improved. This may also impact the results of this study.

In conclusion, LET demonstrates efficacy in preventing csCMVi among Chinese children undergoing alternative donor transplantation, especially in HID recipients, and also has a good safety profile.

ACKNOWLEDGMENTS

This work was supported by grants from the National Natural Science Foundation of China [82070201 (Y.G.)].

AUTHORS' CONTRIBUTION

Conceptualization: Ye Guo, Xiaofan Zhu; Data curation: Xia Chen, Yuanyuan Ren, Yang Wan, Aoli Zhang, Xiaoyan Zhang, Yue Shang, Yao Zou, Xiaojuan Chen, Fang Liu, Wenyu Yang; Formal Analysis: Xin Wang, Chaoqian Jiang, Lipeng Liu; Writing – original draft: Xin Wang, Chaoqian Jiang, Lipeng Liu; Writing – review & editing: Ye Guo, Xiaofan Zhu.

COMPETING OF INTEREST – COPE

The authors have no conflicts of interest declared.

ETHICAL CONDUCT APPROVAL – HELSINKI – IACUC

The retrospective studie design and methods complied with the Declaration of Helsinki and were approved by the Ethics Committee and Institutional Review Board of the Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College.

INFORMED CONSENT STATEMENT

All authors and institutions have confirmed this manuscript for publication.

Table 3. Adverse Events.

Adverse Event	LET group n=67	Non-LET group n=84	X-squared	P.value
aGVHD	47 (70.1)	60 (71.4)	0	1.000
0 grade	20 (29.9)	27 (32.1)	3.418	0.332
1 grade	11 (22.9)	16 (19.0)		
2 grade	9 (13.4)	18 (21.4)		
3-4 grade	27 (40.3)	23 (27.4)		
cGVHD	15 (22.4)	24 (28.6)	0.456	0.499
mild	12 (17.9)	19 (22.6)	0.748	0.731
moderate to severe	3 (4.5)	5 (6.0)		
Hepatic impairment	60 (89.6)	74 (88.1)	< 0.001	0.982
0 grade	7 (10.4)	10 (11.9)	1.202	0.878
1 grade	19 (28.4)	27 (32.1)		
2 grade	16 (23.9)	16 (19.0)		
3 grade	19 (28.4)	26 (31.0)		
4 grade	6 (9.0)	5 (6.0)		
Renal impairment	7 (10.4)	6 (7.1)	0.183	0.669
0 grade	60 (89.6)	78 (92.9)	0.532	0.767
1 grade	6 (9.0)	5 (6.0)		
2 grade	1 (1.5)	1 (1.2)		
Cardiac impairment	4 (6.0)	2 (2.4)	0.494	0.482
0 grade	63 (94.0)	82 (97.6)	0.494	0.482
1 grade	4 (6.0)	2 (2.4)		
Any other infection	32 (47.8)	40 (47.6)	0	1
Other viral infection	29 (43.3)	33 (39.3)	0.109	0.742
Epstein-Barr Virus infection	9 (13.4)	5 (6.0)	1.670	0.196
PTLD	2 (3.0)	2 (2.4)	< 0.001	1
Adenovirus infection	1 (1.5)	1 (1.2)	< 0.001	1
BK Polyomavirus infection	20 (29.9)	27 (32.1)	0.016	0.900
Bacterial infection	4 (6.0)	13 (15.5)	2.487	0.115
Fungal infection	3 (4.5)	4 (4.8)	< 0.001	1
OS	60 (89.6)	80 (95.2)	2.001	0.220
***CIR**	8 (16.7)	5 (8.1)	0.985	0.321
***RFS**	56 (83.6)	76 (90.5)	1.262	0.261
***NRM**	3 (6.3)	2 (3.2)	0.570	0.648
***GRFS**	40 (59.7)	61 (72.6)	3.268	0.071

*Subjects: Malignant disease children，LET group: n=48，non-LET group: n=62.
aGVHD: Acute Graft-versus-Host Disease; cGVHD: Chronic Graft-versus-Host Disease; PTLD: Post Transplant Lymphoproliferative Disease; OS, overall survival; CIR, cumulative incidence of relapse; RFS, relapse free survival; NRM, nonrelapse mortality; GRFS, GVHD-free, relapse-free survival.

DATA AVAILABILITY STATEMENT

All are available upon reasonable request.

Submitted: December 23, 2024 BST. Accepted: January 28, 2025
BST. Published: March 14, 2025 BST.

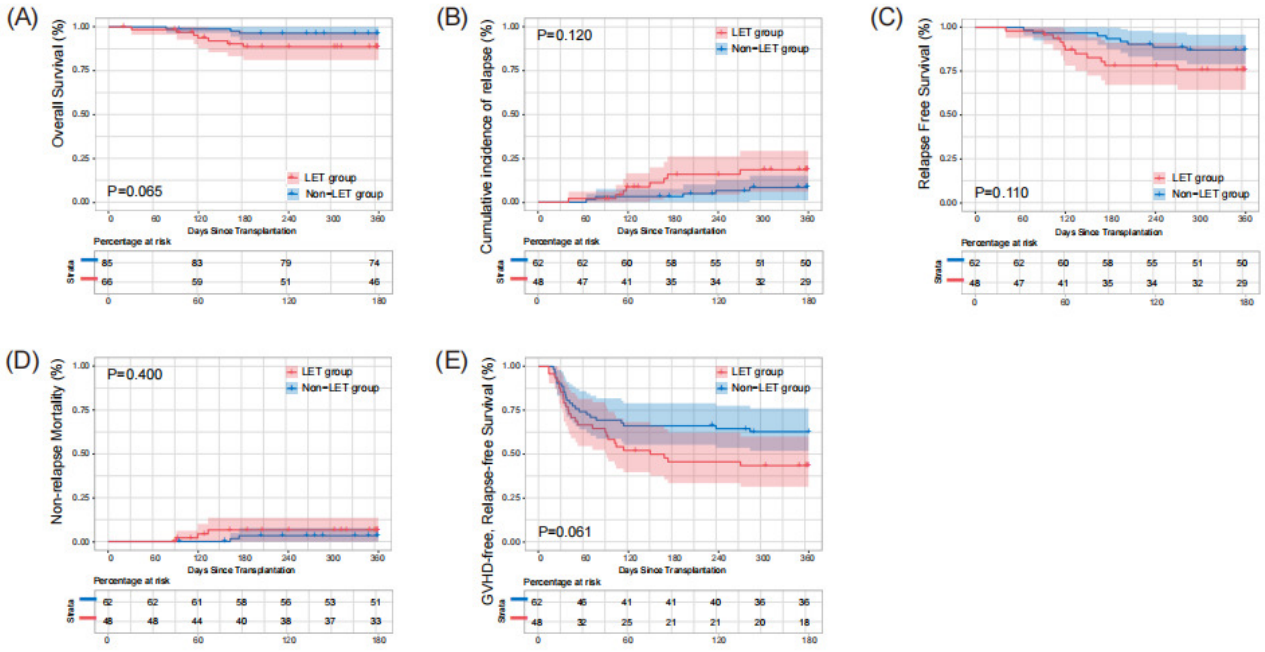


Figure 3. Panel A shows the overall survival (OS) for all children. Panel B, C, D and E show the cumulative incidence of relapse (CIR), relapse free survival (RFS), nonrelapse mortality (NRM) and graft-versus-host disease-free, relapse-free survival (GRFS) in children with malignant diseases. All P values are two-sided.

This is an open-access article distributed under the terms of the Creative Commons Attribution 4.0 International License (CCBY-4.0). View this license's legal deed at http://creativecommons.org/licenses/by/4.0 and legal code at http://creativecommons.org/licenses/by/4.0/legalcode for more information.

REFERENCES

1. Ljungman P et al. Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL 7). *The Lancet Infectious Diseases*. 2019;19:e260-e272. doi:10.1016/S1473-3099(19)30107-0

2. Velardi E et al. The role of the thymus in allogeneic bone marrow transplantation and the recovery of the peripheral T-cell compartment. *Semin Immunopathol*. 2021;43:101-117. doi:10.1007/s00281-020-00828-7

3. Marty FM, Ljungman P. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. *The new england journal of medicine*. Published online 2017. doi:10.1056/NEJMoa1706640

4. Nakagawa D, Shimomura Y, Mitsuyuki S. Efficacy of letermovir in HLA-haploidentical hematopoietic transplantation with posttransplant cyclophosphamide. *International Journal of Hematology*. Published online 2023. doi:10.1007/s12185-023-03635-6

5. Toya T, Mizuno K, Sakurai M. Differential clinical impact of letermovir prophylaxis according to graft sources: a KSGCT multicenter retrospective analysis. *Blood Advances*. Published online 2023.

6. Yan B et al. Letermovir prophylaxis reduced cytomegalovirus reactivation and resistance post umbilical cord blood transplantation.

7. Groll AH et al. Pharmacokinetics, Safety, and Efficacy of Letermovir for Cytomegalovirus Prophylaxis in Adolescent Hematopoietic Cell Transplantation Recipients. *Pediatric Infectious Disease Journal*. 2024;43:203-208. doi:10.1097/INF.0000000000004208

8. Chen TT, David AP, Barthelmess EK, MacBrayne CE. Letermovir for Cytomegalovirus prophylaxis in pediatric hematopoietic stem cell transplantation. *Pediatric Blood & Cancer*. 2023;70:e30608. doi:10.1002/pbc.30608

9. Galaverna F, Baccelli F, Zama D. Letermovir for Cytomegalovirus infection in pediatric patients undergoing allogenic hematopoietic stem cell transplantation: a real-life study by the Infectious Diseases Working Group of Italian Association of Pediatric Hematology-Oncology (AIEOP). *Bone Marrow Transplantation*. Published online 2024. doi:10.1038/s41409-024-02209-2

10. Pfeiffer T et al. Letermovir as cytomegalovirus prophylaxis in children undergoing allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant*. 2024;59:1193-1195. doi:10.1038/s41409-024-02315-1

11. César T et al. Letermovir for CMV Prophylaxis in Very High-Risk Pediatric Hematopoietic Stem Cell Transplantation Recipients for Inborn Errors of Immunity. *J Clin Immunol*. 2024;44(6). doi:10.1007/s10875-023-01617-1

12. Einsele H, Ljungman P, Boeckh M. How I treat CMV reactivation after allogeneic hematopoietic stem cell transplantation. *Blood*. 2020;135:1619-1629. doi:10.1182/blood.2019000956. PMID:32202631

13. Hiraishi I, Ueno R, Watanabe A, Maekawa S. Safety and Effectiveness of Letermovir in Allogenic Hematopoietic Stem Cell Transplantation Recipients: Interim Report of Post-marketing Surveillance in Japan. *Clin Drug Investig*. 2021;41:1075-1086. doi:10.1007/s40261-021-01096-5. PMID:34784011

14. Ljungman P et al. Definitions of Cytomegalovirus Infection and Disease in Transplant Patients for Use in Clinical Trials: Table 1. *Clin Infect Dis*. 2017;64:87-91.

15. Sorror ML et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005;106:2912-2919. doi:10.1182/blood-2005-05-2004. PMID:15994282

16. Sureda A et al. Harmonizing definitions for hematopoietic recovery, graft rejection, graft failure, poor graft function, and donor chimerism in allogeneic hematopoietic cell transplantation: a report on behalf of the EBMT, ASTCT, CIBMTR, and APBMT. *Bone Marrow Transplant*. 2024;59:832-837. doi:10.1038/s41409-024-02251-0. PMID:38443706

17. Iftikhar R et al. Cytomegalovirus Infection Post-Allogeneic Stem Cell Transplantation: Experience from a Country with High Seropositivity. *Transplantation and Cellular Therapy*. 2023;29:521.e1-521.e7. doi:10.1016/j.jtct.2023.04.023

18. Kalwak K et al. Immune reconstitution after haematopoietic cell transplantation in children: immunophenotype analysis with regard to factors affecting the speed of recovery. *Br J Haematol*. 2002;118:74-89. doi:10.1046/j.1365-2141.2002.03560.x

19. Rénard C et al. Lymphocyte subset reconstitution after unrelated cord blood or bone marrow transplantation in children. *Br J Haematol*. 2011;152:322-330. doi:10.1111/j.1365-2141.2010.08409.x

20. Hill JA, Zamora D, Xie H. Delayed-onset cytomegalovirus infection is frequent after discontinuing letermovir in cord blood transplant recipients. *Blood Advances*. 2021;5. doi:10.1182/bloodadvances.2021004362. PMID:34402885

21. Yoshimura H et al. Real-world efficacy of letermovir prophylaxis for cytomegalovirus infection after allogeneic hematopoietic stem cell transplantation: A single-center retrospective analysis. *Journal of Infection and Chemotherapy*. 2022;28:1317-1323. doi:10.1016/j.jiac.2022.05.019

22. Zhen S et al. EBV REACTIVATION AND POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDER AFTER ALLOGENEIC HEMATOPOIETIC CELL TRANSPLANTATION IN THE ERA OF LETERMOVIR FOR CMV PROPHYLAXIS: A RETROSPECTIVE COHORT STUDY. In: *Infectious Complications (Glasgow)*. ; 2024.

23. Pei X, Huang X. LETERMOVIR PROPHYLAXIS FOR CYTOMEGALOVIRUS INFECTION IS THE POTENTIAL RISK OF EBV-POSITIVE POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDERS AFTER HAPLOIDENTICAL STEM-CELL TRANSPLANTATION. In: *Infectious Complications (Glasgow)*. ; 2024.

24. Gooley TA, Sorror ML, Marr KA. Reduced Mortality after Allogeneic Hematopoietic-Cell Transplantation. *n engl j med*. Published online 2010. doi:10.1056/NEJMoa1004383. PMID:21105791

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PREVYMIS safely and effectively. See full prescribing information for PREVYMIS.

PREVYMIS® (letermovir) tablets, for oral use
PREVYMIS® (letermovir) oral pellets
PREVYMIS® (letermovir) injection, for intravenous use
Initial U.S. Approval: 2017

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.1, 1.2)	08/2024
Dosage and Administration (2.1, 2.3, 2.4, 2.5, 2.6, 2.7, 2.9, 2.10)	08/2024
Warnings and Precautions (5.2)	08/2024

----------INDICATIONS AND USAGE----------

PREVYMIS is a CMV DNA terminase complex inhibitor indicated for:

- Prophylaxis of cytomegalovirus (CMV) infection and disease in adult and pediatric patients 6 months of age and older and weighing at least 6 kg who are CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). (1.1)
- Prophylaxis of CMV disease in adult and pediatric patients 12 years of age and older and weighing at least 40 kg who are kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]). (1.2)

----------DOSAGE AND ADMINISTRATION----------

- Adult and Pediatric Patients 12 Years of Age and Older and Weighing at least 30 kg Who Are HSCT Recipients or Adult and Pediatric Patients 12 Years of Age and Older and Weighing at least 40 kg Who Are Kidney Transplant Recipients:
  - *HSCT*: 480 mg administered once daily orally or as an intravenous (IV) infusion over 1 hour through 100 days post-HSCT. In patients at risk for late CMV infection and disease, PREVYMIS may be continued through 200 days post-HSCT. (2.1, 2.3)
  - *Kidney Transplant*: 480 mg administered once daily orally or as an IV infusion over 1 hour through 200 days post-transplant. (2.1, 2.3)
- Pediatric Patients 6 Months to Less than 12 Years of Age or 12 Years of Age and Older and Weighing Less than 30 kg Who Are HSCT Recipients:
  - *HSCT*: Dosing based on weight administered once daily orally or as an IV infusion over 1 hour through 100 days post-HSCT. In patients at risk for late CMV infection and disease, PREVYMIS may be continued through 200 days post-HSCT. (2.1, 2.5)
- PREVYMIS injection must be diluted prior to administration. (2.1)
- PREVYMIS injection must be administered through a sterile 0.2 micron or 0.22 micron polyethersulfone (PES) in-line filter. (2.1, 2.10)
- Following the completion of PREVYMIS prophylaxis, monitoring for CMV reactivation in HSCT recipients is recommended. (2.2)
- Dosage Adjustment: If PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily in adult and pediatric patients 12 years of age and older. (2.4) If PREVYMIS is co-administered with cyclosporine in pediatric patients less than 12 years of age, dose adjustment may be required. (2.6)
- Instructions for Use should be followed for preparation and administration of PREVYMIS oral pellets. (2.9)
- Do not use PREVYMIS injection with IV bags and infusion set materials containing the plasticizer diethylhexyl phthalate (DEHP). (2.10, 2.13)

----------DOSAGE FORMS AND STRENGTHS----------

- Tablet: 240 mg; 480 mg (3)
- Oral Pellets: 20 mg or 120 mg per packet (3)
- Injection: 240 mg/12 mL (20 mg/mL) or 480 mg/24 mL (20 mg/mL) in a single-dose vial (3)

----------CONTRAINDICATIONS----------

PREVYMIS is contraindicated with:

- Pimozide. (4)
- Ergot Alkaloids. (4)
- Pitavastatin and simvastatin when co-administered with cyclosporine. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions: The concomitant use of PREVYMIS with certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions (PREVYMIS or concomitant drugs) or reduced therapeutic effect of PREVYMIS or the concomitant drug. Consult the full prescribing information for contraindications and dosage recommendations for concomitant drugs. (4, 5.1, 7.1, 7.2, 7.3)
- Risks Associated with Hydroxypropyl Betadex Excipient in Intravenous Formulation: Intravenous formulation of PREVYMIS contains the excipient hydroxypropyl betadex. PREVYMIS injection should be used only in patients unable to take oral therapy. If possible, intravenous administration should not exceed 4 weeks. In patients with renal impairment, accumulation of hydroxypropyl betadex may occur. Animal studies have shown the potential for hydroxypropyl betadex to cause ototoxicity. (5.2, 8.6, 13.2)

---------- ADVERSE REACTIONS ----------

- Adult HSCT Patients: Most common adverse events (occurring in at least 10% of subjects in the PREVYMIS group and at a frequency at least 2% greater than placebo) are nausea, diarrhea, vomiting, peripheral edema, cough, headache, fatigue, and abdominal pain. (6.1)
- Adult Kidney Transplant Patients: Most common adverse event (occurring in at least 10% of subjects in the PREVYMIS group and at a frequency greater than valganciclovir) is diarrhea. (6.1)
- Pediatric Patients: Adverse events in pediatric patients are similar to adults. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme LLC at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch .

----------DRUG INTERACTIONS----------

- Dosage Adjustment: If PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily in adult and pediatric patients 12 years of age and older. (2.4) If PREVYMIS is co-administered with cyclosporine in pediatric patients less than 12 years of age, dose adjustment may be required. (2.6)
- Co-administration of PREVYMIS may alter the plasma concentrations of other drugs and other drugs may alter the plasma concentrations of PREVYMIS. Consult the full prescribing information prior to and during treatment for potential drug interactions. (2.4, 2.6, 4, 5.1, 7.1, 7.2, 7.3, 7.4, 12.3)

---------- USE IN SPECIFIC POPULATIONS ----------

- Renal Impairment: Closely monitor serum creatinine levels in patients with CLcr less than 50 mL/min using PREVYMIS injection. (8.6)
- Hepatic Impairment: PREVYMIS is not recommended for patients with severe (Child-Pugh C) hepatic impairment. (8.7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 08/2024

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
- 1.1 CMV Prophylaxis in Hematopoietic Stem Cell Transplant (HSCT) Recipients
- 1.2 CMV Prophylaxis in Kidney Transplant Recipients

2 DOSAGE AND ADMINISTRATION
- 2.1 Important Dosing and Administration Information
- 2.2 Patient Monitoring
- 2.3 Recommended Dosage for Adult and Pediatric Patients 12 Years of Age and Older Who Are HSCT or Kidney Transplant Recipients
- 2.4 Dosage Adjustment When Co-administered with Cyclosporine for Adult and Pediatric Patients 12 Years of Age and Older Who Are HSCT or Kidney Transplant Recipients
- 2.5 Recommended Dosage for Pediatric Patients 6 Months to Less than 12 Years of Age or 12 Years of Age and Older and Weighing Less than 30 kg Who Are HSCT Recipients

2.6 Dosage Adjustment When Co-administered with Cyclosporine for Pediatric Patients 6 Months to Less than 12 Years of Age or 12 Years of Age and Older and Weighing Less than 30 kg Who Are HSCT Recipients
2.7 Use in Patients with Renal Impairment
2.8 Use in Patients with Hepatic Impairment
2.9 Preparation and Administration of Oral Pellets
2.10 Preparation and Administration of Intravenous Solution
2.11 Storage of the Diluted Solution
2.12 Compatible Drug Products Used for Intravenous Administration
2.13 Incompatible Drug Products and Other Materials Used for Intravenous Administration
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions
5.2 Risks Associated with Hydroxypropyl Betadex Excipient in Intravenous Formulation
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
7.1 Potential for Other Drugs to Affect PREVYMIS
7.2 Potential for PREVYMIS to Affect Other Drugs
7.3 Established and Other Potentially Significant Drug Interactions
7.4 Drugs without Clinically Significant Interactions with PREVYMIS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Lactation
8.3 Females and Males of Reproductive Potential
8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
8.7 Hepatic Impairment
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
14.1 Overview of Clinical Studies
14.2 Adult CMV-seropositive Recipients [R+] of an Allogeneic Hematopoietic Stem Cell Transplant (Trial P001 and Trial P040)
14.3 Adult CMV-seronegative Recipients of a Kidney Transplant from a CMV-seropositive Donor [D+/R-] (Trial P002)
14.4 Pediatric Recipients of an Allogeneic HSCT (Trial P030)
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 CMV Prophylaxis in Hematopoietic Stem Cell Transplant (HSCT) Recipients

PREVYMIS® is indicated for prophylaxis of cytomegalovirus (CMV) infection and disease in adult and pediatric patients 6 months of age and older and weighing at least 6 kg who are CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT).

1.2 CMV Prophylaxis in Kidney Transplant Recipients

PREVYMIS is indicated for prophylaxis of CMV disease in adult and pediatric patients 12 years of age and older and weighing at least 40 kg who are kidney transplant recipients at high risk (Donor CMV seropositive/Recipient CMV seronegative [D+/R-]).

2 DOSAGE AND ADMINISTRATION

2.1 Important Dosing and Administration Information

- PREVYMIS is available in 3 dosage forms:
  - PREVYMIS Tablets
    - Administer orally with or without food.
    - Swallow tablets whole.
  - PREVYMIS Oral Pellets
    - Administer orally mixed with soft food or via nasogastric tube (NG tube) or gastric tube (G tube) *[see Dosage and Administration (2.9)]*.
    - Do not crush or chew.
  - PREVYMIS Injection
    - PREVYMIS injection must be diluted prior to administration.
    - Administer PREVYMIS through a sterile 0.2 micron or 0.22 micron polyethersulfone (PES) in-line filter.
    - Administer by intravenous infusion via a peripheral catheter or central venous line at a constant rate over 1 hour.

- Do not administer as an intravenous bolus injection.
- PREVYMIS injection, which contains hydroxypropyl betadex, should be used only in patients unable to take oral therapy. Patients should be switched to oral PREVYMIS as soon as they are able to take oral medications. If possible, intravenous administration should not exceed 4 weeks *[see Warnings and Precautions (5.2)].*

- No dosage adjustment is necessary when switching formulations in adult and pediatric patients 12 years of age and older *[see Dosage and Administration (2.3)]*.

- Dosage adjustment may be necessary for pediatric patients less than 12 years of age when switching between oral and intravenous formulations *(see Table 1 and Table 2) [see Dosage and Administration (2.5)]*.

2.2 Patient Monitoring

Following the completion of PREVYMIS prophylaxis, monitoring for CMV reactivation in HSCT recipients is recommended *[see Clinical Studies (14.2)]*.

2.3 Recommended Dosage for Adult and Pediatric Patients 12 Years of Age and Older Who Are HSCT or Kidney Transplant Recipients

HSCT: Adult and Pediatric Patients 12 Years of Age and Older and Weighing at least 30 kg
The recommended dosage of PREVYMIS is 480 mg administered orally or intravenously once daily. When PREVYMIS is administered orally, the recommended dosage is one 480 mg tablet once daily or two 240 mg tablets once daily. Four 120 mg packets of oral pellets once daily can be used for patients who cannot swallow tablets *[see Dosage and Administration (2.9)]*. For preparation and administration instructions of intravenous dosing refer to instructions in subsection 2.10 *[see Dosage and Administration (2.10)].* For pediatric patients less than 12 years of age or weighing less than 30 kg, refer to weight-based dosing in Table 1 and Table 2 *[see Dosage and Administration (2.5)]*.

Initiate PREVYMIS between Day 0 and Day 28 post-HSCT (before or after engraftment) and continue through Day 100 post-HSCT. In patients at risk for late CMV infection and disease, PREVYMIS may be continued through Day 200 post-HSCT *[see Clinical Studies (14.2)]*.

Dosage of PREVYMIS should be adjusted when co-administered with cyclosporine *[see Dosage and Administration (2.4)]*.

Kidney Transplant: Adult and Pediatric Patients 12 Years of Age and Older and Weighing at least 40 kg
The recommended dosage of PREVYMIS is 480 mg administered orally or intravenously once daily. When PREVYMIS is administered orally, the recommended dosage is one 480 mg tablet once daily or two 240 mg tablets once daily. Four 120 mg packets of oral pellets once daily can be used for patients who cannot swallow tablets *[see Dosage and Administration (2.9)]*. For preparation and administration instructions of intravenous dosing refer to instructions in subsection 2.10 *[see Dosage and Administration (2.10)].*

Initiate PREVYMIS between Day 0 and Day 7 post-transplant and continue through Day 200 post-transplant.

Dosage of PREVYMIS should be adjusted when co-administered with cyclosporine *[see Dosage and Administration (2.4)]*.

2.4 Dosage Adjustment When Co-administered with Cyclosporine for Adult and Pediatric Patients 12 Years of Age and Older Who Are HSCT or Kidney Transplant Recipients

- If oral or intravenous PREVYMIS is co-administered with cyclosporine, the dosage of PREVYMIS should be decreased to 240 mg once daily in the following populations *[see Drug Interactions (7.1, 7.2, 7.3) and Clinical Pharmacology (12.3)]*:

- HSCT: adult and pediatric patients 12 years of age and older and weighing at least 30 kg

or

- Kidney transplant: adult and pediatric patients 12 years of age and older and weighing at least 40 kg.

- If cyclosporine is initiated after starting PREVYMIS, the next dose of PREVYMIS should be decreased to 240 mg once daily.
- If cyclosporine is discontinued after starting PREVYMIS, the next dose of PREVYMIS should be increased to 480 mg once daily.
- If cyclosporine dosing is interrupted due to high cyclosporine levels, no dose adjustment of PREVYMIS is needed.

2.5 Recommended Dosage for Pediatric Patients 6 Months to Less than 12 Years of Age or 12 Years of Age and Older and Weighing Less than 30 kg Who Are HSCT Recipients

The recommended dosages of PREVYMIS for pediatric HSCT recipients 6 months to less than 12 years of age are based on weight and shown in Table 1 (tablets or oral pellets) and Table 2 (injection) *[see Clinical Pharmacology (12.3)]*. PREVYMIS can be administered orally (tablet or pellet) or intravenously once daily. Dosage adjustment may be necessary for pediatric patients less than 12 years of age when switching between oral and intravenous formulations *(see Table 1 and Table 2)*.

Initiate PREVYMIS between Day 0 and Day 28 post-HSCT (before or after engraftment) and continue through Day 100 post-HSCT. In patients at risk for late CMV infection and disease, PREVYMIS may be continued through Day 200 post-HSCT *[see Clinical Studies (14.2)]*.

Table 1: Recommended Daily Oral Dosage of PREVYMIS in Pediatric HSCT Recipients 6 Months to Less than 12 Years of Age or 12 Years of Age and Older and Weighing Less than 30 kg

Body Weight	Daily Oral Dose	Tablets	Oral Pellets
30 kg and above	480 mg	One 480 mg tablet or Two 240 mg tablets	Four 120 mg packets of oral pellets
15 kg to less than 30 kg	240 mg	One 240 mg tablet	Two 120 mg packets of oral pellets
7.5 kg to less than 15 kg	120 mg	Not recommended	One 120 mg packet of oral pellets
6 kg to less than 7.5 kg	80 mg	Not recommended	Four 20 mg packets of oral pellets

Table 2: Recommended Daily IV Dosage of PREVYMIS in Pediatric HSCT Recipients 6 Months to Less than 12 Years of Age or 12 Years of Age and Older and Weighing Less than 30 kg

Body Weight	Daily IV* Dose
30 kg and above	480 mg
15 kg to less than 30 kg	120 mg
7.5 kg to less than 15 kg	60 mg
6 kg to less than 7.5 kg	40 mg

* Refer to Subsection 2.10 for intravenous preparation and administration dosing instructions

2.6 Dosage Adjustment When Co-administered with Cyclosporine for Pediatric Patients 6 Months to Less than 12 Years of Age or 12 Years of Age and Older and Weighing Less than 30 kg Who Are HSCT Recipients

If oral or intravenous PREVYMIS is co-administered with cyclosporine in pediatric HSCT recipients 6 months to less than 12 years of age, the dosage of PREVYMIS may require adjustment as shown in Table 3 *[see Drug Interactions (7.1, 7.2, 7.3) and Clinical Pharmacology (12.3)]*.

- If cyclosporine is initiated after starting PREVYMIS, the next dose of PREVYMIS should be the daily oral or intravenous dose co-administered with cyclosporine (Table 3)
- If cyclosporine is discontinued after starting PREVYMIS, the next dose of PREVYMIS should be the daily oral or intravenous dose administered without cyclosporine (Table 1 or Table 2)
- If cyclosporine dosing is interrupted due to high cyclosporine levels, no dose adjustment of PREVYMIS is needed.

Table 3: Recommended Dosage of PREVYMIS when Co-administered with Cyclosporine in Pediatric HSCT Recipients 6 Months to Less than 12 Years of Age or 12 Years of Age and Older and Weighing Less than 30 kg

Body Weight	Daily Oral Dose	Tablets	Oral Pellets	Daily IV* Dose
30 kg and above	240 mg	One 240 mg tablet	Two 120 mg packets of oral pellets	240 mg
15 kg to less than 30 kg	120 mg	Not recommended	One 120 mg packet of oral pellets	120 mg
7.5 kg to less than 15 kg	60 mg	Not recommended	Three 20 mg packets of oral pellets	60 mg
6 kg to less than 7.5 kg	40 mg	Not recommended	Two 20 mg packets of oral pellets	40 mg

* Refer to Subsection 2.10 for intravenous preparation and administration dosing instructions

2.7 Use in Patients with Renal Impairment

- For adult patients with creatinine clearance (CLcr) greater than 10 mL/min and pediatric patients with a similar degree of renal impairment (based on age-appropriate assessment of renal function), no dosage adjustment of PREVYMIS is required based on renal impairment *[see Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*.
- There are insufficient data in adult patients with CLcr 10 mL/min or less or in patients on dialysis or in pediatric patients with a similar degree of renal impairment (based on age-appropriate assessment of renal function) to make PREVYMIS dosing recommendations.
- In adult patients with CLcr less than 50 mL/min and in pediatric patients with a similar degree of renal impairment (based on age-appropriate assessment of renal function) receiving PREVYMIS injection, accumulation of the intravenous vehicle, hydroxypropyl betadex, may occur. Closely monitor serum creatinine levels in these patients *[see Warnings and Precautions (5.2)]*.

2.8 Use in Patients with Hepatic Impairment

No dosage adjustment of PREVYMIS is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment *[see Use in Specific Populations (8.7)]*.

2.9 Preparation and Administration of Oral Pellets

PREVYMIS oral pellets can be administered:

- orally after mixing with soft food or
- via NG tube or G tube.

Preparation and Administration Mixed with Soft Food

See **Instructions for Use** for details on the preparation and administration of PREVYMIS oral pellets mixed with soft food.

- Do not crush or chew PREVYMIS oral pellets.
- Mix PREVYMIS oral pellets with 1 to 3 teaspoons of soft food (such as applesauce, yogurt, or pudding) that is at or below room temperature. Do not use hot food.
- Administer entire mixture within 10 minutes of mixing PREVYMIS oral pellets with the soft food.

Preparation and Administration via NG Tube or G Tube

See **Instructions for Use**, Table 4 (NG tube) and Table 5 (G tube) for details on the preparation and administration of PREVYMIS oral pellets via NG tube or G tube.

1. Pour PREVYMIS oral pellets into a medicine cup containing room temperature water (see Initial Volume in Table 4 and Table 5). Do not mix PREVYMIS oral pellets with hot or cold (refrigerated) water.

2. Wait 10 minutes. Do not shake or swirl the medicine cup. PREVYMIS oral pellets will not dissolve but will become loose or broken up. The entire mixture should be administered (see steps 3 and 4) within 2 hours.

3. Stir the mixture with the syringe and administer entire mixture right away using the syringe and NG tube or G tube.

4. Add room temperature water (see Rinse Volume in Table 4 and Table 5) to the medicine cup for rinsing, stir with a syringe and administer the entire rinse mixture using the syringe and NG tube or G tube.

5. Flush the NG tube or G tube with the volume of water recommended by the NG or G tube manufacturer.

Table 4: Recommendations for Administration of PREVYMIS Oral Pellets Via NG Tube

<table>
<tr><th>Dosage</th><th>NG Tube*</th><th>Syringe Type†</th><th>Mixing Container</th><th>Initial Volume (mL)</th><th>Rinse Volume (mL)</th></tr>
<tr><td>120 mg to 480 mg</td><td>Any ≥ 8 Fr NG tube</td><td rowspan="2">Appropriately sized ENFit or catheter-tipped syringe</td><td rowspan="2">Medicine Cup</td><td>15</td><td>15</td></tr>
<tr><td>40 mg to 80 mg</td><td>5 Fr PUR NG tube
or
Any ≥ 6 Fr NG tube</td><td>3</td><td>2</td></tr>
<tr><td colspan="6">* Fr = French; PUR = polyurethane
† With ENFit syringe, a medicine straw (large bore) is needed to aid withdrawal of the mixture from the medicine cup.</td></tr>
</table>

Table 5: Recommendations for Administration of PREVYMIS Oral Pellets Via G Tube

Dosage	G Tube*	Syringe Type†	Mixing Container	Initial Volume (mL)	Rinse Volume (mL)
120 mg to 480 mg	Any G tube	Appropriately sized ENFit or catheter-tipped syringe	Medicine Cup	15	15
40 mg to 80 mg	Any 12 Fr G tube			3	2

* Fr = French; PUR = polyurethane
† With ENFit syringe, a medicine straw (large bore) is needed to aid withdrawal of the mixture from the medicine cup.

2.10 Preparation and Administration of Intravenous Solution

PREVYMIS 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).

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

Preparation Instructions

- PREVYMIS must be diluted prior to intravenous (IV) use. Only 0.9% Sodium Chloride and 5% Dextrose are chemically and physically compatible with PREVYMIS injection.
- Do not shake PREVYMIS vial.
- Inspect vial contents for discoloration and particulate matter prior to dilution. PREVYMIS injection is a clear colorless solution and may contain a few product-related small translucent or white particles.
- Do not use the vial if the solution is cloudy, discolored, or contains matter other than a few small translucent or white particles.
- Once diluted, the solution of PREVYMIS is clear, and ranges from colorless to yellow. Variations of color within this range do not affect the quality of the product.
- Do not use PREVYMIS injection with IV bags and infusion set materials containing the plasticizer diethylhexyl phthalate (DEHP). Use only with IV bags and infusion set materials that are DEHP-free. Materials that are phthalate-free are also DEHP-free.
- Use compatible IV bags and infusion set materials. PREVYMIS injection is compatible with the following IV bags and infusion set materials. PREVYMIS injection is not recommended with any IV bags or infusion set materials not listed below (note that PREVYMIS 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:
      Tris (2-ethylhexyl) trimellitate (TOTM), benzyl butyl phthalate (BBP)

- Catheters:
  Radiopaque polyurethane

- For the **480 mg or 240 mg dose**, add PREVYMIS injection (see Table 6) 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.

- For the **120 mg or 60 mg dose**, add PREVYMIS injection into a pre-filled IV bag containing either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP (see Table 6) and mix bag gently. Do not shake.

Table 6: Preparation of PREVYMIS Intravenous Solution for Doses of 60 mg or Greater

PREVYMIS Dose	Volume of PREVYMIS 20 mg/mL to be Withdrawn from Vial	Volume of Diluent
480 mg	24 mL	250 mL
240 mg	12 mL	250 mL
120 mg	6 mL	100 mL
60 mg	3 mL	50 mL

- For the **40 mg dose**, prepare a dilution of PREVYMIS injection according to Table 7 in either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP and mix bag gently. Transfer 20 mL from the prepared dilution into an appropriately sized IV bag or syringe. Do not shake.

Table 7: Preparation of PREVYMIS Intravenous Solution for Doses of 40 mg

PREVYMIS Dose	Preparation of 2 mg/mL PREVYMIS Dilution	Final Infusion Volume of the Prepared 2 mg/mL PREVYMIS Dilution
40 mg	Add 5 mL of 20 mg/mL PREVYMIS to 45 mL of diluent (0.9% Sodium Chloride Injection or 5% Dextrose Injection) and mix gently	20 mL

Administration Instructions

- Administer the entire contents of the intravenous bag or syringe by intravenous infusion via a peripheral catheter or central venous line at a constant rate over 1 hour *[see Dosage and Administration (2.1)]*.

- The diluted solution must be administered through a sterile 0.2 micron or 0.22 micron polyethersulfone (PES) in-line filter. Do not administer through a filter other than a sterile 0.2 micron or 0.22 micron PES in-line filter.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

- Discard if the diluted solution is cloudy, discolored, or contains matter other than a few small translucent or white particles.

2.11 Storage of the Diluted Solution

The diluted solutions (as prepared in Table 6 or Table 7) are 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).

2.12 Compatible Drug Products Used for Intravenous Administration

Compatible Drug Products

The physical compatibility of PREVYMIS injection with selected injectable drug products was evaluated in two commonly available diluents. PREVYMIS 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 PREVYMIS 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 PREVYMIS 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 PREVYMIS. However, Amphotericin B (liposomal) is incompatible *[see Dosage and Administration (2.13)]*.

2.13 Incompatible Drug Products and Other Materials Used for Intravenous Administration

Incompatible Drug Products

PREVYMIS 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.

Incompatible IV Bags and Infusion Set Materials

PREVYMIS injection is incompatible with diethylhexyl phthalate (DEHP) plasticizers and polyurethane-containing IV administration set tubing.

3 DOSAGE FORMS AND STRENGTHS

Tablets

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

Oral Pellets

- PREVYMIS oral pellets: beige round pellets in packets. Each packet contains 20 mg letermovir.
- PREVYMIS oral pellets: beige round pellets in packets. Each packet contains 120 mg letermovir.

Injection

- PREVYMIS 240 mg/12 mL (20 mg/mL) injection: clear and colorless solution in a single-dose vial.
- PREVYMIS 480 mg/24 mL (20 mg/mL) injection: clear and colorless solution in a single-dose vial.

4 CONTRAINDICATIONS

- PREVYMIS is contraindicated in patients receiving pimozide or ergot alkaloids:
    - Pimozide: Concomitant administration of PREVYMIS in patients receiving pimozide may result in increased concentrations of pimozide due to inhibition of cytochrome P450 3A (CYP3A) by letermovir, which may lead to QT prolongation and torsades de pointes *[see Warnings and Precautions (5.1) and Drug Interactions (7.2, 7.3)]*.
    - Ergot alkaloids: Concomitant administration of PREVYMIS in patients receiving ergot alkaloids may result in increased concentrations of ergot alkaloids (ergotamine and dihydroergotamine) due to inhibition of CYP3A by letermovir, which may lead to ergotism *[see Warnings and Precautions (5.1) and Drug Interactions (7.2, 7.3)]*.
- PREVYMIS is contraindicated with pitavastatin and simvastatin when co-administered with cyclosporine. Concomitant administration of PREVYMIS in combination with cyclosporine may result in significantly increased pitavastatin or simvastatin concentrations, which may lead to myopathy or rhabdomyolysis *[see Warnings and Precautions (5.1) and Drug Interactions (7.2, 7.3)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions

The concomitant use of PREVYMIS and certain drugs may result in potentially significant drug interactions, some of which may lead to adverse reactions (PREVYMIS or concomitant drugs) or reduced therapeutic effect of PREVYMIS or the concomitant drug *[see Contraindications (4) and Drug Interactions (7.1, 7.2, 7.3)]*.

See Table 11 for steps to prevent or manage these possible or known significant drug interactions, including dosing recommendations. Consider the potential for drug interactions prior to and during PREVYMIS therapy; review concomitant medications during PREVYMIS therapy; and monitor for adverse reactions associated with PREVYMIS and concomitant medications.

5.2 Risks Associated with Hydroxypropyl Betadex Excipient in Intravenous Formulation

Intravenous formulation of PREVYMIS contains the excipient hydroxypropyl betadex. PREVYMIS injection should be used only in patients unable to take oral therapy and patients should be switched to oral PREVYMIS as soon as they are able to take oral medications. If possible, intravenous administration should not exceed 4 weeks *[see Dosage and Administration (2.1)].*

In patients with renal impairment, accumulation of hydroxypropyl betadex may occur. In adult patients with CLcr less than 50 mL/min and in pediatric patients with a similar degree of renal impairment (based on age-appropriate assessment of renal function) receiving PREVYMIS injection, closely monitor serum creatinine levels *[see Dosage and Administration (2.7) and Use in Specific Populations (8.6)]*.

Animal studies have shown the potential for hydroxypropyl betadex to cause ototoxicity *[see Nonclinical Toxicology (13.2)].* The active ingredient, letermovir, is not known to be associated with ototoxicity.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adult CMV-seropositive Recipients [R+] of an Allogeneic HSCT
Prophylaxis Through Week 14 (~100 days) Post-HSCT
The safety of PREVYMIS was evaluated in a Phase 3 randomized, double-blind, placebo-controlled trial (P001) in which 565 subjects were randomized and treated with PREVYMIS (N=373) or placebo (N=192) through Week 14 post-HSCT. 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 PREVYMIS arm compared to the placebo arm.

Cardiac Adverse Events
The cardiac adverse event rate was higher in subjects receiving PREVYMIS (13%) compared to subjects receiving placebo (6%). The most common cardiac adverse events were tachycardia (reported in 4% of PREVYMIS subjects and in 2% of placebo subjects) and atrial fibrillation (reported in 3% of PREVYMIS subjects and in 1% of placebo subjects). Among those subjects who experienced one or more cardiac adverse events, 85% of PREVYMIS 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 PREVYMIS group and at a frequency at least 2% greater than placebo are outlined in Table 8.

Table 8: Trial P001 All Grade Adverse Events Reported in ≥ 10% of PREVYMIS-Treated HSCT Recipients at a Frequency at least 2% Greater than Placebo

Adverse Events	PREVYMIS (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 PREVYMIS subjects vs. 12% of placebo subjects). The most frequently reported adverse event that led to study drug discontinuation was nausea, occurring in 2% of PREVYMIS subjects and 1% of placebo subjects. Hypersensitivity reaction, with associated moderate dyspnea, occurred in one subject following the first infusion of IV PREVYMIS after switching from oral PREVYMIS, leading to treatment discontinuation.

Laboratory Abnormalities
Selected laboratory abnormalities reported during treatment or within 2 weeks of stopping treatment are presented in Table 9.

Table 9: Trial P001 Selected Laboratory Abnormalities

	PREVYMIS 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/mm^3 on 3 consecutive days after transplantation) was 19 days in the PREVYMIS group and 18 days in the placebo group.

Prophylaxis From Week 14 (~100 days) Through Week 28 (~200 days) Post-HSCT
The safety of PREVYMIS was evaluated in a Phase 3 randomized, double-blind, placebo-controlled trial (P040) in which 218 subjects who completed PREVYMIS prophylaxis through ~100 days post-HSCT were randomized to treatment with PREVYMIS (N=144) or placebo (N=74) through Week 28 (~200 days) post-HSCT. Adverse events were those reported while subjects were on study drug or within two weeks of study drug completion/discontinuation.

The most commonly reported adverse events in P040 were similar to those reported in P001. Study drug was discontinued due to an adverse event in 5% of PREVYMIS subjects and 1% of placebo subjects. The cardiac adverse event rate was 4% in the PREVYMIS and placebo groups.

The rates of hematologic laboratory abnormalities were comparable in the PREVYMIS and placebo groups. Serum creatinine abnormalities > 1.5 mg/dL occurred in 15% of PREVYMIS and 8% of placebo subjects.

Adult Kidney Transplant Recipients [D+/R-]
The safety of PREVYMIS was evaluated in a Phase 3 randomized, double-blind, active comparator-controlled trial (P002) in which 589 subjects were treated with PREVYMIS (N=292) or valganciclovir (N=297) through Week 28 post-transplant. Adverse events were those reported while subjects were on study medication or within two weeks of study medication completion/discontinuation. In these subjects, diarrhea was reported in at least 10% of subjects in the PREVYMIS group and at a frequency greater than valganciclovir (PREVYMIS, 32%; valganciclovir, 29%). Study drug was discontinued due to an adverse

event in 4% of PREVYMIS subjects and 14% of valganciclovir subjects. The most frequently reported adverse events that led to study drug discontinuation were neutropenia (PREVYMIS, 1%; valganciclovir, 2%) and leukopenia (PREVYMIS, 1%; valganciclovir, 5%).

Laboratory Abnormalities
Selected laboratory abnormalities reported through Week 28 post-transplant are presented in Table 10.

Table 10: Trial P002 Selected Laboratory Abnormalities

	PREVYMIS N=292	**Valganciclovir N=297**
Absolute neutrophil count (cells/μL)		
< 500	2%	7%
500 – < 750	1%	4%
750 – < 1000	1%	8%
Total < 1000	5%	18%
Hemoglobin (g/dL)		
< 6.5	2%	0%
6.5 – < 8.0	4%	5%
8.0 – < 9.5	29%	32%
Total < 9.5	34%	37%
Platelets (cells/μL)		
< 50000	0%	0%
50000 – < 100000	1%	3%
Total < 100000	1%	3%
Leukocytes (cells/μL)		
< 1000	1%	2%
1000 – < 2000	5%	19%
2000 – < 2500	4%	14%
Total < 2500	10%	35%
Serum creatinine (mg/dL)		
> 2.5	24%	22%
> 1.5 – 2.5	49%	52%
Total > 1.5	73%	73%

Pediatric Recipients of an Allogeneic HSCT

The safety of PREVYMIS was evaluated in 63 pediatric subjects aged 2 months to less than 18 years of age who received an allogeneic HSCT (P030). PREVYMIS was administered orally (tablet or pellet) or intravenously. The duration of PREVYMIS exposure ranged from 3 days to 102 days (median duration 84 days). The safety profile was consistent with the safety profile observed in clinical trials of PREVYMIS in adults *[see Use in Specific Populations (8.4) and Clinical Studies (14.4)].*

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect PREVYMIS

Letermovir is a substrate of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) and P-glycoprotein (P-gp) transporters and UDP-glucuronosyltransferase 1A1/3 (UGT1A1/3) enzymes. Co-administration of PREVYMIS with drugs that are inhibitors of OATP1B1/3 transporters may result in increases in letermovir plasma concentrations (Table 11).

Co-administration of PREVYMIS with inducers of transporters (e.g., P-gp) and/or enzymes (e.g., UGTs) is not recommended due to the potential for a decrease in letermovir plasma concentrations *(see Table 11)*.

7.2 Potential for PREVYMIS to Affect Other Drugs

Co-administration of PREVYMIS with midazolam results in increased midazolam plasma concentrations, indicating that letermovir is a moderate inhibitor of CYP3A *[see Clinical Pharmacology (12.3)]*. Co-administration of PREVYMIS with drugs that are CYP3A substrates may result in clinically relevant increases in the plasma concentrations of co-administered CYP3A substrates (Table 11) *[see Contraindications (4) and Warnings and Precautions (5.1)]*.

Letermovir is an inhibitor of OATP1B1/3 transporters. Co-administration of PREVYMIS with drugs that are substrates of OATP1B1/3 transporters may result in a clinically relevant increase in plasma concentrations of co-administered OATP1B1/3 substrates (Table 11).

The magnitude of CYP3A- and OATP1B1/3-mediated drug interactions on co-administered drugs may be different when PREVYMIS is co-administered with cyclosporine. See the prescribing information for cyclosporine for information on drug interactions with cyclosporine.

7.3 Established and Other Potentially Significant Drug Interactions

If dose adjustments of concomitant medications are made due to treatment with PREVYMIS, doses should be readjusted after treatment with PREVYMIS is completed.

Table 11 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on adult studies conducted with PREVYMIS or are predicted drug interactions that may occur with PREVYMIS *[see Contraindications (4), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

Table 11: Potentially Significant Drug Interactions: Alteration in Dose May Be Recommended Based on Results from Adult Drug Interaction Studies or Predicted Interactions* (Information in the Table Applies to Co-administration of PREVYMIS 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 PREVYMIS.
Antibiotics		
nafcillin	↓ letermovir	Co-administration of PREVYMIS and nafcillin is not recommended due to potential for loss of efficacy of PREVYMIS.
Anticoagulants		
warfarin	↓ warfarin	When PREVYMIS is co-administered with warfarin, frequently monitor International Normalized Ratio (INR)‡.
Anticonvulsants		
carbamazepine	↓ letermovir	Co-administration of PREVYMIS and carbamazepine is not recommended due to potential for loss of efficacy of PREVYMIS.
phenobarbital	↓ letermovir	Co-administration of PREVYMIS and phenobarbital is not recommended due to potential for loss of efficacy of PREVYMIS.
phenytoin	↓ letermovir ↓ phenytoin	Co-administration of PREVYMIS and phenytoin is not recommended due to potential for loss of efficacy of PREVYMIS.
Antidiabetic Agents		
Examples: glyburide, repaglinide, rosiglitazone	↑ glyburide ↑ repaglinide ↑ rosiglitazone	When PREVYMIS is co-administered with glyburide, repaglinide, or rosiglitazone, frequently monitor glucose concentrations‡. When PREVYMIS 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‡.
Antimycobacterials		
rifabutin	↓ letermovir	Co-administration of PREVYMIS and rifabutin is not recommended due to potential for loss of efficacy of PREVYMIS.

rifampin§	↓ letermovir	Co-administration of PREVYMIS and rifampin is not recommended due to potential for loss of efficacy of PREVYMIS.
Antipsychotics		
pimozide	↑ pimozide	Co-administration is contraindicated due to risk of QT prolongation and torsades de pointes *[see Contraindications (4)]*.
thioridazine	↓ letermovir	Co-administration of PREVYMIS and thioridazine is not recommended due to potential for loss of efficacy of PREVYMIS.
Endothelin Antagonists		
bosentan	↓ letermovir	Co-administration of PREVYMIS and bosentan is not recommended due to potential for loss of efficacy of PREVYMIS.
Ergot Alkaloids		
ergotamine, dihydroergotamine	↑ ergotamine, dihydroergotamine	Co-administration is contraindicated due to risk of ergotism *[see Contraindications (4)]*.
Herbal Products		
St. John's wort (*Hypericum perforatum*)	↓ letermovir	Co-administration of PREVYMIS and St. John's wort is not recommended due to potential for loss of efficacy of PREVYMIS.
HIV Medications		
efavirenz	↓ letermovir	Co-administration of PREVYMIS and efavirenz is not recommended due to potential for loss of efficacy of PREVYMIS.
etravirine	↓ letermovir	Co-administration of PREVYMIS and etravirine is not recommended due to potential for loss of efficacy of PREVYMIS.
nevirapine	↓ letermovir	Co-administration of PREVYMIS and nevirapine is not recommended due to potential for loss of efficacy of PREVYMIS.
HMG-CoA Reductase Inhibitors		
atorvastatin§	↑ atorvastatin	When PREVYMIS is co-administered with atorvastatin, do not exceed an atorvastatin dosage of 20 mg daily‡. Closely monitor patients for myopathy and rhabdomyolysis. When PREVYMIS is co-administered with cyclosporine, use of atorvastatin is not recommended.

pitavastatin, simvastatin	↑ HMG-CoA reductase inhibitors	Co-administration of PREVYMIS and pitavastatin or simvastatin is not recommended. When PREVYMIS 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 *[see Contraindications (4)]*.
fluvastatin, lovastatin, pravastatin, rosuvastatin	↑ HMG-CoA reductase inhibitors	When PREVYMIS is co-administered with these statins, a statin dosage reduction may be necessary‡. Closely monitor patients for myopathy and rhabdomyolysis. When PREVYMIS is co-administered with cyclosporine, use of lovastatin is not recommended. When PREVYMIS is co-administered with cyclosporine, refer to the statin prescribing information for specific statin dosing recommendations.
Immunosuppressants		
cyclosporine§	↑ cyclosporine ↑ letermovir	Decrease the dosage of PREVYMIS to 240 mg once daily in adult and pediatric patients 12 years of age and older *[see Dosage and Administration (2.4) and Clinical Pharmacology (12.3)]*. Dose adjustment may be required in pediatric patients less than 12 years of age *[see Dosage and Administration (2.6) and Clinical Pharmacology (12.3)]*. Frequently monitor cyclosporine whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of cyclosporine accordingly‡.
sirolimus§	↑ sirolimus	When PREVYMIS is co-administered with sirolimus, frequently monitor sirolimus whole blood concentrations during treatment and after discontinuation of PREVYMIS and adjust the dose of sirolimus accordingly§. When PREVYMIS 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 PREVYMIS and adjust the dose of tacrolimus accordingly‡.
Proton Pump Inhibitors		

omeprazole	↓ omeprazole	Clinical monitoring and dose adjustment may be needed.
pantoprazole	↓ pantoprazole	Clinical monitoring and dose adjustment may be needed.
Wakefulness-Promoting Agents		
modafinil	↓ letermovir	Co-administration of PREVYMIS and modafinil is not recommended due to potential for loss of efficacy of PREVYMIS.
CYP3A Substrates		
Examples: alfentanil, fentanyl, midazolam, and quinidine	↑ CYP3A substrate	When PREVYMIS is co-administered with a CYP3A substrate, refer to the prescribing information for dosing of the CYP3A substrate with a moderate CYP3A inhibitor‡. When PREVYMIS 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 *[see Contraindications (4)]*.

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

7.4 Drugs without Clinically Significant Interactions with PREVYMIS

No clinically significant interactions were observed in adult clinical drug-drug interaction studies of letermovir and acyclovir, digoxin, mycophenolate mofetil, fluconazole, itraconazole, posaconazole, ethinyl estradiol, and levonorgestrel.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

Data
Animal Data

Letermovir was administered orally to pregnant rats at 0, 10, 50 or 250 mg/kg/day from gestation days 6 to 17. Developmental toxicities, including skeletal malformations and umbilical cord shortening, were observed at 250 mg/kg/day (approximately 11 times higher than human exposure at the RHD). In addition, decreased fetal body weight and skeletal variations (due to maternal toxicity) were observed at this dose. No embryo-fetal toxicities were observed at 50 mg/kg/day (approximately 3 times higher than human exposure at the RHD).

Letermovir was administered orally to pregnant rabbits at 0, 25, 75 or 225 mg/kg/day from gestation days 6 to 20. Developmental toxicities, including spontaneous abortion, increased post-implantation loss, and skeletal variations, were observed at a maternally toxic dose (225 mg/kg/day; approximately 2 times higher than human exposure at the RHD). No embryo-fetal toxicities were observed at 75 mg/kg/day (less than human exposure at the RHD).

In the pre/post-natal development study, letermovir was administered orally to pregnant rats at 0, 10, 45 or 180 mg/kg/day from gestation day 6 to lactation day 22. At 180 mg/kg/day (approximately 2 times higher than human exposure at the RHD), total litter loss due to stillbirth or possible maternal neglect was observed in 5 of 23 pregnant females by post-partum/lactation day 4. In surviving offspring, slight developmental delays in vaginal opening and pinna unfolding were accompanied by reduced body weight gain at this dose. No toxicities were observed at 45 mg/kg/day (similar to human exposure at the RHD).

8.2 Lactation

Risk Summary
It is not known whether letermovir is present in human breast milk, affects human milk production, or has effects on the breastfed child.

When administered to lactating rats, letermovir was present in the milk of lactating rats as well as the blood of nursing pups *(see Data)*.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for PREVYMIS and any potential adverse effects on the breastfed child from PREVYMIS or from the underlying maternal condition.

Data
In a lactation study, letermovir was excreted in milk when administered intravenously (at 10 mg/kg) to lactating rats on post-partum/lactation day 10. Letermovir was also detected in the blood of nursing pups on post-partum/lactation day 21 in the pre/post-natal developmental study.

8.3 Females and Males of Reproductive Potential

Infertility
There are no data on the effect of letermovir on human fertility. Decreased fertility due to testicular toxicity was observed in male rats *[see Nonclinical Toxicology (13.1, 13.2)]*.

8.4 Pediatric Use

The safety and effectiveness of PREVYMIS have been established for:

- Prophylaxis of CMV infection and disease in pediatric CMV-seropositive recipients of an allogeneic HSCT 6 months of age and older and weighing at least 6 kg, and

- Prophylaxis of CMV disease in pediatric kidney transplant recipients 12 years of age and older and weighing at least 40 kg who are at high risk [D+/R-].

HSCT Recipients: The use of PREVYMIS for prophylaxis of CMV infection and disease in pediatric recipients of an allogeneic HSCT is supported by evidence from adequate and well-controlled studies in adults with additional pharmacokinetic and safety data from pediatric patients in Trial P030. The safety and pharmacokinetic results were similar to those in adults *[see Warnings and Precautions (5.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical studies (14.2, 14.4)]*.

Kidney Transplant Recipients: The use of PREVYMIS for prophylaxis of CMV disease in high-risk [D+/R-] kidney transplant recipients 12 years of age and older and weighing at least 40 kg is supported by evidence from an adequate and well-controlled study in adults and safety data from pediatric HSCT recipients (Trial P030). Letermovir exposures are expected to be similar between adult and pediatric patients 12 years of age and older and weighing at least 40 kg *[see Warnings and Precautions (5.2), Adverse Reactions (6.1), Clinical Pharmacology (12.3), Clinical studies (14.3, 14.4)]*.

The safety and effectiveness of PREVYMIS have not been established for:
- HSCT recipients less than 6 months of age or weighing less than 6 kg, or
- Kidney transplant recipients less than 12 years of age or weighing less than 40 kg.

8.5 Geriatric Use

Of the 373 subjects treated with PREVYMIS in Trial P001, 56 (15%) subjects were 65 years of age or older. Of the 144 subjects treated with PREVYMIS in Trial P040, 32 (22%) subjects were 65 years of age or older. Of the 292 subjects treated with PREVYMIS in Trial P002, 48 (16%) subjects were 65 years of age or older. Safety and efficacy were similar across older and younger subjects in each trial. No dosage adjustment of PREVYMIS is required based on age *[see Clinical Pharmacology (12.3)]*.

8.6 Renal Impairment

For adult patients with CLcr greater than 10 mL/min (by Cockcroft-Gault equation), and pediatric patients with a similar degree of renal impairment (based on age-appropriate assessment of renal function), no dosage adjustment of PREVYMIS is required based on renal impairment *[see Clinical Pharmacology (12.3)]*. The safety of PREVYMIS in adult patients with end-stage renal disease (CLcr less than 10 mL/min) or in pediatric patients with a similar degree of renal impairment (based on age-appropriate assessment of renal function), including patients on dialysis, is unknown.

In adult patients with CLcr less than 50 mL/min and in pediatric patients with a similar degree of renal impairment (based on age-appropriate assessment of renal function) receiving PREVYMIS injection, accumulation of the intravenous vehicle, hydroxypropyl betadex, could occur. Closely monitor serum creatinine levels in these patients *[see Dosage and Administration (2.7) and Warnings and Precautions (5.2)]*.

8.7 Hepatic Impairment

No dosage adjustment of PREVYMIS is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. PREVYMIS is not recommended for patients with severe (Child-Pugh Class C) hepatic impairment *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

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

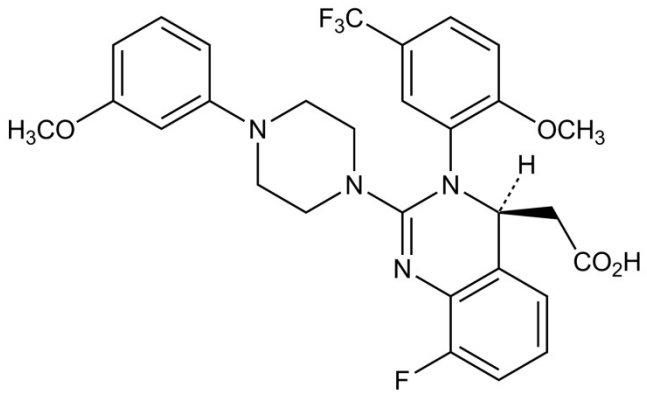
It is unknown whether dialysis will result in meaningful removal of PREVYMIS from systemic circulation.

11 DESCRIPTION

PREVYMIS contains letermovir, an inhibitor of the CMV DNA terminase complex, and is administered orally or by intravenous infusion.

Letermovir has a molecular formula of $C_{29}H_{28}F_4N_4O_4$ and a molecular weight of 572.55. The chemical name for letermovir is (4*S*)-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:



PREVYMIS is available as 240 mg and 480 mg tablets. PREVYMIS 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.

PREVYMIS is available as 20 mg and 120 mg packets of oral pellets. PREVYMIS packets of oral pellets contain either 20 mg or 120 mg of letermovir. PREVYMIS oral pellets contain the following inactive ingredients: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, povidone K-29/32, and are film-coated with a coating material containing the following inactive ingredients: hypromellose 2910, iron oxide red, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.

PREVYMIS is available as 240 mg/12 mL (20 mg/mL) and 480 mg/24 mL (20 mg/mL) injection for intravenous infusion. PREVYMIS injection is a clear, preservative-free sterile solution and may contain a few small translucent or white particles in single-dose vials of either 240 mg or 480 mg per vial. Each 1 mL of solution contains 20 mg letermovir, hydroxypropyl betadex (150 mg), sodium chloride (3.1 mg), sodium hydroxide (1.2 mg), and Water for Injection. The amount of sodium hydroxide may be adjusted to achieve a pH of approximately 7.5.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

PREVYMIS is an antiviral drug against CMV *[see Microbiology (12.4)]*.

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a thorough QT trial in healthy adult subjects, letermovir at the therapeutic IV dose or at a dose of 2 times the approved IV dose did not prolong QTc to any clinically relevant extent.

12.3 Pharmacokinetics

The pharmacokinetic properties of letermovir are displayed in Table 12.

Table 12: Absorption, Distribution, Metabolism, Elimination (ADME), and Pharmacokinetic Properties of PREVYMIS*

Pharmacokinetics in Adult HSCT Recipients	
Treatment Regimen	Steady-state median (90% prediction interval) AUC (ng•hr/mL) of PREVYMIS
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 Adult Kidney Transplant Recipients	
Treatment Regimen	Steady-state median (90% prediction interval) AUC (ng•hr/mL) of PREVYMIS
480 mg oral once daily, no cyclosporine	62,700 (17,500, 139,000)
240 mg oral once daily, with cyclosporine	71,900 (42,400, 125,000)
Pharmacokinetics in Healthy Adult Subjects	
Treatment Regimen	Steady-state geometric mean AUC and Cmax of PREVYMIS
480 mg oral once daily	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 PREVYMIS 240 mg and 480 mg
Accumulation ratio†	Cmax: 1.03 AUC: 1.22
Time to steady-state	9-10 days
Absorption	

Bioavailability	Healthy adult subjects administered PREVYMIS without cyclosporine: 94% at an oral dose range of 240 mg to 480 mg Adult HSCT recipients administered PREVYMIS without cyclosporine: 35% with 480 mg oral once daily Adult HSCT recipients administered PREVYMIS with cyclosporine: 85% with 240 mg oral once daily Adult kidney transplant recipients administered PREVYMIS without cyclosporine: 56%‡ with 480 mg oral once daily
Median Tmax (hr)	1.5 to 3.0 hr
Effect of food (relative to fasting)§	AUC: 99.63% [84.27% - 117.80%] Cmax: 129.82% [104.35% -161.50%]
Oral pellets versus tablet (fasting)	AUC and Cmax values were comparable when comparing PREVYMIS tablet (240 mg) and PREVYMIS oral pellets (2 X 120 mg)
Distribution	
Mean steady-state volume of distribution	45.5 L following IV administration in adult 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 PREVYMIS 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 adult subjects unless otherwise indicated. † Based on geometric mean data.	

‡ 95% CI (46%, 65%)

§ 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.

Specific Populations

Pediatric Patients
Letermovir AUC in pediatric HSCT recipients was estimated using population pharmacokinetic analysis using Trial P030 data (see Table 13 and Table 14). Exposures for pediatric HSCT recipients for body weight bands 6 kg and above are within the range of exposures observed at the recommended doses of PREVYMIS in adults (see Table 12).

Table 13: PREVYMIS AUC (ng•hr/mL) Values Following Once Daily Oral Administration in Pediatric HSCT Recipients

Body Weight	Oral Dose, No Cyclosporine	Steady-state Median (90% Prediction Interval)*	Oral Dose, With Cyclosporine	Steady-state Median (90% Prediction Interval)*
30 kg and above†	480 mg	38,500 (18,100, 78,100)	240 mg	50,200 (24,100, 102,000)
15 kg to less than 30 kg	240 mg	39,600 (21,300, 71,800)	120 mg	53,200 (27,800, 102,000)
7.5 kg to less than 15 kg	120 mg	32,900 (16,800, 61,200)	60 mg	42,300 (22,300, 81,500)
6 kg to less than 7.5 kg‡	80 mg	29,400 (16,600, 54,100)	40 mg	39,200 (20,900, 71,800)

* Medians and 90% prediction intervals are based on simulations using the pediatric HSCT population PK model with inter-individual variability.
† Includes pediatric patients 12 years of age and older or weighing ≥ 30 kg.
‡ Includes pediatric patients 6 months of age and older and weighing 6 kg to < 7.5 kg.

Table 14: PREVYMIS AUC (ng•hr/mL) Values Following Once Daily IV Administration in Pediatric HSCT Recipients

Body Weight	IV Dose, No Cyclosporine	Steady-state Median (90% Prediction Interval)*	IV Dose, With Cyclosporine	Steady-state Median (90% Prediction Interval)*
30 kg and above†	480 mg	114,000 (53,900, 230,000)	240 mg	61,400 (29,300, 128,000)
15 kg to less than 30 kg	120 mg	56,400 (29,100, 110,000)	120 mg	62,300 (32,100, 114,000)
7.5 kg to less than 15 kg	60 mg	45,900 (24,500, 86,400)	60 mg	49,900 (26,300, 96,300)
6 kg to less than 7.5 kg‡	40 mg	42,800 (23,800, 79,200)	40 mg	46,400 (26,300, 86,500)

* Medians and 90% prediction intervals are based on simulations using the pediatric HSCT population PK model with inter-individual variability.

† Includes pediatric patients 12 years of age and older or weighing ≥ 30 kg.
‡ Includes pediatric patients 6 months of age and older and weighing 6 kg to < 7.5 kg.

Age, Gender, Race, and Weight
Age (18 to 82 years), gender, race, and body weight (up to 100 kg) did not have a clinically significant effect on the pharmacokinetics of letermovir in adult subjects.

Renal Impairment
Clinical Study in a Renally Impaired Population
Letermovir AUC was approximately 1.9- and 1.4-fold higher in adult subjects with moderate (eGFR greater than or equal to 30 to 59 mL/min/1.73m^2) and severe (eGFR less than 30 mL/min/1.73m^2) renal impairment, respectively, compared to healthy adult subjects.

Post-kidney Transplant
Based on population pharmacokinetic analysis, letermovir AUC was approximately 1.1-, 1.3- and 1.4-fold higher in adult subjects with mild (CLcr greater than or equal to 60 to less than 90 mL/min), moderate (CLcr greater than or equal to 30 to less than 60 mL/min) and severe (CLcr greater than or equal to 15 to less than 30 mL/min) renal impairment, respectively, compared to adult subjects with CLcr greater than or equal to 90 mL/min.

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

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

Drug Interaction Studies
Drug interaction studies were performed in healthy adult subjects with PREVYMIS and drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interactions *(see Table 15 and Table 16)*.

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/BCRP by itraconazole were not clinically relevant. Changes in letermovir plasma concentrations due to inhibition of 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 PREVYMIS with midazolam resulted in increased exposure of midazolam, indicating that the net effect of letermovir on CYP3A is moderate inhibition *(see Table 16)*. Based on these results, co-administration of PREVYMIS with CYP3A substrates may increase the plasma concentrations of the CYP3A substrates *[see Contraindications (4), Warnings and Precautions (5.1), Drug Interactions (7.2, 7.3), and Table 11]*. Letermovir is a reversible inhibitor of CYP2C8 *in vitro*. When co-administered with PREVYMIS, plasma concentrations of CYP2C8 substrates are predicted to be increased *[see Table 11 in Drug Interactions (7.3)].* Co-administration of PREVYMIS reduced the exposure of voriconazole, most likely due to the

induction of voriconazole elimination pathways, CYP2C9 and CYP2C19. Co-administration of PREVYMIS with CYP2C9 and CYP2C19 substrates may decrease the plasma concentrations of the CYP2C9 and CYP2C19 substrates *[see Table 11 in Drug Interactions (7.3)]*. 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 PREVYMIS 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 11 in Drug Interactions (7.3)]*. There were no clinically relevant changes in plasma concentrations of digoxin, a P-gp substrate, or acyclovir, an OAT3 substrate, following co-administration with PREVYMIS in clinical studies *(see Table 16)*. 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 OATP2B1, OCT1, OCT2, or OAT1 *in vitro*.

Table 15: 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*
Antifungals					
fluconazole	400 mg single dose PO	480 mg single dose PO	1.11 (1.01, 1.23)	1.06 (0.93, 1.21)	1.28 (1.15, 1.43)
itraconazole	200 mg once daily PO	480 mg once daily PO	1.33 (1.17, 1.51)	1.21 (1.05, 1.39)	1.90 (1.58, 2.28)
Antimycobacterials					
rifampin	600 mg single dose PO	480 mg single dose PO	2.03 (1.84, 2.26)	1.59 (1.46, 1.74)	2.01 (1.59, 2.54)
	600 mg single dose IV	480 mg single dose PO	1.58 (1.38, 1.81)	1.37 (1.16, 1.61)	0.78 (0.65, 0.93)
	600 mg once daily PO	480 mg once daily PO	0.81 (0.67, 0.98)	1.01 (0.79, 1.28)	0.14 (0.11, 0.19)
	600 mg once daily PO (24 hours after rifampin)†	480 mg once daily PO	0.15 (0.13, 0.17)	0.27 (0.22, 0.31)	0.09 (0.06, 0.12)
Immunosuppressants					

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*
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 (0.92, 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 † These data are the effect of rifampin on letermovir 24 hours after final rifampin dose.					

Table 16: 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)
	2 mg single dose PO	240 mg once daily PO	2.25 (2.04, 2.48)	1.72 (1.55, 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)

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*
fluconazole	400 mg single dose PO	480 mg single dose PO	1.03 (0.99, 1.08)	0.95 (0.92, 0.99)	1.04 (1.00, 1.08)
itraconazole	200 mg once daily PO	480 mg once daily PO	0.76 (0.71, 0.81)	0.84 (0.76, 0.92)	0.67 (0.61, 0.73)
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.					

12.4 Microbiology

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.

Antiviral Activity

The median EC_{50} 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 EC_{50} value by CMV gB genotype (gB1=29; gB2=27; gB3=11; and gB4=3).

Combination Antiviral Activity

No antagonism of the antiviral activity was seen when letermovir was combined with CMV DNA polymerase inhibitors (cidofovir, foscarnet, or ganciclovir).

Viral Resistance

In Cell Culture

CMV mutants with reduced susceptibility to letermovir have been selected in cell culture and the resistance mutations map to UL51, UL56, and UL89. Resistance-associated substitutions were found in pUL51 (P91S, A95V), pUL56 (C25F, S229F, V231A/L, N232Y, V236A/L/M, E237D, L241P, T244K/R, L254F, L257F/I, K258E, F261C/L/S, Y321C, C325F/R/W/Y, L328V, M329T, A365S, N368D, R369G/M/S), and pUL89 (N320H, D344E). EC_{50} values for recombinant CMV mutants expressing these substitutions are 1.6- to 9,300-fold higher than those for the wild-type reference virus.

In Clinical Studies
In a Phase 2b trial evaluating letermovir or placebo in 131 adult HSCT recipients, DNA sequence analysis of a select region of UL56 (amino acids 231 to 369) was performed on samples obtained from 12 letermovir-treated subjects who experienced prophylaxis failure and for whom on-treatment samples were available for analysis. One subject had a letermovir resistance substitution, pUL56 V236M (19-50-fold reduction in susceptibility).

In a Phase 3 trial (P001), DNA sequence analysis of the entire coding regions of UL56 and UL89 was performed on samples obtained from 50 letermovir-treated adult subjects who had received at least one dose of study drug and experienced prophylaxis failure and for whom samples were available for analysis. The pUL56 substitutions V236M (19-50-fold reduction), E237G (13-fold reduction), C325W (9300-fold reduction), and R369T (52-fold reduction) were detected in 3 subjects; however, no 2 subjects had substitutions at the same positions.

In a Phase 3 trial (P040), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 32 adult subjects (regardless of treatment group) who experienced prophylaxis failure or who discontinued early with CMV viremia. No letermovir resistance-associated substitutions were detected above the validated assay limit.

In a Phase 3 trial (P002), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 52 letermovir-treated adult subjects who experienced CMV disease or who discontinued early with CMV viremia. No previously characterized resistance-associated substitutions were identified. Novel substitutions were detected in letermovir-treated subjects at resistance-associated positions (pUL56 S229Y [n=1], pUL56 M329I [n=9], and pUL89 D344Y [n=5]) at low frequencies, ranging between 0.05 to 0.07. The clinical significance of these substitutions is unknown; phenotypic analysis is planned.

In a Phase 2b trial (P030), DNA sequence analysis of the entire coding regions of UL51, UL56 and UL89 was performed on samples obtained from 10 letermovir-treated pediatric subjects at a visit for evaluation of CMV infection. A total of 2 letermovir resistance-associated substitutions both mapping to pUL56 were detected in 2 subjects. One subject had the substitution C325W (9300-fold reduction), and the other had R369S (38-fold reduction).

Cross Resistance
Cross resistance is not likely with drugs outside of this class. Letermovir is fully active against viral populations with substitutions conferring resistance to CMV DNA polymerase inhibitors (cidofovir, foscarnet, and ganciclovir). These DNA polymerase inhibitors are expected to be fully active against viral populations with substitutions conferring resistance to letermovir.

13 NONCLINICAL TOXICOLOGY

13.1 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.

Letermovir was not carcinogenic in a 6-month RasH2 transgenic mouse study up to the highest doses tested (150 mg/kg/day in males and 300 mg/kg/day in females). Based on a comprehensive assessment of the available toxicology data and the CMV-specific target, letermovir is not expected to be carcinogenic in humans.

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)]*.

13.2 Animal Toxicology and/or 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).

The excipient, hydroxypropyl betadex, present in the IV letermovir formulation, has been associated with hearing loss resulting from damage to the inner ear in multiple animal species. In published studies in rats, a single subcutaneous dose of 2000 mg/kg hydroxypropyl betadex resulted in changes in hearing parameters and associated decreases in outer hair cells in the inner ear. These findings were observed at hydroxypropyl betadex levels approximately 3 times higher than those present in the letermovir IV drug product at the MRHD, based on body surface area (BSA) comparisons. No adverse changes in hearing parameters or hair cell populations in the inner ear were observed in rats following a single subcutaneous dose of 1000 mg/kg hydroxypropyl betadex, which corresponds to levels approximately 1.5 times higher than those present in the letermovir IV drug product at the MRHD, based on BSA comparisons *[see Warnings and Precautions (5.2)]*.

14 CLINICAL STUDIES

14.1 Overview of Clinical Studies

An overview of the trials contributing to the assessment of efficacy and safety of PREVYMIS in HSCT and kidney transplant recipients is provided in Table 17.

Table 17: Trials Conducted with PREVYMIS

Trial (NCT Number)	Population	Trial Arms (N)*	Duration of Prophylaxis Post-Transplant	Efficacy Endpoint
P001 (NCT02137772)	Adult allogeneic HSCT recipients [R+]	PREVYMIS (373) Placebo (192)	Through Week 14	Clinically significant CMV infection through Week 24 post-HSCT
P040 (NCT03930615)	Adult allogeneic HSCT recipients [R+] at risk for late CMV infection and disease	PREVYMIS (144) Placebo (74)	Extension of prophylaxis from Week 14 through Week 28	Clinically significant CMV infection through Week 28 post-HSCT
P002 (NCT03443869)	Adult kidney transplant recipients [D+/R-]	PREVYMIS (292) Valganciclovir (297)	Through Week 28	CMV disease through Week 52 post-kidney transplant
P030 (NCT03940586)	Pediatric allogeneic HSCT recipients	PREVYMIS (63)	Through Week 14	Clinically significant CMV infection through

				Week 24 post-HSCT

* N represents the number of subjects treated.

14.2 Adult CMV-seropositive Recipients [R+] of an Allogeneic Hematopoietic Stem Cell Transplant (Trial P001 and Trial P040)

Prophylaxis Through Week 14 (~100 days) Post-HSCT (Trial P001)

To evaluate PREVYMIS prophylaxis as a preventive strategy for CMV infection or disease in transplant recipients at high risk for CMV reactivation, the efficacy of PREVYMIS 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 PREVYMIS 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-HSCT) and continued through Week 14 post-HSCT. Study drug was administered either orally or intravenously; the dose of PREVYMIS was the same regardless of the route of administration. Subjects received CMV DNA monitoring weekly until post-HSCT Week 14 and then bi-weekly until post-HSCT 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-HSCT.

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 PREVYMIS (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 PREVYMIS 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 5% were other (American Indian or Alaska Native, multiple, and missing). 7% were Hispanic or Latino; 89% not Hispanic or Latino; and 4% other (not reported, unknown, and missing).

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-HSCT (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-HSCT or had a missing outcome at Week 24 post-HSCT were counted as failures.

Efficacy results from Trial P001 are shown in Table 18.

Table 18: Trial P001 Incidence of Clinically Significant CMV Infection in HSCT Recipients (NC=F Approach, FAS Population) Through Week 24

Parameter	PREVYMIS (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 (PREVYMIS-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 PREVYMIS 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.

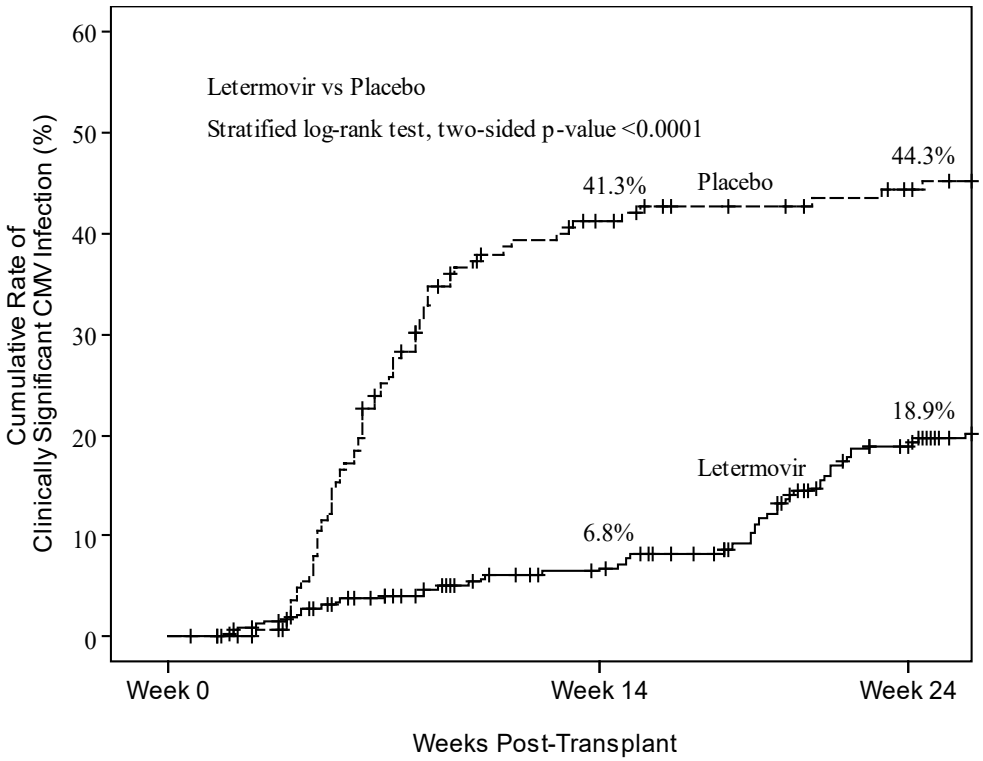
§ 95% CI and p-value for the treatment differences in percent response were calculated using stratum-adjusted Mantel-Haenszel method with the difference weighted by the harmonic mean of sample size per arm for each stratum (high or low risk).

¶ 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-HSCT 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 Figure 1. Among subjects in the PREVYMIS group, the cumulative rate of clinically significant CMV infection increased from 6.8% at the end of prophylaxis (Week 14) to 18.9% at Week 24. In the placebo group, the cumulative rate of clinically significant CMV infection increased from 41.3% at Week 14 to 44.3% at Week 24 *[see Dosage and Administration (2.2)].*

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 PREVYMIS-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-HSCT.

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

Prophylaxis From Week 14 (~100 days) Through Week 28 (~200 days) Post-HSCT (Trial P040)
The efficacy of extending PREVYMIS prophylaxis from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT in patients at risk for late CMV infection and disease was assessed in a multicenter, double-blind, placebo-controlled Phase 3 trial (P040, NCT03930615) in adult CMV-seropositive recipients [R+] of an allogeneic HSCT. Eligible subjects who completed PREVYMIS prophylaxis through ~100 days post-HSCT were randomized (2:1) to receive PREVYMIS or placebo from Week 14 through Week 28 post-HSCT. Subjects received PREVYMIS at a dose of 480 mg once daily (adjusted to 240 mg when co-

administered with cyclosporine) or placebo. Study drug was administered either orally or IV; the dose of PREVYMIS was the same regardless of the route of administration. One subject received IV PREVYMIS for 2 days. Subjects were monitored through Week 28 post-HSCT for the primary efficacy endpoint with continued off-treatment follow-up through Week 48 post-HSCT.

Among the 218 treated subjects, 144 subjects received PREVYMIS and 74 received placebo. The median age was 55 years (range: 20 to 74 years); 62% were male; 79% were white; 11% were Asian; 2% were Black; 1% were multiple races; 6% had missing race; and 10% were Hispanic or Latino.

At study entry, all subjects had risk factors for late CMV infection and disease, with 64% having two or more risk factors. The risk factors included: HLA-related (sibling) 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; receipt of anti-thymocyte globulin; receipt of alemtuzumab; use of systemic prednisone (or equivalent) at a dose of ≥1 mg/kg of body weight per day. The most common reasons for transplant were acute myeloid leukemia (42%), acute lymphocytic leukemia (15%), and myelodysplastic syndrome (11%).

Clinically Significant CMV Infection
The primary efficacy endpoint of Trial P040 was the incidence of clinically significant CMV infection through Week 28 post-HSCT. Clinically significant CMV infection was defined as the occurrence of either CMV end-organ disease, or initiation of anti-CMV PET based on documented CMV viremia and the clinical condition of the subject. The Observed Failure (OF) approach was used, where subjects who discontinued prematurely from the study without viremia or were missing data at the timepoint were not counted as failures. The number of subjects who discontinued from the study before Week 28 without viremia was 14 (9.7%) in the PREVYMIS arm and 0 in the placebo arm. The number of subjects with a missing outcome in the Week 28 visit window was 3 (2.1%) in the PREVYMIS arm and 4 (5.4%) in the placebo arm, none had prior viremia.

Efficacy results from Trial P040 are shown in Table 19. Efficacy was consistent across subgroups based on participant characteristics (age, gender, race) and risk factors for late CMV infection and disease.

Table 19: Trial P040 Efficacy Results in HSCT Recipients at Risk for Late CMV Infection and Disease (OF Approach, FAS Population)

Parameter	PREVYMIS (~200 days PREVYMIS) (N=144)	Placebo (~100 days PREVYMIS) (N=74)
Failures*	**2.8%**	**18.9%**
Clinically significant CMV infection from Week 14 through Week 28†	1.4%	17.6%
Initiation of PET based on documented CMV viremia	0.7%	14.9%
CMV end-organ disease	0.7%	2.7%
Discontinued from study with CMV viremia before Week 28	1.4%	1.4%
Stratum-adjusted treatment difference (PREVYMIS (~200 days PREVYMIS)-Placebo (~100 days PREVYMIS))‡		
Difference (95% CI)	-16.1 (-25.8, -6.5)§	

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

† Clinically significant CMV infection was defined as CMV end-organ disease (proven or probable) or initiation of PET based on documented CMV viremia and the clinical condition of the subject.

‡ The 95% CIs 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 (haploidentical donor yes or no). A one-sided p-value ≤0.0249 was used for declaring statistical significance.

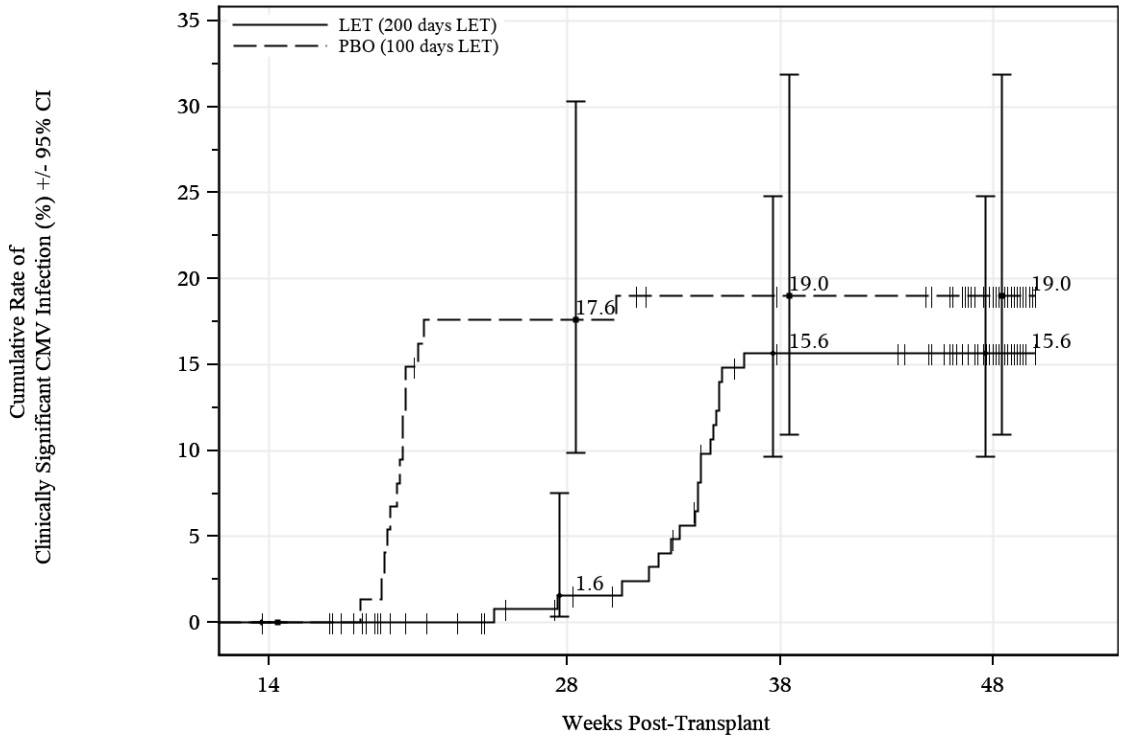
§ p-value = 0.0005

Approach to handling missing values: Observed Failure (OF) approach. With the OF approach, failure was defined as all subjects who developed clinically significant CMV infection or discontinued prematurely from the study with CMV viremia from Week 14 (~100 days) through Week 28 (~200 days) post-HSCT.

N = Number of subjects in each treatment group.

The time to clinically significant CMV infection is shown in Figure 2. Among subjects in the PREVYMIS group, the cumulative rate of clinically significant CMV infection increased from 1.6% at the end of prophylaxis (Week 28) to 15.6% at Week 38. In the placebo group, the cumulative rate of clinically significant CMV infection increased from 17.6% at Week 28 to 19.0% at Week 38. There were no additional cases of clinically significant CMV infection in either group between Weeks 38 and 48 *[see Dosage and Administration (2.2)]*.

Figure 2: Trial P040 Kaplan-Meier Plot of Time to Onset of Clinically Significant CMV Infection From Week 14 Through Week 48 Post-transplant in HSCT Recipients at Risk for Late CMV Infection and Disease (FAS Population)



Number of subjects at risk

LET (200 days LET)	143	123	99	74
PBO (100 days LET)	74	60	55	38

LET = Letermovir; PBO = Placebo

14.3 Adult CMV-seronegative Recipients of a Kidney Transplant from a CMV-seropositive Donor [D+/R-] (Trial P002)

To evaluate PREVYMIS prophylaxis as a preventive strategy for CMV disease in kidney transplant recipients, the efficacy of PREVYMIS was assessed in a multicenter, double-blind, active comparator-controlled non-inferiority Phase 3 trial (P002, NCT03443869) in adult kidney transplant recipients at high risk [D+/R-]. Subjects were randomized (1:1) to receive either PREVYMIS or valganciclovir. PREVYMIS was administered at a dose of 480 mg once daily (adjusted to 240 mg when co-administered with cyclosporine). PREVYMIS was given concomitantly with acyclovir. Valganciclovir was given concomitantly with a placebo to acyclovir. Randomization was stratified by the use or nonuse of highly cytolytic, anti-lymphocyte immunotherapy during induction. Study drug was initiated between Day 0 and Day 7 post-kidney transplant and continued through Week 28 (~200 days) post-transplant. Study drug was administered either orally or IV; the dose of PREVYMIS was the same regardless of the route of administration. Three subjects received IV PREVYMIS for a mean duration of 1.7 days. Subjects were monitored through Week 52 post-transplant.

Among the 589 treated subjects, 292 subjects received PREVYMIS and 297 received valganciclovir. The median age was 51 years (range: 18 to 82 years); 72% were male; 84% were White; 9% were Black; 3% were multiple; 2% were Asian; 1% Alaskan native or American Indian; 17% were Hispanic or Latino; and 60% received a kidney from a deceased donor. The most common primary reasons for transplant were congenital cystic kidney disease (17%), hypertension (16%), and diabetes/diabetic nephropathy (14%).

CMV Disease
The primary efficacy endpoint of Trial P002 was the incidence of CMV disease (CMV end-organ disease or CMV syndrome, confirmed by an independent adjudication committee) through Week 52 post-transplant. The Observed Failure (OF) approach was used, where subjects who discontinued prematurely from the study for any reason or were missing data at the timepoint were not counted as failures. The number of subjects who discontinued from the study before Week 52 was 32 (11%) in the PREVYMIS arm and 28 (9%) in the valganciclovir arm. The number of subjects with a missing outcome in the Week 52 visit window was 24 (8%) in the PREVYMIS arm and 25 (8%) in the valganciclovir arm.

Efficacy results from Trial P002 are shown in Table 20.

Table 20: Trial P002 Incidence of CMV Disease in Kidney Transplant Recipients (OF Approach, FAS Population) Through Week 52

Parameter	PREVYMIS (N=289)	Valganciclovir (N=297)
CMV Disease* Through Week 52	**10%**	**12%**
CMV Syndrome†	8%	11%
CMV End-organ Disease	2%	<1%
Stratum-adjusted Treatment Difference‡ (PREVYMIS – Valganciclovir)	-1.4 (-6.5, 3.8)§	

* CMV disease cases confirmed by an independent adjudication committee.

† Defined as evidence of CMV in blood by viral isolation, rapid culture, antigenemia, or nucleic acid testing, and two or more of the following: 1) fever ≥38°C for at least 2 days, 2) new or increased malaise/fatigue, 3) leukopenia or neutropenia on two separate measurements at least 24 hours apart, 4) ≥5% atypical lymphocytes, 5) thrombocytopenia, 6) elevation of ALT or AST to 2x ULN.

‡ The 95% CIs 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 (use/non-use of highly cytolytic, anti-lymphocyte immunotherapy during induction).

§ Based on a non-inferiority margin of 10%, PREVYMIS is non-inferior to valganciclovir.

Note: Approach to handling missing values: Observed failure (OF) approach. With OF approach, subjects who discontinued from the study before Week 52 or had a missing outcome in the Week 52 visit window were not counted as failures.

Efficacy was comparable across all subgroups, including the use/nonuse of highly cytolytic, anti-lymphocyte immunotherapy during induction.

In an exploratory analysis of the incidence of CMV disease through Week 28 post-transplant, the difference (PREVYMIS – Valganciclovir) was -1.7% with 95% CI of (-3.4, 0.1). No subjects in the PREVYMIS group experienced CMV disease through Week 28 post-transplant (end of treatment period) compared with 5 subjects in the valganciclovir group.

14.4 Pediatric Recipients of an Allogeneic HSCT (Trial P030)

Sixty-three children 2 months to less than 18 years of age who had an allogeneic HSCT were enrolled in a multicenter, open-label, single-arm pharmacokinetic, safety and effectiveness study of PREVYMIS (P030, NCT03940586). Subjects received PREVYMIS daily either orally or intravenously for CMV prophylaxis within 28 days post-HSCT through Week 14 post-HSCT. The intravenous formulation was used for up to four weeks in subjects who were unable to take oral therapy. The daily doses of PREVYMIS were based on body weight *[see Dosage and Administration (2.3, 2.5)].* Among the 63 treated subjects, 8 were 2 months to less than 2 years of age, 27 were 2 to less than 12 years of age and 28 were 12 to less than 18 years of age. The median age was 11 years; 70% were male; 70% were White; 14% were Asian; 5% were Black; and 22% were Hispanic or Latino *[see Use in Specific Populations (8.4)].*

The efficacy analyses population consisted of 56 subjects who received at least one dose of study drug and had no detectable CMV DNA at baseline. The proportion of subjects who failed CMV prophylaxis through Week 24 post-HSCT was 25% (14 of the 56 subjects). Six subjects had initiation of pre-emptive therapy based on CMV viremia and 8 subjects discontinued from the study before Week 24. None of the subjects had CMV end-organ disease.

PREVYMIS is indicated for pediatric recipients of an allogeneic HSCT aged 6 months and older and weighing at least 6 kg.

16 HOW SUPPLIED/STORAGE AND HANDLING

Tablets:

Each PREVYMIS 240 mg tablet is a yellow oval tablet; each tablet is debossed with “591” on one side and corporate logo on the other side. Each PREVYMIS 480 mg tablet is a pink oval, bi-convex tablet debossed with “595” on one side and corporate logo on the other side.

The 240 mg tablets are packaged into a carton (NDC 0006-3075-02) containing four (4) Child Resistant (CR) Dosepaks®, each containing a 7-count blister card for a total of 28 tablets, or into a carton (NDC 0006-3075-04) containing two (2) unit-dose 7-count blister cards for a total of 14 tablets.

The 480 mg tablets are packaged into a carton (NDC 0006-3076-02) containing four (4) Child Resistant (CR) Dosepaks®, each containing a 7-count blister card for a total of 28 tablets, or into a carton (NDC 0006-3076-04) containing two (2) unit-dose 7-count blister cards for a total of 14 tablets.

Store PREVYMIS tablets in the original package until use to protect from moisture.

Store PREVYMIS 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) [see USP Controlled Room Temperature].

Oral Pellets:

PREVYMIS oral pellets are supplied as beige round pellets in packets. Each packet contains 20 mg of letermovir.

PREVYMIS oral pellets are supplied as beige round pellets in packets. Each packet contains 120 mg of letermovir.

The 20 mg packets of PREVYMIS oral pellets are packaged into a carton (NDC 0006-5086-01). Each carton contains 30 child resistant packets.

The 120 mg packets of PREVYMIS oral pellets are packaged into a carton (NDC 0006-5085-01). Each carton contains 30 child resistant packets.

Store PREVYMIS oral pellets in the original packet until use.

Store PREVYMIS oral pellets at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Injection:

PREVYMIS is supplied as a sterile, clear and colorless solution for intravenous use of 240 mg/12 mL (20 mg/mL) or 480 mg/24 mL (20 mg/mL) that may contain a few product-related small translucent or white particles.

The single-dose vials are supplied in cartons that contain a 240 mg single-dose vial (NDC 0006-5003-01) or a 480 mg single-dose vial (NDC 0006-5004-01).

Store PREVYMIS 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) [see USP Controlled Room Temperature].

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

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information and Instructions for Use).

Drug Interactions
Inform patients that PREVYMIS may interact with some drugs; therefore, advise patients to report the use of any prescription, non-prescription medication, or herbal products to their healthcare provider *[see Dosage and Administration (2.4, 2.6), Contraindications (4), Warnings and Precautions (5.1), and Drug Interactions (7)]*.

Risks Associated with Hydroxypropyl Betadex Excipient in Intravenous Formulation
Inform patients that the intravenous formulation of PREVYMIS contains hydroxypropyl betadex which is eliminated through glomerular filtration and may accumulate in patients with renal impairment. In animals, hydroxypropyl betadex has been shown to cause ototoxicity *[see Warnings and Precautions (5.2), Use in Specific Populations (8.6) and Nonclinical Toxicology (13.2)]*.

Administration
Inform patients that it is important not to miss or skip doses and to take PREVYMIS for the duration that is recommended by the healthcare provider. Instruct patients that if they miss a dose of PREVYMIS, they

should take it as soon as they remember. If they do not remember until it is time for the next dose, instruct them to skip the missed dose and go back to the regular schedule. Instruct patients not to double their next dose or take more than the prescribed dose.

Advise patients that PREVYMIS injection should be used only in patients unable to take oral therapy and that patients should be switched to oral therapy as soon as they are able *[see Dosage and Administration (2.1)]*.

For PREVYMIS oral pellets, advise patients or caregivers to read and follow the Instructions for Use for preparing and taking the correct dose *[see Dosage and Administration (2.3, 2.4, 2.5, 2.6, 2.9)]*.

Storage
Advise patients to store PREVYMIS tablets and oral pellets in the original package until use *[see How Supplied/Storage and Handling (16)]*.

Distributed by: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: www.msd.com/research/patent

The trademarks depicted herein are owned by their respective companies.

Copyright © 2017-XXXX Merck & Co., Inc., Rahway, NJ, USA, and its affiliates.
All rights reserved.

uspi-mk8228-mf-XXXXrXXX

Patient Information

PREVYMIS® (PREH-vih-miss) (letermovir) tablets	PREVYMIS® (PREH-vih-miss) (letermovir) oral pellets	PREVYMIS® (PREH-vih-miss) (letermovir) injection, for intravenous use

What is PREVYMIS?

PREVYMIS is a prescription medicine used to help prevent:

- cytomegalovirus (CMV) infection and disease in adults and children 6 months and older weighing at least 13.2 pounds (lbs) or 6 kilograms (kg) who:
  - have received an allogeneic hematopoietic stem cell (bone marrow) transplant, **and**
  - have a high risk for getting CMV infection and disease.
- CMV disease in adults and children 12 years of age and older weighing at least 88.2 lbs (40 kg) who:
  - have received a kidney transplant, **and**
  - have a high risk for getting CMV disease.

It is not known if PREVMYIS is safe and effective in:

- children under 6 months of age or weighing less than 13.2 lbs (6 kg) who received a hematopoietic stem cell transplant, **or**
- children under 12 years of age or weighing less than 88.2 lbs (40 kg) who received a kidney transplant.

Who should not take PREVYMIS?

Do not take PREVYMIS if you take:

- pimozide
- ergot alkaloids

If you are taking PREVYMIS with cyclosporine, do not take:

- pitavastatin or simvastatin

What should I tell my healthcare provider before taking PREVYMIS?

Before taking PREVYMIS, tell your healthcare provider about all your medical conditions, including if you:

- have kidney or liver problems.
- are pregnant or plan to become pregnant. It is not known if PREVYMIS will harm your unborn baby.
- are breastfeeding or plan to breastfeed. It is not known if PREVYMIS passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking PREVYMIS.

Tell your healthcare provider about all of the medicines you take, including prescription and over-the-counter medicines, vitamins and herbal supplements. PREVYMIS may affect the way other medicines work, and other medicines may affect how PREVYMIS works and cause serious side effects.

Know the medicines you take. Keep a list of medicines and show it to your healthcare provider and pharmacist when you get a new medicine. Your healthcare provider or pharmacist will tell you if it is safe to take PREVYMIS with other medicines. Do not start or stop taking another medicine without telling your healthcare provider first.

How should I take PREVYMIS?

- PREVYMIS comes as a tablet, oral pellets, or can be given by your healthcare provider through an IV line (intravenously).
- PREVYMIS given intravenously should be used only if you are unable to take PREVYMIS tablets or PREVYMIS oral pellets. You should switch to PREVYMIS tablets or PREVYMIS oral pellets as soon as you are able to.

- Take PREVYMIS tablets or oral pellets exactly as your healthcare provider tells you to take it. Do not stop taking PREVYMIS without talking to your healthcare provider first.
- Take PREVYMIS tablets or oral pellets 1 time a day.
- It is important that you do not miss or skip doses of PREVYMIS.
- If you miss a dose of PREVMYIS tablets or oral pellets, take it as soon as you remember. If you do not remember until it is time for your next dose, skip the missed dose and take your dose at the next scheduled time. Do not take 2 doses of PREVYMIS at the same time or take more than your prescribed dose to make up for a missed dose.
- If you take too much PREVYMIS tablets or oral pellets, call your healthcare provider right away.

- **If you take PREVYMIS tablets:**
  - Take PREVYMIS with or without food.
  - Swallow PREVYMIS tablets whole.
- **If you take PREVYMIS oral pellets:**
  - Your healthcare provider will tell you the number of PREVYMIS oral pellet packets to take for your prescribed dose.
  - PREVMYIS oral pellets can be taken by mouth after mixing with soft food or given through a nasogastric tube (NG tube) or gastric tube (G tube).
  - **See the Instructions for Use for the right way to prepare and take a dose of PREVYMIS oral pellets.** Keep the Instructions for Use and follow it each time you prepare and take PREVYMIS oral pellets.
  - Do not crush or chew PREVYMIS oral pellets.
- **If you receive PREVYMIS through an IV line (intravenously):**
  - You will receive PREVYMIS 1 time each day given over 1 hour.
  - If you miss or skip your dose of PREVYMIS, call your healthcare provider right away.

What are the possible side effects of PREVYMIS?

The most common side effects of PREVYMIS in adults who have received a hematopoietic stem cell transplant include:

- nausea
- diarrhea
- vomiting
- swelling in your arms and legs
- cough
- headache
- tiredness
- stomach (abdominal) pain

The most common side effect of PREVYMIS in adults who have received a kidney transplant is diarrhea.

The side effects of PREVYMIS in children are similar to the side effects in adults.

These are not all the possible side effects of PREVYMIS.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store PREVYMIS?

- Store PREVYMIS tablets, PREVYMIS oral pellets, and PREVYMIS injection at room temperature between 68°F to 77°F (20°C to 25°C).
- Store PREVYMIS tablets in the original package until you are ready to take it to protect from moisture.
- Store PREVYMIS oral pellets in the original packet until you are ready to take them.
- Store PREVYMIS injection in the original carton to protect from exposure to light.

Keep PREVYMIS and all medicines out of the reach of children.

General information about the safe and effective use of PREVYMIS.

Medicines are sometimes prescribed for purposes other than those listed in the Patient Information leaflet. Do not use PREVYMIS for a condition for which it was not prescribed. Do not give PREVYMIS to other people, even if they have the

same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about PREVYMIS that is written for healthcare professionals.

What are the ingredients in PREVYMIS?

Active ingredient: letermovir
Inactive ingredients:
Tablets: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone 25.
Film coating: 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.
Oral Pellets: colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, and povidone K-29/32.
Film coating: hypromellose 2910, iron oxide red, iron oxide yellow, lactose monohydrate, titanium dioxide, and triacetin.
Injection: hydroxypropyl betadex, sodium chloride, sodium hydroxide, and Water for Injection.

Distributed by: Merck Sharp & Dohme LLC
Rahway, NJ 07065, USA

For patent information: http://www.msd.com/research/patent
The trademarks depicted herein are owned by their respective companies.
Copyright © 2017-#### Merck & Co., Inc., Rahway, NJ, USA, and its affiliates.
All rights reserved.
usppi-mk8228-mf-XXXXrXXX

For more information go to www.PREVYMIS.com or call 1-800-444-2080.

This Patient Information has been approved by the U.S. Food and Drug Administration. Revised: 08/2024