ORIGINAL ARTICLE

Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation

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ABSTRACT

BACKGROUND

Cytomegalovirus (CMV) infection remains a common complication after allogeneic hematopoietic-cell transplantation. Letermovir is an antiviral drug that inhibits the CMV–terminase complex.

METHODS

In this phase 3, double-blind trial, we randomly assigned CMV-seropositive transplant recipients, 18 years of age or older, in a 2:1 ratio to receive letermovir or placebo, administered orally or intravenously, through week 14 after transplantation; randomization was stratified according to trial site and CMV disease risk. Letermovir was administered at a dose of 480 mg per day (or 240 mg per day in patients taking cyclosporine). Patients in whom clinically significant CMV infection (CMV disease or CMV viremia leading to preemptive treatment) developed discontinued the trial regimen and received anti-CMV treatment. The primary end point was the proportion of patients, among patients without detectable CMV DNA at randomization, who had clinically significant CMV infection through week 24 after transplantation. Patients who discontinued the trial or had missing end-point data at week 24 were imputed as having a primary end-point event. Patients were followed through week 48 after transplantation.

RESULTS

From June 2014 to March 2016, a total of 565 patients underwent randomization and received letermovir or placebo beginning a median of 9 days after transplantation. Among 495 patients with undetectable CMV DNA at randomization, fewer patients in the letermovir group than in the placebo group had clinically significant CMV infection or were imputed as having a primary end-point event by week 24 after transplantation (122 of 325 patients [37.5%] vs. 103 of 170 [60.6%], P<0.001). The frequency and severity of adverse events were similar in the two groups overall. Vomiting was reported in 18.5% of the patients who received letermovir and in 13.5% of those who received placebo; edema in 14.5% and 9.4%, respectively; and atrial fibrillation or flutter in 4.6% and 1.0%, respectively. The rates of myelotoxic and nephrotoxic events were similar in the letermovir group and the placebo group. All-cause mortality at week 48 after transplantation was 20.9% among letermovir recipients and 25.5% among placebo recipients.

CONCLUSIONS

Letermovir prophylaxis resulted in a significantly lower risk of clinically significant CMV infection than placebo. Adverse events with letermovir were mainly of low grade. (Funded by Merck; ClinicalTrials.gov number, NCT02137772; EudraCT number, 2013-003831-31.)

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Cytomegalovirus (CMV) remains the most common clinically significant infection after allogeneic hematopoietic-cell transplantation.[1-4] Although ganciclovir and valganciclovir are routinely used in solid-organ transplantation,[5,6] ganciclovir[7,8] and valganciclovir[9,10] prophylaxis for CMV is limited by clinically unacceptable myelosuppression after hematopoietic-cell transplantation. Over the past 20 years, clinicians have adopted a preemptive strategy[11] in which CMV surveillance and detection in blood by different methods trigger antiviral treatment to prevent clinical CMV disease and minimize the toxic effects of these antiviral agents.[9,10,12] This strategy has become standard and has been successful in reducing the incidence of CMV disease,[13,14] yet CMV seropositivity and early CMV reactivation after hematopoietic-cell transplantation remain associated with increased mortality.[3,4] Thus, the development of safe and effective antiviral agents for CMV prophylaxis remains a major goal in transplantation.

CMV replication involves the cleaving of concatemeric genomic viral DNA (i.e., CMV genome units generated in tandem) and the packaging of each genome into preformed virus capsids, a process that is mediated by the CMV–terminase complex (UL51, UL56, and UL89).[15,16] Letermovir is an antiviral agent that inhibits CMV replication by binding to components of the terminase complex (UL51, UL56, or both).[17-21] In a phase 2, dose-escalation trial,[22] letermovir at a dose of 240 mg per day was highly effective in preventing CMV viremia after engraftment in transplant recipients and had little toxicity. In this phase 3, randomized, double-blind, placebo-controlled, superiority trial, we sought to confirm the efficacy and safety of letermovir for CMV prophylaxis after transplantation in CMV-seropositive recipients.

Methods

Patients and Trial Design

We recruited patients 18 years of age or older who were undergoing allogeneic hematopoietic-cell transplantation at 67 centers in 20 countries (Section 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients were eligible if they were CMV-seropositive, had an undetectable level of CMV DNA in plasma within 5 days before randomization, and could start taking the trial regimen by day 28 after transplantation. Exclusion criteria included severe liver impairment, an estimated creatinine clearance of less than 10 ml per minute, and either current or recent receipt of antiviral agents with anti-CMV activity. Neutrophil engraftment was not required for randomization. Detailed eligibility criteria are provided in Section 3 in the Supplementary Appendix. The protocol (available at NEJM.org) was amended on June 30, 2014, to exclude patients of Asian ancestry while additional pharmacokinetic studies were completed; however, this exclusion was removed on December 10, 2014.

Randomization and Masking

Eligible patients underwent randomization in a 2:1 ratio by means of an interactive Web-response system and concealed assignment, with the use of permuted blocks of six, to receive letermovir or placebo through week 14 (approximately 100 days) after transplantation. Randomization was stratified according to trial site and CMV disease risk (Section 4 in the Supplementary Appendix).[9] High risk of CMV reactivation and CMV disease was defined as meeting one or more of the following criteria at the time of randomization: having a related donor with at least one mismatch at one of the specified three HLA gene loci (HLA-A, B, or DR); having an unrelated donor with at least one mismatch at one of the specified four HLA gene loci (HLA-A, B, C, and DRB1); having a haploidentical donor; the use of umbilical cord blood as the stem-cell source; the use of ex vivo T-cell–depleted grafts; and having graft-versus-host disease (GVHD) of grade 2 or greater that led to the use of 1 mg or more of prednisone (or its equivalent) per kilogram of body weight per day. All the patients who did not meet the definition of being at high risk were considered to be at low risk.

Patients who were assigned to the letermovir group received 480 mg per day. Patients who were receiving concomitant cyclosporine received 240 mg of letermovir (or matching placebo) per day owing to a drug–drug interaction that is mediated by the organic anion transporters OATP1B1 and OATP1B3.[23,24]

Dose selection was based on the pharmacokinetic analyses of a phase 2 trial[22] to ensure adequate letermovir exposure in all the patients assigned to receive letermovir (Section 5 in the Supplementary Appendix). Patients received letermovir or placebo either orally (as 240-mg or

480-mg tablets or matching placebo) or intravenously (dissolved in hydroxypropyl-β-cyclodextrin, in a ratio of 1800 mg per 240 mg of letermovir, or matching placebo solution)[25] at the discretion of the site investigators. Interruptions of the trial regimen for less than 7 days were allowed. Patients, site staff, and the sponsor were unaware of the trial-group assignments. Intravenous letermovir and placebo were prepared by pharmacists who were aware of the trial-group assignments but who were not involved in the care of the patients at each site. Investigators assessed for drug interactions because letermovir is a weak-to-moderate inhibitor of cytochrome P-450 3A (CYP3A) and a weak-to-moderate inducer of CYP2C9 and CYP2C19 enzymes (encoding cytochrome P-450, family 2, subfamily C, polypeptides 9 and 19, respectively). Levels of drugs, including cyclosporine, tacrolimus, and voriconazole, were monitored according to local practice. All the patients continued herpesvirus prophylaxis with acyclovir (at a dose of ≤3200 mg per day), valacyclovir (at a dose of ≤3000 mg per day), or famciclovir (at a dose of ≤1500 mg per day), according to local practice.

PROCEDURES

Patients were evaluated weekly through week 14, then every 2 weeks through week 24, and every other month thereafter through week 48 after transplantation. The plasma level of CMV DNA was measured at every visit in the central laboratories (lower limit of quantitation, 151 copies per milliliter [137 IU per milliliter]). Additional trial-specific assessments are described in Sections 6 and 7 and Tables S1 and S2 in the Supplementary Appendix.

Patients in whom clinically significant CMV infection (defined as CMV disease[26] or CMV viremia leading to preemptive treatment) developed discontinued the trial regimen and began anti-CMV therapy according to local practice. Results of CMV testing at the central laboratory or individual sites could trigger preemptive treatment; an additional plasma sample was obtained and submitted to the central laboratory if such treatment was initiated. If CMV viremia was not confirmed, treatment could be stopped and patients could resume letermovir or placebo. The protocol suggested thresholds for the preemptive treatment of CMV viremia of more than 150 copies per milliliter for high-risk patients and more than 300 copies per milliliter for low-risk patients through week 14 after transplantation and a threshold of more than 300 copies per milliliter for all the patients thereafter.

END POINTS

The primary end point was the proportion of patients with clinically significant CMV infection through week 24 after transplantation among patients without detectable CMV DNA at randomization (primary efficacy population). Patients who discontinued the trial before week 24 for any reason or who had missing data at week 24 were imputed as having a primary end-point event. Key prespecified secondary end points were the proportion of patients with clinically significant CMV infection through week 14 and the time to clinically significant CMV infection in the primary efficacy population.

All the patients who received any dose of letermovir or placebo (safety population) were included in the safety analyses. Data on all adverse events were collected through week 16 after transplantation. Thereafter, only serious adverse events that were considered by the investigators to be related to the trial regimen or serious adverse events that led to death were reported through week 48. Prespecified exploratory end points included cumulative all-cause mortality and the rates of engraftment, GVHD, and infection during the trial.

TRIAL OVERSIGHT

After licensing letermovir from AiCuris, the sponsor (Merck) designed the protocol with input from several authors. All the investigators and central laboratories provided trial data. The trial statisticians performed the analyses and vouch for the integrity and validity of the analyses; the authors affirm that the trial was conducted as specified in the protocol. The first author wrote the manuscript with critical input from the other authors; all the authors agreed to submit the manuscript for publication. No one who is not an author contributed to the manuscript.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines. The institutional review board at each center approved the trial. All the patients provided written informed consent.

STATISTICAL ANALYSIS

We estimated that the rate of clinically significant CMV infection by week 24 after transplan-

tation would be 35% in the placebo group[22] and that the rate in the letermovir group would be 50% lower than the rate in the placebo group. Assuming a 20% rate of discontinuation for non-CMV reasons and assuming that 15% of the patients would have detectable CMV DNA at baseline, we calculated that at least 540 patients (360 patients in the letermovir group and 180 in the placebo group) would be required in order to provide the trial with more than 90% power for the primary efficacy analysis.

The Mantel–Haenszel method, with stratification according to CMV risk group, was used to test the superiority of letermovir over placebo for the prevention of clinically significant CMV infection through week 24 after transplantation, with the use of a one-sided test with an alpha level of 0.0249. An interim analysis for futility was conducted when approximately 40% of the patients had completed the trial regimen ($\alpha = 0.0001$ for the power cost for the interim look at the data results for the futility analysis). Kaplan–Meier plots were used for time-to-event analyses, with data censoring for discontinuation at the last assessment. We estimated differences in adverse events and their 95% confidence intervals using the method of Miettinen and Nurminen.[27] Secondary and exploratory analyses did not control for multiplicity of inferences. All the analyses were performed with the use of SAS software, version 9.3 (SAS Institute). Post hoc analyses of the primary end point with the use of multiple-imputation models for missing data under missing-at-random and missing-not-at-random assumptions were performed (Section 11 in the Supplementary Appendix).

RESULTS

TRIAL POPULATION

From June 20, 2014, to March 7, 2016, a total of 738 patients consented to participate in the trial and were assessed for eligibility. A total of 168 patients were excluded, mainly owing to detectable CMV DNA before randomization (117 patients [69.6%]) or receipt of anti-CMV antiviral agents (16 patients [9.5%]) (Fig. 1). Of the 570 patients who underwent randomization, 5 (3 patients in the letermovir group and 2 in the placebo group) did not receive any dose of the assigned trial regimen and discontinued trial participation. The most common reasons for discontinuation through week 24 after transplantation were death (65 patients [11.4%]) and withdrawal of consent (39 patients [6.8%]). Deviations from eligibility criteria were noted in 51 patients (8.9%) who had undergone randomization (Section 10 in the Supplementary Appendix); all these patients continued in the trial. The CMV risk-stratification group was misclassified at randomization in 27 patients (4.7%); data from these patients were analyzed according to the confirmed CMV risk.

The trial groups were well balanced with regard to the characteristics at baseline (Table 1, and Table S3 in the Supplementary Appendix). Overall, 175 of 565 patients (31.0%) were considered to be at high risk for CMV, including 81 patients (14.3%) with haploidentical donors and 78 (13.8%) with mismatched, unrelated donors. There were similar proportions of myeloablative and less intense conditioning regimens and of cyclosporine-based and non–cyclosporine-based GVHD prophylaxis regimens. Antithymocyte globulin was used in 198 patients (35.0%).

Patients began letermovir or placebo a median of 9 days (range, 0 to 28) after transplantation; 206 patients (36.5%) had engraftment at randomization. The median duration of the trial regimen was 82 days (range, 1 to 113) in the letermovir group, as compared with 56 days (range, 4 to 115) in the placebo group. A total of 147 patients (26.0%) received the assigned regimen intravenously (99 patients in the letermovir group and 48 in the placebo group) for a median of 12 days (range, 1 to 88). Pharmacokinetic analyses showed similar exposures among patients who received oral letermovir at a dose of 240 mg per day with concomitant cyclosporine and those who received oral letermovir at a dose of 480 mg per day without cyclosporine. Patients of Asian ancestry had letermovir exposures that were similar to those of patients who were not of Asian ancestry (Section 6 and Tables S4 and S5 in the Supplementary Appendix).

PRIMARY END POINT

Of the 565 patients who received the trial regimen, 70 had detectable CMV DNA at randomization, including 48 patients in the letermovir group and 22 in the placebo group; these patients were excluded from the primary efficacy population (Fig. 1). Among the remaining 495 patients, the percentage of patients in whom clinically significant CMV infection developed or who were imputed as having a primary end-

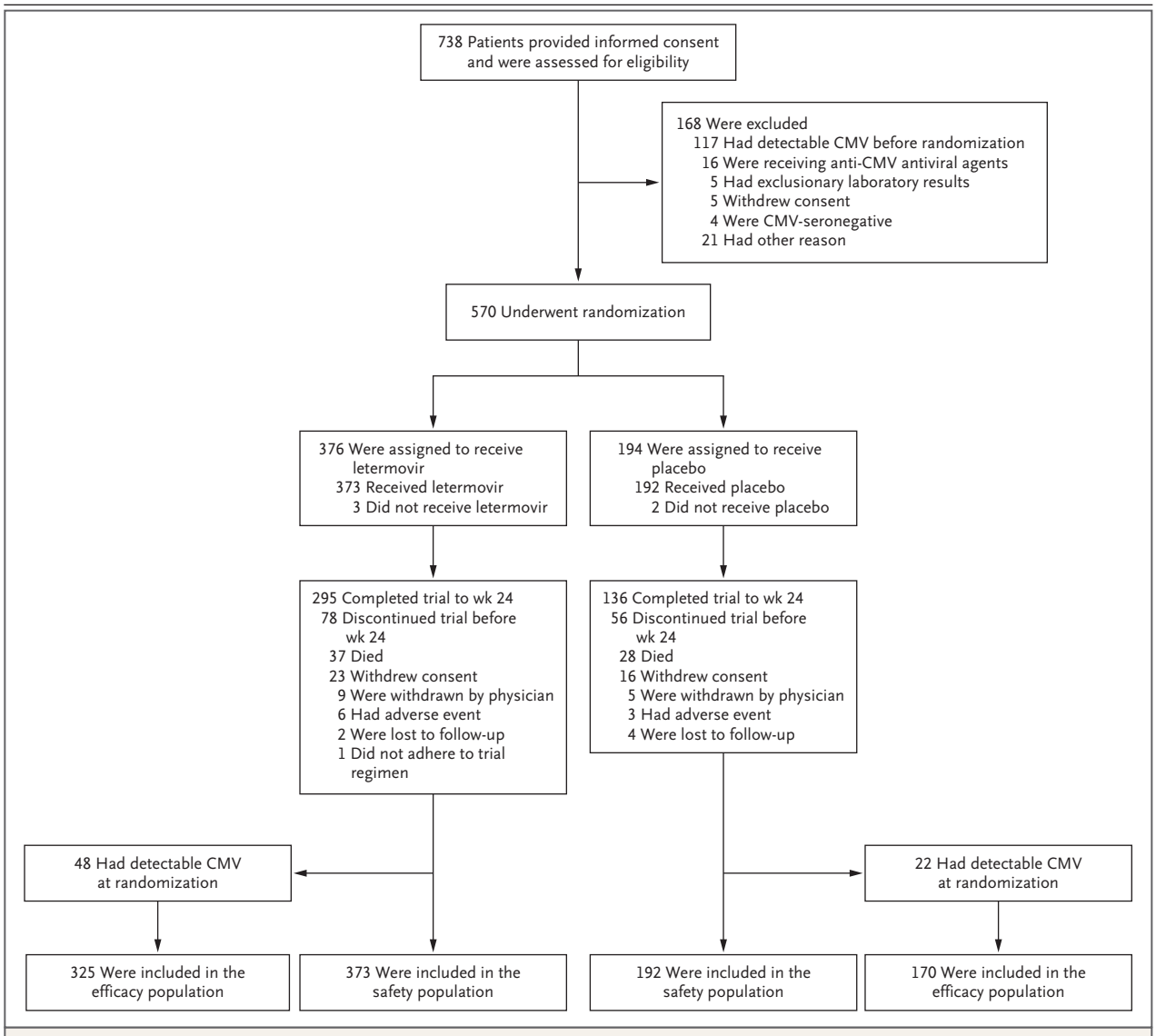

Figure 1. Consent, Screening, Enrollment, Randomization, and Follow-up.
CMV denotes cytomegalovirus.

point event by week 24 after transplantation was significantly lower among letermovir recipients (122 of 325 [37.5%]) than among placebo recipients (103 of 170 [60.6%]). The difference, with adjustment for CMV risk stratum, was –23.5 percentage points (95% confidence interval [CI], –32.5 to –14.6; P<0.001). The difference was driven by clinically significant CMV infection; the proportions of patients who discontinued the trial or had missing outcomes were similar in the two groups (Table 2). The between-group difference was –30.7 percentage points (95% CI, –34.8 to –26.6) when multiple-imputation models that considered missing-at-random assumptions to imputed missing data were used and –24.5 percentage points (95% CI, –28.4 to –20.7) when multiple-imputation models that considered missing-not-at-random assumptions to imputed missing data were used (Section 11 in the Supplementary Appendix).

CMV disease was uncommon (occurring in 1.5% of the patients in the letermovir group and 1.8% of those in the placebo group) and involved the gastrointestinal tract in all cases. Details regarding CMV DNA levels and antiviral treatments that were used in patients with clinically significant CMV infection are provided in Tables S7 through S9 in the Supplementary Appendix.

Table 1. Characteristics at Baseline of All the Patients Who Underwent Randomization and Received the Trial Regimen (Safety Population).*

Characteristic	Letermovir Group (N=373)	Placebo Group (N=192)
Age — yr		
Median	53	54
Range	18–75	19–78
Male sex — no. (%)	211 (56.6)	116 (60.4)
Race — no. (%)†		
White	301 (80.7)	162 (84.4)
Asian	40 (10.7)	18 (9.4)
Other	32 (8.6)	12 (6.2)
CMV-seropositive donor — no. (%)	230 (61.7)	114 (59.4)
Primary reason for hematopoietic-cell transplantation — no. (%)		
Acute myeloid leukemia	142 (38.1)	72 (37.5)
Myelodysplastic syndrome	63 (16.9)	22 (11.5)
Non-Hodgkin's lymphoma	47 (12.6)	28 (14.6)
Acute lymphocytic leukemia	35 (9.4)	17 (8.9)
Other disease	86 (23.1)	53 (27.6)
HLA matching and donor type — no. (%)		
Matched unrelated	138 (37.0)	78 (40.6)
Matched related	121 (32.4)	63 (32.8)
Mismatched related	63 (16.9)	24 (12.5)
Mismatched unrelated	51 (13.7)	27 (14.1)
Haploidentical related donor — no. (%)	60 (16.1)	21 (10.9)
Stem-cell source — no. (%)		
Peripheral blood	279 (74.8)	134 (69.8)
Bone marrow	82 (22.0)	47 (24.5)
Cord blood	12 (3.2)	11 (5.7)
Myeloablative conditioning regimen — no. (%)	186 (49.9)	97 (50.5)
Antithymocyte globulin use — no. (%)	140 (37.5)	58 (30.2)
Alemtuzumab use — no. (%)	12 (3.2)	11 (5.7)
Ex vivo T-cell depletion — no. (%)‡	9 (2.4)	5 (2.6)
Immunosuppressant use — no. (%)		
Cyclosporine	193 (51.7)	100 (52.1)
Tacrolimus	160 (42.9)	79 (41.1)
Mycophenolate§	120 (32.2)	51 (26.6)
Sirolimus or everolimus	30 (8.0)	20 (10.4)
Acute GVHD of grade ≥2 at randomization — no. (%)	2 (0.5)	1 (0.5)
Risk of CMV disease — no. (%)¶		
High risk	121 (32.4)	54 (28.1)
Low risk	252 (67.6)	138 (71.9)

* The two groups were well balanced at baseline. Additional characteristics of the patients at baseline are presented in Table S3 in the Supplementary Appendix. CMV denotes cytomegalovirus, and GVHD graft-versus-host disease.
† Race was reported by the patient.
‡ The use of ex vivo T-cell depletion included the ex vivo use of alemtuzumab.
§ Mycophenolate included mycophenolate mofetil, mycophenolate sodium, and mycophenolic acid.
¶ A high risk of CMV disease was defined as meeting one or more of the following criteria at the time of randomization: having a related donor with at least one mismatch at one of the specified three HLA gene loci (HLA-A, B, or DR); having an unrelated donor with at least one mismatch at one of the specified four HLA gene loci (HLA-A, B, C, and DRB1); having a haploidentical donor; the use of umbilical cord blood as the stem-cell source; the use of ex vivo T-cell–depleted grafts; and having GVHD of grade 2 or greater that led to the use of prednisone (or its equivalent) at a dose of 1 mg or more per kilogram of body weight per day. All the patients who did not meet the definition of being at high risk were considered to be at low risk.

Table 2. Efficacy End Points (Primary Efficacy Population).*

End Point	Letermovir Group (N=325)	Placebo Group (N=170)	Difference (95% CI)	P Value
	number of patients (percent)		*percentage points*	
Primary end point at wk 24 after transplantation	122 (37.5)	103 (60.6)	−23.5 (−32.5 to −14.6)	<0.001
Clinically significant CMV infection	57 (17.5)	71 (41.8)		
Initiation of preemptive therapy	52 (16.0)	68 (40.0)		
CMV disease†	5 (1.5)	3 (1.8)		
Discontinued trial before wk 24	56 (17.2)	27 (15.9)		
Owing to adverse event	6 (1.8)	1 (0.6)		
Owing to death without CMV	28 (8.6)	12 (7.1)		
Owing to other reason‡	22 (6.8)	14 (8.2)		
Missing outcome in wk 24 visit window	9 (2.8)	5 (2.9)		
Key secondary end point at wk 14 after transplantation	62 (19.1)	85 (50.0)	−31.3 (−39.9 to −22.6)	<0.001
Clinically significant CMV infection	25 (7.7)§	67 (39.4)		
Initiation of preemptive therapy	24 (7.4)	65 (38.2)		
CMV disease†	1 (0.3)	2 (1.2)		
Discontinued trial before wk 14	33 (10.2)	16 (9.4)		
Owing to adverse event	5 (1.5)	1 (0.6)		
Owing to death without CMV	14 (4.3)	6 (3.5)		
Owing to other reason‡	14 (4.3)	9 (5.3)		
Missing outcome in wk 14 visit window	4 (1.2)	2 (1.2)		

* The primary end point was the proportion of patients with clinically significant CMV infection through week 24 after transplantation among patients without detectable CMV DNA at randomization (primary efficacy population); patients who discontinued the trial for any reason before week 24 (day 168) after transplantation or who had missing data at week 24 were imputed as having a primary end-point event. The proportion of patients with clinically significant CMV infection (or an imputed primary end-point event) through week 14 (day 100) after transplantation (end of the trial) was a key secondary end point. The 95% confidence intervals and P values for the differences in the percent response were calculated with the use of the stratum-adjusted Mantel–Haenszel method, with the difference weighted by the harmonic mean of sample size per group for each stratum (high risk or low risk). Two-sided P values and 95% confidence intervals are presented. The protocol-specified calculations for the week 24 primary end point and the week 14 end point with the use of a one-sided P value with an alpha level of 0.0249 yielded the same results.

† All the cases of CMV disease were adjudicated by a clinical adjudication committee whose members were unaware of the trial-group assignments. All the confirmed events of CMV disease through week 24 after transplantation affected the gastrointestinal tract.

‡ Other reasons for discontinuation from the trial included loss to follow-up, physician's decision, and withdrawal by patient.

§ A total of 12 patients (3.7%) had discontinued letermovir a median of 43 days (range, 15 to 75) before the development of clinically significant CMV infection. One patient had completed the trial regimen 6 days within the week 14 window before clinically significant CMV infection developed. The other 12 events occurred while patients were receiving letermovir for a median of 15 days (range, 3 to 61). Central CMV DNA levels were less than 151 copies per milliliter in 10 of these patients when preemptive therapy was initiated. Next-generation sequencing of the CMV *UL56* gene in plasma obtained from these 12 patients showed the V236M mutation[28] in one of two successfully sequenced specimens.

KEY SECONDARY END POINTS

By week 14 after transplantation, significantly fewer patients in the primary efficacy population had clinically significant CMV infection or were imputed as having a primary end-point event among letermovir recipients (62 of 325 patients [19.1%]) than among placebo recipients (85 of 170 [50.0%]). The difference, with adjustment for CMV risk stratum, was −31.3 percentage points (95% CI, −39.9 to −22.6; P<0.001) (Table 2).

The Kaplan–Meier event rate of clinically significant CMV infection among letermovir recipients was 18.9% (95% CI, 14.4 to 23.5), as compared with 44.3% (95% CI, 36.4 to 52.1%) among placebo recipients, by week 24 after transplantation (P<0.001) (Fig. 2). Beginning around week 18, the incidence of clinically significant CMV infection after prophylaxis increased among patients who had received letermovir — a finding that reflected ongoing or new periods of CMV risk, mostly as a result of GVHD and glucocorticoid use. Results were similar when the safety population was analyzed (Figs. S1 and S2 in the Supplementary Appendix).

PRESPECIFIED EXPLORATORY END POINTS

All-cause mortality at week 24 after transplantation was lower among letermovir recipients than among placebo recipients in the primary efficacy population (10.2% [95% CI, 6.8 to 13.6] vs. 15.9%

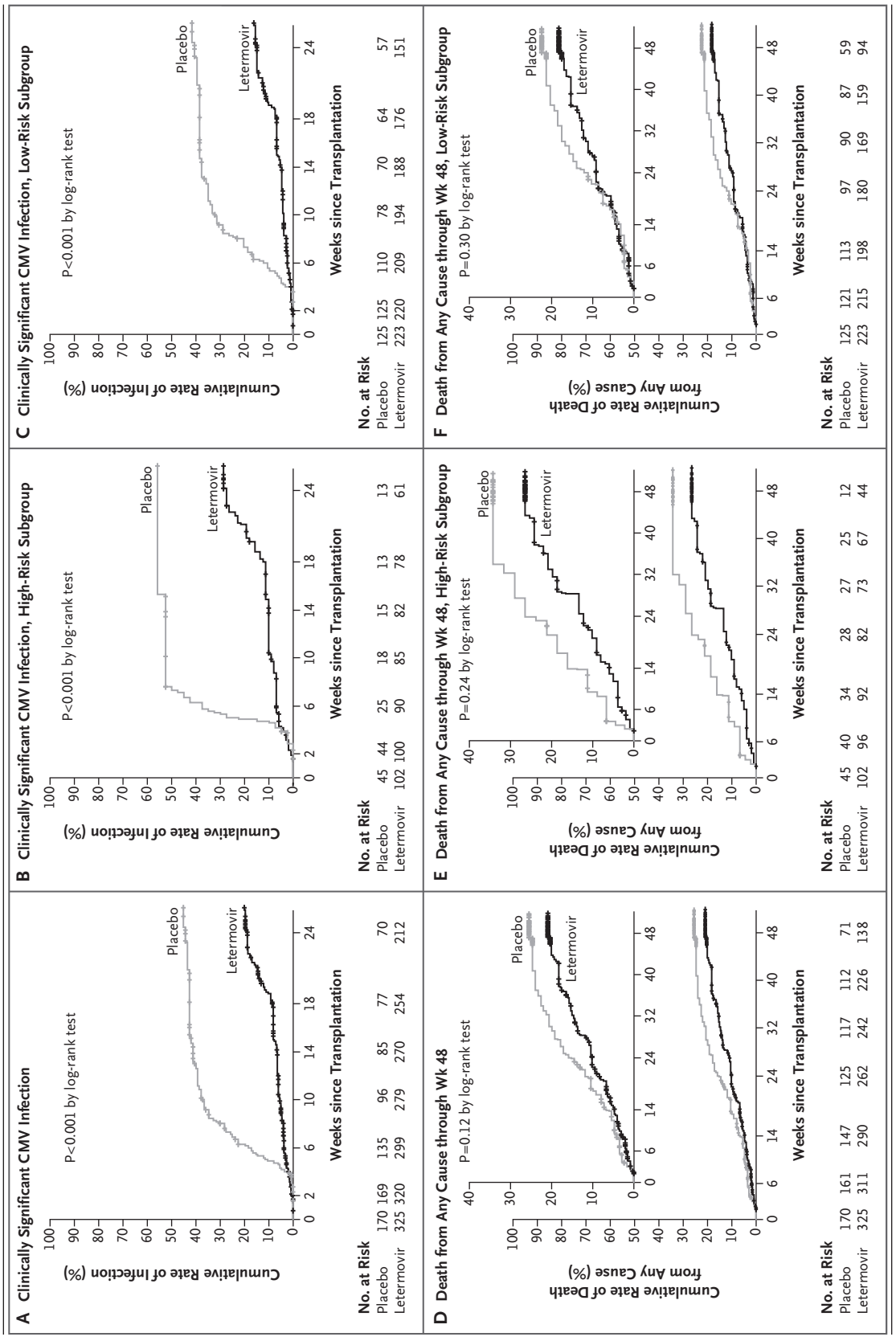

Figure 2 (facing page). Time-to-Event Analyses of Clinically Significant CMV Infection and Mortality in the Primary Efficacy Population and According to Risk Subgroup.

Panel A shows the incidence of clinically significant CMV infection, according to trial group in a time-to-event analysis, through week 24 after allogeneic hematopoietic-cell transplantation among patients without detectable CMV DNA at randomization (primary efficacy population). Panel B shows the results with regard to the primary end point in the subgroup of patients who were considered to be at high risk for CMV infection, and Panel C the results in the subgroup of patients who were considered to be at low risk. High risk was defined as meeting one or more of the following criteria at the time of randomization: having a related donor with at least one mismatch at one of the specified three HLA gene loci (HLA-A, B, or DR); having an unrelated donor with at least one mismatch at one of the specified four HLA gene loci (HLA-A, B, C, and DRB1); having a haploidentical donor; the use of umbilical cord blood as the stem-cell source; the use of ex vivo T-cell–depleted grafts; and having graft-versus-host disease of grade 2 or greater that led to the use of 1 mg or more of prednisone (or its equivalent) per kilogram of body weight per day. All the patients who did not meet the definition of being at high risk were considered to be at low risk. Panel D shows all-cause mortality through week 48 after transplantation, and Panels E and F show all-cause mortality in the high-risk and low-risk subgroups, respectively. The insets show the same data on an enlarged y axis. All P values are two-sided.

[95% CI, 10.2 to 21.6], P=0.03). All-cause mortality through week 48 was 20.9% (95% CI, 16.2 to 25.6) in the letermovir group and 25.5% (95% CI, 18.6 to 32.5) in the placebo group (P=0.12) (Fig. 2) and reflected a nonsignificantly lower nonrelapse-related mortality among letermovir recipients than among placebo recipients (Fig. S3 and Section 12 in the Supplementary Appendix).

The prevention of clinically significant CMV infection by letermovir was consistent in patients at high risk for CMV disease and in those at low risk. The lower mortality among letermovir recipients than among placebo recipients was more pronounced among high-risk patients than among low-risk patients (Fig. 2). The treatment effect of letermovir in preventing clinically significant CMV infection was consistent across various prespecified and post hoc subgroups both at week 14 and at week 24 after transplantation (Figs. S4 and S5 in the Supplementary Appendix).

SAFETY

Among all the patients who had undergone randomization, 267 of 376 patients (71.0%) in the letermovir group completed the trial regimen to week 14, as compared with 80 of 194 (41.2%) in the placebo group (Table S6 in the Supplementary Appendix). Clinically significant CMV infection was the most common reason for discontinuation of the trial regimen in the placebo group (82 patients [42.3%]). More patients in the letermovir group than in the placebo group had withdrawn consent by week 14 (20 patients [5.3%] vs. 4 [2.1%]); the reasons for discontinuation were similar in the two groups.

Table 3 lists the most common adverse events that were noted through week 16 after transplantation. Detailed analyses of the adverse events according to system organ class are presented in Tables S10 through S12 in the Supplementary Appendix. The frequency and severity of adverse events were similar in the two groups overall.

Vomiting was reported in 18.5% of the patients who received letermovir and in 13.5% of those who received placebo; edema in 14.5% and 9.4%, respectively; dyspnea in 8.0% and 3.1%; myalgia in 5.1% and 1.6%; atrial fibrillation or flutter in 4.6% and 1.0%; and alanine aminotransferase levels of more than 5 times the upper limit of the normal range in 3.5% and 1.6%. Although the term "hyperkalemia" was reported more frequently in patients in the letermovir group (7.2%) than in the placebo group (2.1%), potassium levels were similar in the two groups in the central laboratory measurements. Acute kidney injury was reported in 9.7% of the letermovir recipients and in 13.0% of the placebo recipients.

Further analysis of atrial arrhythmias did not show a relationship with letermovir exposure (Figs. S7 and S8 in the Supplementary Appendix). No patient discontinued letermovir owing to these events, and only two events met the criteria for being a serious adverse event.

The time to engraftment among patients who started letermovir or placebo before engraftment was similar in the two groups (Fig. S6 in the Supplementary Appendix) without evidence of myelotoxicity. No appreciable between-group differences in the frequency and intensity of GVHD, other infections, or relapse of hematologic disease were noted.

One patient had breakthrough CMV viremia during letermovir treatment (Table 2). CMV genotyping in this patient showed the *UL56* V236M mutation, which is known to confer letermovir resistance.[28]

Table 3. Adverse Events (Safety Population).*

Event	Letermovir Group (N=373)	Placebo Group (N=192)	Difference (95% CI)	P Value
	number of patients with event (percent)		*percentage points*	
Any adverse event	365 (97.9)	192 (100)	–2.1 (–4.2 to –0.2)	0.07
GVHD	146 (39.1)	74 (38.5)	0.6 (–8.0 to 8.9)	0.96
Diarrhea	97 (26.0)	47 (24.5)	1.5 (–6.3 to 8.8)	0.77
Nausea	99 (26.5)	45 (23.4)	3.1 (–4.6 to 10.3)	0.49
Fever	77 (20.6)	43 (22.4)	–1.8 (–9.2 to 5.2)	0.70
Rash	76 (20.4)	41 (21.4)	–1.0 (–8.4 to 5.9)	0.87
Vomiting	69 (18.5)	26 (13.5)	5.0 (–1.7 to 11.0)	0.17
Cough	53 (14.2)	20 (10.4)	3.8 (–2.2 to 9.2)	0.25
Peripheral edema	54 (14.5)	18 (9.4)	5.1 (–0.8 to 10.4)	0.11
Fatigue	50 (13.4)	21 (10.9)	2.5 (–3.6 to 7.8)	0.49
Mucosal inflammation	46 (12.3)	24 (12.5)	–0.2 (–6.4 to 5.3)	0.99
Headache	52 (13.9)	18 (9.4)	4.6 (–1.3 to 9.8)	0.15
Abdominal pain	44 (11.8)	18 (9.4)	2.4 (–3.3 to 7.5)	0.47
Acute kidney injury	36 (9.7)	25 (13.0)	–3.4 (–9.5 to 1.9)	0.28
Decreased appetite	38 (10.2)	22 (11.5)	–1.3 (–7.2 to 3.9)	0.74
Hypertension	31 (8.3)	21 (10.9)	–2.6 (–8.4 to 2.3)	0.38
Constipation	27 (7.2)	20 (10.4)	–3.2 (–8.8 to 1.5)	0.26

* Shown here are adverse events of any severity that were reported in at least 10% of the patients through week 16 after transplantation. Differences were based on the method of Miettinen and Nurminen.[27] P values were calculated by a two-sided Fisher's exact test.

DISCUSSION

We found that letermovir prophylaxis to prevent clinically significant CMV infection in CMV-seropositive patients beginning a median of 9 days after hematopoietic-cell transplantation and administered through week 14 (approximately day 100 after transplantation) was highly effective, led to minimal side effects, and was associated with lower all-cause mortality than placebo through week 24 after transplantation. Patients who were considered to be at high risk for CMV disease benefited the most from letermovir prophylaxis.

This trial culminates more than a decade of efforts to identify new, highly effective antiviral agents that can be safely prescribed prophylactically after hematopoietic-cell transplantation.[22,29-32] During this period, we learned that preemptive therapy with the use of polymerase chain reaction–based surveillance consistently reduced the incidence of CMV disease among transplant recipients,[10,14,30,33] which made CMV disease[26] by itself not a suitable clinical-trial end point. The end point of clinically significant CMV infection was accepted among regulators, sponsors, and investigators as a meaningful outcome that would capture the potential benefits of new antiviral agents to prevent clinical disease, the potential detrimental effects of subclinical CMV disease, and the adverse effects of available antiviral agents that are used for preemptive treatment. Although we did not expect letermovir to have a sustained antiviral effect after day 100, we established a prolonged follow-up and a time point at week 24 after transplantation to claim primary efficacy on the basis of previous trial designs in solid-organ transplantation[5] and to assess for postprophylaxis events and long-term safety. This trial was strict in defining CMV prophylaxis, because it excluded patients with detectable CMV viremia during screening and considered only patients without detectable CMV DNA on the day of randomization in the primary efficacy analysis.

The risk of CMV reactivation and CMV disease among patients undergoing transplantation is dynamic over time — its duration, intensity, and recurrence depend on multiple factors, including donor type, conditioning regimens, and GVHD prevention, occurrence, and treatment strategies.[2,10,13] Although universal prophylaxis with letermovir early after transplantation through

day 100 was highly effective as an overall strategy, the notable frequency of postprophylactic[34] CMV events among high-risk patients points to the importance of personalizing the therapy[35] on the basis of risk. Extended CMV prophylaxis with letermovir may maximize the benefit in high-risk patients, including those in whom immune reconstitution may be delayed owing to T-cell–depleted grafts and those being treated for GVHD. In addition to benefitting patients who are unable to take the drug orally, the intravenous formulation of letermovir is particularly important for the care of patients with severe gastrointestinal GVHD, because of the rapid CMV-replication kinetics in this context[36] that render preemptive strategies less effective.

Letermovir use was safe overall, but we found a modestly higher incidence of vomiting and edema in the letermovir group than in the placebo group, a finding that was also seen in the phase 2 trial.[22] Similarly, the higher frequency of atrial fibrillation and flutter events with letermovir than with placebo, although rarely serious, will require further evaluation in future studies.

The absence of myelotoxic effects allowed the initiation of letermovir prophylaxis before engraftment. No increased nephrotoxicity was observed with letermovir despite cyclodextrin use in its intravenous formulation and the potential for increased levels of calcineurin inhibitor owing to CYP3A-mediated drug–drug interactions. These characteristics, in addition to the lack of cross-resistance of letermovir with other antiviral agents,[19,37] provide an attractive profile as compared with ganciclovir, valganciclovir, foscarnet, and cidofovir, although it is important to take into account that the activity of letermovir is limited to CMV. Letermovir prophylaxis may be of benefit in transplant recipients who cannot take other anti-CMV agents. The development of breakthrough CMV viremia with confirmed *UL56* mutations that confer letermovir resistance[28,38,39] can occur; these CMV mutants remain susceptible to ganciclovir.[28,39]

A small trial of preemptive treatment with letermovir,[40] with doses that we now know would be insufficient for sustained efficacy,[22] and an emergency-use case report of multidrug-resistant CMV disease that resolved only with letermovir[41] treatment are the only documentation of the potential role of letermovir in the treatment of active CMV infection. These medically relevant areas need further study, as does the potential use of letermovir treatment in patients with congenital CMV disease.[42]

In conclusion, in a diverse population of patients who had undergone hematopoietic-cell transplantation, letermovir prophylaxis was effective in preventing clinically significant CMV infection when used through day 100 after transplantation. Letermovir was associated with only mild toxic effects, which allows for the administration before hematologic engraftment, was not associated with a higher rate of myelotoxic or nephrotoxic events, and was associated with lower all-cause mortality than placebo.

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APPENDIX

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