ORIGINAL ARTICLE

Maribavir for Preemptive Treatment of Cytomegalovirus Reactivation

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ABSTRACT

BACKGROUND

Maribavir is a benzimidazole riboside with activity against cytomegalovirus (CMV). The safety and efficacy of maribavir for preemptive treatment of CMV infection in transplant recipients is not known.

METHODS

In a phase 2, open-label, maribavir dose–blinded trial, recipients of hematopoietic-cell or solid-organ transplants (≥18 years of age, with CMV reactivation [1000 to 100,000 DNA copies per milliliter]) were randomly assigned to receive maribavir at a dose of 400, 800, or 1200 mg twice daily or the standard dose of valganciclovir for no more than 12 weeks. The primary efficacy end point was the percentage of patients with a response to treatment, defined as confirmed undetectable CMV DNA in plasma, within 3 weeks and 6 weeks after the start of treatment. The primary safety end point was the incidence of adverse events that occurred or worsened during treatment.

RESULTS

Of the 161 patients who underwent randomization, 159 received treatment, and 156 had postbaseline data available — 117 in the maribavir group and 39 in the valganciclovir group. The percentage of patients with postbaseline data available who had a response to treatment within 3 weeks was 62% among those who received maribavir and 56% among those who received valganciclovir. Within 6 weeks, 79% and 67% of patients, respectively, had a response (risk ratio, 1.20; 95% confidence interval, 0.95 to 1.51). The percentages of patients with a response to treatment were similar among the maribavir dose groups. Two patients who had a response to treatment had a recurrence of CMV infection within 6 weeks after starting maribavir at a dose of 800 mg twice daily; T409M resistance mutations in CMV UL97 protein kinase developed in both patients. The incidence of serious adverse events that occurred or worsened during treatment was higher in the maribavir group than in the valganciclovir group (52 of 119 patients [44%] vs. 13 of 40 [32%]). A greater percentage of patients in the maribavir group discontinued the trial medication because of an adverse event (27 of 119 [23%] vs. 5 of 40 [12%]). A higher incidence of gastrointestinal adverse events was reported with maribavir, and a higher incidence of neutropenia was reported with valganciclovir.

CONCLUSIONS

Maribavir at a dose of at least 400 mg twice daily had efficacy similar to that of valganciclovir for clearing CMV viremia among recipients of hematopoietic-cell or solid-organ transplants. A higher incidence of gastrointestinal adverse events — notably dysgeusia — and a lower incidence of neutropenia were found in the maribavir group. (Funded by ViroPharma/Shire Development; EudraCT number, 2010-024247-32.)

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Cytomegalovirus (CMV) infection commonly complicates hematopoietic-cell and solid-organ transplantation[1,2] and is associated with increased morbidity and mortality.[3-5] The available anti-CMV agents[6-8] are effective but are limited by their toxic effects, including myelosuppression (ganciclovir and valganciclovir),[9,10] nephrotoxicity (foscarnet and cidofovir), and electrolyte imbalances (foscarnet).[11] In addition, infection with drug-resistant CMV (which is associated with poor outcomes[12-15]) develops in 5 to 14% of transplant recipients.[16-18] Hence, there is a need for effective anti-CMV agents with more favorable safety profiles and different mechanisms of action.

Maribavir is a potent, selective, orally bioavailable benzimidazole riboside that is active against CMV infection in humans.[19] Unlike the available anti-CMV agents that inhibit DNA polymerase, maribavir blocks nuclear egress of viral capsids through the inhibition of protein kinase UL97.[20-22] Maribavir is active in vitro against CMV strains that are resistant to ganciclovir, foscarnet, or cidofovir.[23] In addition, maribavir has a favorable safety profile, without associated myelosuppression or nephrotoxicity.[24,25]

In this trial, we sought to assess the safety and side-effect profile (primary objective) and antiviral activity (a secondary objective) of different doses of maribavir as compared with valganciclovir for preemptive treatment of CMV infection (in most cases, reactivation) for up to 12 weeks among hematopoietic-cell and solid-organ transplant recipients without CMV organ disease.

Methods

Trial Design and Patients

In this phase 2, randomized, dose-ranging, parallel-group trial, we recruited patients who had undergone allogeneic hematopoietic-cell and solid-organ transplantation at any time previously and were at least 18 years of age from 38 sites in six European countries. Patients were eligible if they had a screening CMV DNA level of 1000 to 100,000 copies per milliliter in blood or plasma. Exclusion criteria included documented CMV organ disease (per published definitions[26]) or infection with CMV that was known to be genotypically resistant to ganciclovir, valganciclovir, foscarnet, or cidofovir. Additional details are provided in the Supplementary Appendix and the protocol and statistical analysis plan, available with the full text of this article at NEJM.org.

Eligible patients were randomly assigned (in a 1:1:1:1 ratio), with the use of a central block (block size, 4) and an interactive voice and Web response system, to receive oral maribavir (Shire) at a dose of 400 mg, 800 mg, or 1200 mg twice daily or valganciclovir (Roche) at a dose of 900 mg twice daily for weeks 1 through 3 and 900 mg once daily after week 3 (with dose adjustment for renal function). Randomization was stratified according to transplant type (hematopoietic cell or solid organ). Adjustments of the doses of the trial drugs were permitted to manage toxic effects associated with treatment. Site personnel and patients were aware of the randomly assigned drug but were not aware of the dose of maribavir.

Treatment was given for up to 12 weeks. Patients could continue treatment (at the investigator's discretion) beyond week 3 if they had any decrease in CMV DNA level from baseline at week 2, and they could continue treatment beyond week 6 if they had a 2-log or greater decrease in CMV DNA level from baseline at week 5. Further details regarding the criteria for discontinuing treatment and the trial assessment schedule are provided in the Supplementary Appendix. Patient follow-up continued for 12 weeks after treatment cessation.

Adverse events were monitored throughout the trial and for a minimum of 1 week after the cessation of trial treatment. Serious adverse events and adverse events with a fatal outcome were recorded up to 30 days and 12 weeks, respectively, after the cessation of trial treatment. New clinically relevant CMV infection was recorded as an adverse event or serious adverse event as appropriate, and occurrences of CMV organ disease were recorded as serious adverse events.

Trial Oversight

The trial was designed and initially sponsored by ViroPharma. On April 29, 2014, sponsorship was transferred to Shire Development. Employees of Shire were involved in the trial design, as well as in the collection, analysis, and interpretation of data and in the fact checking of information; however, the authors are independently responsible for the content of the submitted manuscript, the final interpretation of the data, and the decision to submit the manuscript for publication. The authors vouch for the completeness and accuracy of the data presented and for the

fidelity of the trial to the protocol. Under the direction of the authors, medical writers who were paid by the sponsor wrote the first draft of the manuscript. There were confidentiality agreements between the authors and the sponsor.

The trial was conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki of 1964. Before the trial, the documentation was approved by relevant ethics committees. An independent, unblinded data and safety monitoring committee reviewed the available safety and safety-related efficacy data at predefined time points during the trial. All the patients provided written informed consent before undergoing any trial-specific procedures.

CMV TESTING AND TRIAL DEFINITIONS

For the determination of eligibility for enrollment, viral load (plasma or blood) was measured by quantitative polymerase-chain-reaction (PCR) or comparable quantitative CMV assay and could be measured at the central or a local laboratory. For all protocol-specified time points, CMV PCR testing of plasma was performed at a central laboratory (LGC, formerly Quotient Bioresearch) with the Artus CMV TM PCR kit (Qiagen). Additional details are provided in the Supplementary Appendix.

Confirmed undetectable plasma CMV DNA was defined as two consecutive plasma CMV DNA PCR assay values measured during treatment that were below the level of quantitation (i.e., <200 copies per milliliter according to the central laboratory) separated by at least 5 days. Recurrence was defined as two consecutive plasma CMV DNA PCR assay values that were above the level of quantitation (i.e., ≥200 copies per milliliter), separated by at least 5 days, after the confirmation of undetectable CMV.

TRIAL OBJECTIVES AND END POINTS

The primary objective of the trial was to determine the safety and side-effect profiles of different doses of maribavir as compared with valganciclovir for preemptive treatment of CMV reactivation or infection (i.e., treatment administered to prevent viremia from progressing to clinical disease) for up to 12 weeks. The primary safety analysis was the evaluation of adverse events that occurred or worsened during the treatment period (i.e., the period from the start of treatment through day 7 after the last dose; see the Supplementary Appendix).

The primary efficacy end point was the percentage of patients with a response to treatment, defined as central laboratory–confirmed undetectable CMV DNA in plasma within 3 weeks or 6 weeks after the start of treatment. Patients who did not meet these criteria for any reason (including early withdrawal from the trial, lack of efficacy of the assigned drug, or death) were considered not to have had a response. Secondary efficacy end points included the time to first undetectable CMV DNA in plasma within the first 6 weeks after the start of treatment, CMV infection recurrence, and time to first recurrence of CMV infection during the trial after virologic response. Efficacy was also evaluated in prespecified subgroups that were based on transplant and CMV infection characteristics at baseline.

STATISTICAL ANALYSIS

Sample size was based on the feasibility of assessing the safety of the trial drugs and the antiviral activity of maribavir. Enrollment of 160 patients was planned (40 per treatment group). The primary efficacy and safety analyses included all patients who underwent randomization and who received at least one dose of trial drug (intention-to-treat safety population).

The primary efficacy analysis of interest was the evaluation of the treatment effect in the pooled maribavir dose group as compared with that in the valganciclovir group. In addition, estimates of the treatment effect in each separate dose group were compared with those in the valganciclovir group. The valganciclovir group provided a reference for the assessment of treatment effect. Point estimates and 95% confidence intervals are provided for binary end points. The relationship between the trial treatments and the binary end points was explored with the use of a general linear regression model. Risk ratios and associated 95% confidence intervals for treatment response within 3 weeks and 6 weeks were computed with the use of the GENMOD procedure in SAS, version 9.2 (SAS Institute); a Cox proportional-hazards model was used for assessment of time-to-event end points. All models included terms of treatment, baseline plasma CMV DNA level, and transplant type. Statistical

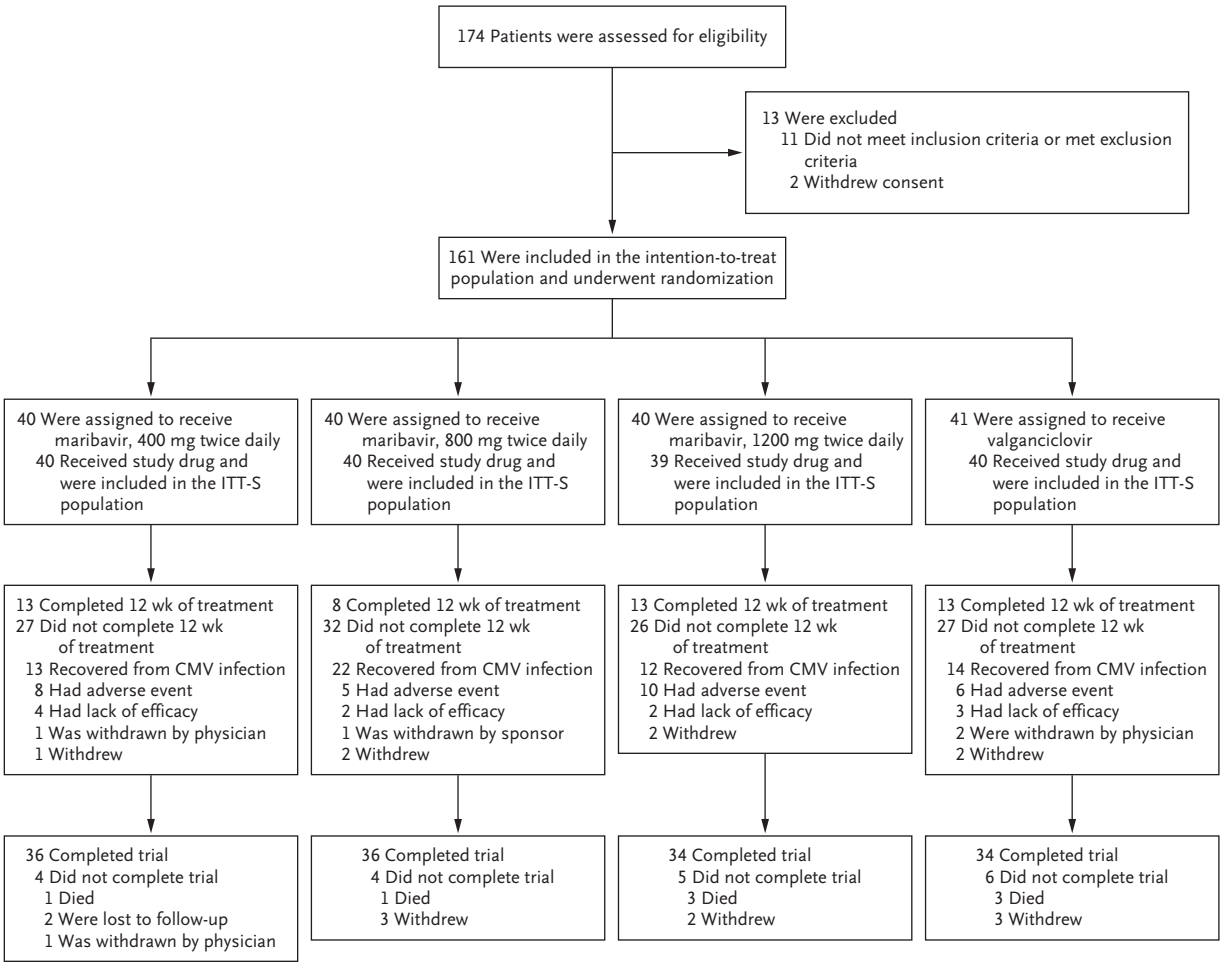


Figure 1. Enrollment, Randomization, and Follow-up.

Patients were randomly assigned to receive maribavir at a dose of 400 mg, 800 mg, or 1200 mg twice daily or valganciclovir at a dose of 900 mg twice daily for weeks 1 through 3 and 900 mg once daily after week 3 (with dose adjustment for renal function). One patient who was assigned to receive the 1200-mg dose of maribavir was ineligible (inclusion or exclusion violation), and one patient who was assigned to receive valganciclovir had a medical condition that prevented dosing. Recovery from cytomegalovirus (CMV) infection (i.e., CMV infection responded adequately, and further treatment was not considered necessary) was a prespecified reason for discontinuation of treatment before week 12 and was determined by the investigator. ITT-S denotes intention-to-treat safety.

model analyses were exploratory in nature, and no adjustment was made for multiplicity. Additional information is provided in the Supplementary Appendix.

RESULTS

PATIENTS

From May 14, 2012, to July 25, 2014, a total of 174 patients were screened, 161 underwent randomization, and 159 received treatment and were included in the intention-to-treat safety population (Fig. 1); 140 patients completed the trial. The median time from transplantation to the first dose of trial drug was 65 days (range, 13 days to >25 years) in the overall maribavir group and 75 days (range, 20 days to >16 years) in the valganciclovir group. Data regarding patients' adherence to treatment are reported in the Supplementary Appendix. Demographic and other key characteristics of the patients are shown in Table 1, and in Table S2 in the Supplementary Appendix; overall, 52% of patients were hematopoietic-cell transplant recipients and 48%

Table 1. Patient Demographic Characteristics (Intention-to-Treat Safety Population).*

Characteristic	Maribavir				Valganciclovir (N=40)
	400 mg (N=40)	800 mg (N=40)	1200 mg (N=39)	Overall (N=119)	
Age — yr					
Median (IQR)	56.5 (41–65)	58.5 (50–63)	58.0 (51–64)	58.0 (49–64)	58.5 (46–63)
Range	29–76	18–74	25–74	18–76	28–76
Male sex — no. (%)	22 (55)	27 (68)	22 (56)	71 (60)	27 (68)
Race — no. (%)†					
White	37 (92)	37 (92)	39 (100)	113 (95)	32 (80)
Asian	2 (5)	1 (2)	0	3 (3)	4 (10)
Black	1 (2)	2 (5)	0	3 (3)	3 (8)
Other	0	0	0	0	1 (2)
CMV serostatus — no./total no. (%)					
Hematopoietic-cell transplant					
Donor positive, recipient positive	6/20 (30)	9/21 (43)	13/20 (65)	28/61 (46)	8/21 (38)
Donor negative, recipient positive	13/20 (65)	12/21 (57)	7/20 (35)	32/61 (52)	13/21 (62)
Donor positive, recipient negative	1/20 (5)	0	0	1/61 (2)	0
Solid-organ transplant					
Donor positive, recipient positive	7/20 (35)	8/19 (42)	11/19 (58)	26/58 (45)	10/19 (53)
Donor negative, recipient positive	4/20 (20)	1/19 (5)	1/19 (5)	6/58 (10)	3/19 (16)
Donor positive, recipient negative	9/20 (45)	10/19 (53)	4/19 (21)	23/58 (40)	6/19 (32)
Donor negative, recipient negative	0	0	3/19 (16)	3/58 (5)	0
Most recent transplant — no. (%)					
Hematopoietic-cell transplant	20 (50)	21 (52)	20 (51)	61 (51)	21 (52)
Solid-organ transplant‡	20 (50)	19 (48)	19 (49)	58 (49)	19 (48)
Liver	6 (30)	6 (32)	6 (32)	18 (31)	7 (37)
Kidney	14 (70)	7 (37)	9 (47)	30 (52)	10 (53)
Other	0	6 (32)	5 (26)	11 (19)	3 (16)
Time from transplantation to first dose of trial treatment — days					
Mean	172.7±213.33	118.0±155.18	578.0±1956.13	287.1±1139.01	320.7±943.97
Median (range)	82.5 (25–854)	64.5 (13–836)	61.0 (21–9395)	65.0 (13–9395)	75.0 (20–5991)
Primary CMV infection — no. (%)§	29 (72)	34 (85)	34 (87)	97 (82)	27 (68)
Viral load at baseline — $\log_{10}$ copies/ml	3.56±0.853	3.69±0.966	3.64±0.919	3.63±0.908	3.57±0.840

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Denominators for the calculation of percentages are the numbers of patients in the intention-to-treat safety population (i.e., all patients who underwent randomization and received at least one dose of trial drug) unless otherwise specified. CMV denotes cytomegalovirus, and IQR interquartile range.
† Race was reported by the patient.
‡ Denominator is the number of solid-organ transplants. Because patients may have had more than one solid-organ transplant, percentages may not total 100%.
§ Primary CMV infection was defined as the first known CMV infection since the date of the most recent transplantation.

were solid-organ transplant recipients. In addition to the key results reported below, further results (including pharmacokinetic data and efficacy results) are reported in the Supplementary Appendix.

EFFICACY

Of the 117 patients who received maribavir and for whom postbaseline data were available, 72 (62%; 95% confidence interval [CI], 52 to 70) had a response to treatment within 3 weeks, as compared with 22 of the 39 patients (56%; 95% CI, 40 to 72) who received valganciclovir and had data available (risk ratio, 1.12; 95% CI, 0.84 to 1.49); the percentages of patients with a response were similar among the maribavir dose groups (Table 2, and Table S3 in the Supplementary Appendix). The percentage of patients for whom postbaseline data were available who had a response within 6 weeks was 79% (95% CI, 70 to 86) in the overall maribavir group and 67% (95% CI, 50 to 81) in the valganciclovir group, and the risk ratio based on the estimates of the treatment effect was 1.20 (95% CI, 0.95 to 1.51) (Table 2).

The median estimates from a Kaplan–Meier plot of time to confirmed undetectable plasma CMV DNA within 6 weeks were 21 days (95% CI, 15 to 22; interquartile range, 9 to 29) in the overall maribavir group and 17 days (95% CI, 8 to 25; interquartile range, 8 to 30) in the valganciclovir group, a difference that was not significant (hazard ratio [HR], 1.17) (Fig. 2). Among the patients who had confirmed undetectable plasma CMV DNA (Table 2), two patients in the 800-mg maribavir group had CMV recurrence within 6 weeks after starting the trial treatment. The T409M mutation in the CMV UL97 protein kinase developed after baseline in both patients (at week 12 in one patient and at week 1 of post-treatment follow-up in the other; additional details are provided in the Supplementary Appendix). The percentage of patients with recurrence of CMV infection at any time during the trial period was 22% in the overall maribavir group and 18% in the valganciclovir group (Table 2). The median observed time from confirmed undetectable CMV DNA in plasma to the recurrence of CMV infection was calculated as 72 days in the overall maribavir group, as compared with 80 days in the valganciclovir group (Fig. S1 in the Supplementary Appendix).

The percentage of patients who had a response to treatment within 6 weeks in the overall maribavir group was greater in association with low baseline levels of CMV DNA in plasma than it was with high levels (87% of patients with levels <10,000 copies per milliliter vs. 59% of those with levels ≥10,000 copies per milliliter) (Table S4 in the Supplementary Appendix). A greater percentage of hematopoietic-cell transplant recipients in the overall maribavir group than in the valganciclovir group had a response to treatment within 6 weeks (75% vs. 48%).

SAFETY

The median duration of exposure to trial treatment was 45 days (range, 1 to 96) in the overall maribavir group and 33 days (range, 1 to 88) in the valganciclovir group (Table S5 in the Supplementary Appendix). A summary of adverse events, adverse events that occurred or worsened during treatment, and serious adverse events that occurred or worsened during treatment is shown in Table 3, and in Table S6 in the Supplementary Appendix. Most patients reported at least one adverse event that occurred or worsened during treatment, and in 67% of patients in the overall maribavir group and 22% of those in the valganciclovir group such events were considered by the investigator to be related to the trial treatment. The majority of these events were mild to moderate in severity (Table S7 in the Supplementary Appendix); the most common adverse event associated with maribavir was dysgeusia (40% in the overall group, with no evidence of a dose-dependent effect), which was reported more frequently than in the valganciclovir group (2%). None of the discontinuations of maribavir treatment and one of the dose reductions (<1%) were due to dysgeusia. Other frequently reported events associated with maribavir were gastrointestinal adverse events (nausea, vomiting, and diarrhea), which were proportionally more frequent with maribavir (20 to 23% in the overall group) than with valganciclovir (10 to 15%).

The most frequently reported serious adverse events that occurred or worsened during treatment in the overall maribavir group were acute graft-versus-host disease, diarrhea, renal failure,

Table 2. Efficacy of Maribavir (Intention-to-Treat Safety Population).

Outcome	Maribavir				Valganciclovir (N=40)
	400 mg (N=40)	800 mg (N=40)	1200 mg (N=39)	Overall (N=119)	
Confirmed undetectable plasma CMV DNA within 3 wk*					
No. of patients with outcome/no. of patients with postbaseline data	26/39	23/40	23/38	72/117	22/39
Percent of patients with outcome (95% CI)	67 (50–81)	58 (41–73)	61 (43–76)	62 (52–70)	56 (40–72)
Risk ratio (95% CI)	1.18 (0.86–1.63)	1.06 (0.75–1.51)	1.12 (0.79–1.58)	1.12 (0.84–1.49)	Reference
Confirmed undetectable plasma CMV DNA within 6 wk*					
No. of patients with outcome/no. of patients with postbaseline data	31/39	33/40	28/38	92/117	26/39
Percent of patients with outcome (95% CI)	79 (64–91)	83 (67–93)	74 (57–87)	79 (70–86)	67 (50–81)
Risk ratio (95% CI)	1.19 (0.92–1.55)	1.26 (0.98–1.62)	1.12 (0.85–1.48)	1.20 (0.95–1.51)	Reference
CMV recurrence within 6 wk†					
No. of patients with outcome/no. of patients with confirmed undetectable plasma CMV DNA in recurrence analysis‡	0/33	2/34§	0/31	2/98	0/28
Percent of patients with outcome (95% CI)	0 (0–11)	6 (1–20)	0 (0–11)	2 (0–7)	0 (0–12)
CMV recurrence during trial period¶					
No. of patients with outcome/no. of patients with confirmed undetectable plasma CMV DNA in recurrence analysis‡	10/33	8/34	4/31	22/98	5/28
Percent of patients with outcome (95% CI)	30 (16–49)	24 (11–41)	13 (4–30)	22 (15–32)	18 (6–37)

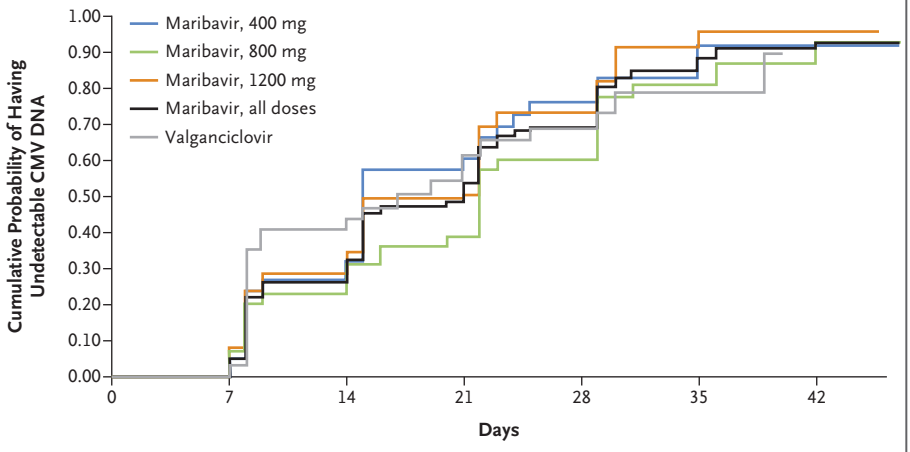
* Confirmed undetectable CMV DNA in plasma was defined as two consecutive CMV DNA polymerase-chain-reaction assay values measured during treatment that were below the level of quantitation (i.e., <200 copies per milliliter according to the central laboratory) separated by at least 5 days. For the primary analyses of confirmed undetectable CMV DNA within 3 weeks and 6 weeks, data were missing for 3 patients: 1 each in the 400-mg maribavir group, the 1200-mg maribavir group, and the valganciclovir group.

† Patients with this outcome had a recurrence within 6 weeks after the start of trial treatment; patients who withdrew early from the trial and had a recurrence before withdrawal from the trial are included. Recurrence was defined as two consecutive plasma CMV DNA PCR assay values that were above the level of quantitation (i.e., ≥200 copies per milliliter), separated by at least 5 days, after CMV DNA had been confirmed as undetectable.

‡ Patients with confirmed undetectable plasma CMV DNA in the recurrence analysis had at least two test results indicating undetectable CMV DNA separated by at least 5 days; patients who withdrew early from the trial are included. In the recurrence analysis, only the first undetectable result had to be from a specimen obtained during treatment (i.e., the second could have been obtained during follow-up).

§ One of the patients who had a recurrence was receiving maribavir at the time of recurrence; the other patient had the first detectable viral load while receiving maribavir, which was discontinued at that time. Maribavir resistance mutations developed in both patients.

¶ Patients with this outcome had a recurrence during the trial; the category includes those who withdrew early from the trial and had a recurrence before withdrawal from the trial.



No. at Risk							
Maribavir, 400 mg	39	38	26	15	7	4	2
Maribavir, 800 mg	40	39	30	23	14	6	3
Maribavir, 1200 mg	38	35	24	13	6	2	1
Maribavir, all doses	117	112	80	51	27	12	6
Valganciclovir	39	37	20	13	8	2	0

Figure 2. Time to Confirmed Undetectable CMV DNA in Plasma within 6 Weeks (Intention-to-Treat Safety Population with Postbaseline CMV DNA Measurements).

The intention-to-treat safety population included all patients who underwent randomization and received at least one dose of trial drug. Confirmed undetectable CMV DNA in plasma was defined as two consecutive CMV DNA polymerase-chain-reaction assay values measured during treatment that were below the level of quantitation (i.e., <200 copies per milliliter according to the central laboratory) separated by at least 5 days.

and urinary tract infection, each reported by 3% of patients (3 of 119). In the valganciclovir group, the most frequently reported serious adverse event that occurred or worsened during treatment was bacterial sepsis, reported by 8% of patients (3 of 40). Deaths were reported in all three maribavir dose groups and in the valganciclovir group (5% of patients [6 of 119] in the overall maribavir group and 8% of patients [3 of 40] in the valganciclovir group).

Increased immunosuppressant drug levels in blood were reported in 8% of patients (10 of 119) in the overall maribavir group (tacrolimus in 9 patients and cyclosporine in 1 patient) and in no patients in the valganciclovir group. The incidence was 5% in the 400-mg and 800-mg maribavir dose groups and was 15% in the 1200-mg dose group.

There were 10 reports of renal failure that occurred or worsened during treatment, occurring in 9 (8%) of the 119 patients who received maribavir (3 in the 400-mg dose group, 1 in the 800-mg dose group, and 5 in the 1200-mg dose group). Renal failure was reported as a serious adverse event in 3 of the 119 patients (3%) who received maribavir. There were no reports of renal failure as an adverse event that occurred or worsened during treatment or as a serious adverse event among the patients who received valganciclovir.

Trial treatment was discontinued because of an adverse event in 23% of patients (27 of 119) receiving maribavir (with no apparent dose effect) and in 12% of patients (5 of 40) receiving valganciclovir (Table 3). The most frequent reason for discontinuation of maribavir treatment was CMV infection (5% [6 of 119]); there were no discontinuations due to renal impairment or myelosuppression. The most frequent reason for discontinuation of valganciclovir treatment was leukopenia (5% [2 of 40]). Overall, 8% of patients (10 of 119) who received maribavir had dose adjustments because of adverse events, as compared with 48% of patients (19 of 40) who received valganciclovir.

Valganciclovir was associated with a greater incidence of neutropenia (absolute neutrophil count <1000 per cubic millimeter) that occurred

Table 3. Safety Results (Intention-to-Treat Safety Population).

Adverse Event*	Maribavir				Valganciclovir (N=40)
	400 mg (N=40)	800 mg (N=40)	1200 mg (N=39)	Overall (N=119)	
	number of patients (percent)				
Adverse event that occurred or worsened during treatment	39 (98)	38 (95)	39 (100)	116 (97)	33 (82)
Adverse event that occurred or worsened during treatment, considered by the investigator to be related to trial drug	25 (62)	25 (62)	30 (77)	80 (67)	9 (22)
Serious adverse event that occurred or worsened during treatment†	16 (40)	17 (42)	19 (49)	52 (44)	13 (32)
Serious adverse event that occurred or worsened during treatment, considered by the investigator to be related to trial drug	3 (8)	1 (2)	8 (21)	12 (10)	1 (2)
Adverse event that led to treatment discontinuation					
All	12 (30)	5 (12)	10 (26)	27 (23)	5 (12)
Related to study drug	5 (12)	4 (10)	7 (18)	16 (13)	4 (10)
Adverse event with outcome of death‡	2 (5)	1 (2)	3 (8)	6 (5)	3 (8)
Adverse events that occurred or worsened during treatment in categories of interest reported in at least 4 patients in any treatment group§					
Dysgeusia	18 (45)	16 (40)	14 (36)	48 (40)	1 (2)
Nausea	9 (22)	7 (18)	11 (28)	27 (23)	6 (15)
Diarrhea	7 (18)	7 (18)	10 (26)	24 (20)	4 (10)
Vomiting	4 (10)	8 (20)	12 (31)	24 (20)	4 (10)
Cough	5 (12)	6 (15)	6 (15)	17 (14)	5 (12)
Urinary tract infection	5 (12)	5 (12)	6 (15)	16 (13)	4 (10)
Headache	4 (10)	4 (10)	6 (15)	14 (12)	1 (2)
Nasopharyngitis	7 (18)	5 (12)	0	12 (10)	2 (5)
Dyspnea	3 (8)	3 (8)	6 (15)	12 (10)	2 (5)
Anemia	2 (5)	7 (18)	3 (8)	12 (10)	1 (2)
CMV infection	5 (12)	3 (8)	1 (3)	9 (8)	2 (5)
Renal failure	3 (8)	1 (2)	5 (13)	9 (8)¶	0
Abdominal pain	2 (5)	3 (8)	4 (10)	9 (8)	3 (8)
Constipation	2 (5)	3 (8)	4 (10)	9 (8)	2 (5)
Oral herpes	3 (8)	2 (5)	3 (8)	8 (7)	0
Abdominal pain upper	4 (10)	2 (5)	1 (3)	7 (6)	1 (2)
Acute graft-versus-host disease	3 (8)	1 (2)	3 (8)	7 (6)	3 (8)
Hypotension	2 (5)	2 (5)	2 (5)	6 (5)	3 (8)
Tremor	1 (2)	1 (2)	4 (10)	6 (5)	1 (2)
Hypertension	3 (8)	0	2 (5)	5 (4)	1 (2)
Pneumonia	2 (5)	1 (2)	2 (5)	5 (4)	3 (8)
Nephrogenic anemia	1 (2)	1 (2)	3 (8)	5 (4)	0
Neutropenia	1 (2)	3 (8)	1 (3)	5 (4)	2 (5)
Dry mouth	1 (2)	2 (5)	2 (5)	5 (4)	3 (8)
Leukopenia	2 (5)	2 (5)	0	4 (3)	3 (8)

Table 3. (Continued.)

Adverse Event*	Maribavir				Valganciclovir (N=40)
	400 mg (N=40)	800 mg (N=40)	1200 mg (N=39)	Overall (N=119)	
	number of patients (percent)				
Dysuria	1 (2)	0	3 (8)	4 (3)	1 (2)
Neutropenia that occurred or worsened during treatment‖					
Through week 6	2/40 (5)	1/40 (2)	2/38 (5)	5/118 (4)	6/39 (15)
Through week 12	2/40 (5)	1/40 (2)	3/38 (8)	6/118 (5)	7/39 (18)

* Adverse events that occurred or worsened during treatment were defined as those that occurred during the period from the start of treatment with maribavir or valganciclovir through 7 days after the last dose.
† The serious adverse events that occurred in at least 5% of patients in any treatment (or dose) group were acute graft-versus-host disease (3 patients), diarrhea (3), renal failure (3), urinary tract infection (3), CMV infection (2), gastroenteritis (2), malaise (2), and sepsis (2) among the patients who received maribavir and bacterial sepsis (3), acute graft-versus-host disease (2), CMV infection (1), and sepsis (1) among the patients who received valganciclovir.
‡ Adverse events with an outcome of death were acute myeloid leukemia (maribavir, 1 patient), acute respiratory distress syndrome (maribavir, 1), multiorgan failure (maribavir, 1; valganciclovir, 1), *Pneumocystis jirovecii* pneumonia (valganciclovir, 1), pneumonia (maribavir, 1), respiratory syncytial virus infection (maribavir, 1), sepsis (maribavir, 2; valganciclovir, 1), and thrombotic microangiopathy (maribavir, 1). No deaths were considered by the investigator to have been related to the trial drugs.
§ Events were classified according to preferred terms from the *Medical Dictionary for Regulatory Activities*, version 17.0.
¶ Nine patients were recorded as having renal insufficiency, and one patient also had acute kidney injury; none of these events was considered by the investigator to be related to maribavir. Four of these patients had a history of renal insufficiency; one patient had a recorded history of nephrotic syndrome, and another had a history of surgery for the treatment of renal lithiasis.
‖ Included are patients with an absolute neutrophil count of less than 1000 per cubic millimeter (1.0×10^9 per liter). The denominator is the number of patients with a baseline measurement and at least one postbaseline measurement of absolute neutrophil count.

or worsened during treatment than was any dose of maribavir (Table 3). Shifts in the National Cancer Institute Common Terminology Criteria for Adverse Events grade for myelosuppression measures from grade 0, 1, or 2 to grade 3 or 4 in the intention-to-treat safety population were substantially more common among patients receiving valganciclovir than among those receiving any dose of maribavir (leukopenia: 28% [11 of 40] vs. 8% [9 of 119]; lymphopenia: 18% [7 of 40] vs. 3% [4 of 119]; and neutropenia: 22% [9 of 40] vs. 6% [7 of 119]). Hematopoietic growth factors were used more often for the treatment of neutropenia in the valganciclovir group than in the overall maribavir group (15% [6 of 40] vs. 7% [8 of 119]).

DISCUSSION

Maribavir, at doses of at least 400 mg twice a day for no more than 12 weeks, had efficacy similar to that of standard-dose valganciclovir for clearing CMV viremia in transplant recipients with early CMV reactivation. Moreover, there was no convincing evidence of differentiation among the doses of maribavir in the percentage of patients with confirmed undetectable plasma CMV DNA within 3 or 6 weeks after the start of treatment.

In phase 3 studies, a lower dose of maribavir (100 mg twice a day) did not prevent CMV disease[27,28]; however, data on maribavir for the treatment of resistant or refractory CMV infection among patients for whom the drug was approved for emergency use[29] and from a French study under the European named patient program[30] suggested that higher doses may provide effective antiviral activity without compromising safety, and this finding is supported by the findings of a phase 2 study.[31] By enrolling patients who were relatively early in the course of CMV reactivation or infection, this dose-finding trial provided a reasonable time frame in which to observe the response to preemptive treatment.

In the analysis of data according to transplant type, a greater percentage of hematopoietic-cell transplant recipients were found to have had a response within 6 weeks in the overall maribavir group than in the valganciclovir group. Myelosuppression with valganciclovir among hematopoietic-cell transplant recipients may have con-

tributed to this apparent difference, although further study is needed to confirm these findings.

A mutation known to confer resistance to maribavir (T409M) was detected after baseline in 2 of 119 patients, both of whom were in the 800-mg dose group. However, it should be noted that this was a phase 2 trial in a small patient population, and therefore it is difficult to draw conclusions from these findings.

Although this was an open-label trial, the adverse events that occurred or worsened during treatment (dysgeusia, gastrointestinal events, and elevated immunosuppressant drug levels) that were reported more frequently with maribavir than with valganciclovir were in line with the known safety profile of maribavir. The incidence of dysgeusia was similar among the maribavir dose groups, with one report of dose reduction and no discontinuations of treatment due to taste disturbance.

Increased immunosuppressant drug levels were reported in 8% of the patients who received maribavir and in none of the patients who received valganciclovir. Coadministration of maribavir and tacrolimus is known to increase tacrolimus concentrations in plasma.[32] Close monitoring of calcineurin inhibitor levels in patients receiving maribavir is recommended.[33]

In the current trial, and as expected on the basis of previous studies,[25,27,28] neutropenia occurred less frequently with maribavir than with valganciclovir, and analyses of shifts in toxic-effect grade showed that worsening of myelosuppression measures was more common in the valganciclovir group than in the maribavir group.

Dose adjustments to manage toxic effects occurred in a greater percentage of patients who received valganciclovir than of those who received maribavir, a finding consistent with the established need to adjust valganciclovir dose according to renal function.[34] In contrast, maribavir does not require dose adjustment based on renal function.[35] In this trial, maribavir dose adjustments were generally related to gastrointestinal adverse events of nausea, vomiting, or diarrhea.

We acknowledge the limitations of this exploratory trial, such as the small sample size that is inherent to a phase 2 trial. The open-label design could potentially have incurred some bias with respect to the reporting of safety data. To represent the diverse population of patients who are at risk for CMV reactivation, we included different transplant populations (balanced by stratifying according to transplant type at enrollment). However, the natural history of CMV reactivation in recipients of hematopoietic-cell transplants differs from that in recipients of solid-organ transplants,[36] and therefore these two populations may not necessarily be comparable. The criteria for treatment response in this trial were based on viral load; however, in the clinical context, treatment failure could be considered as breakthrough disease that leads to other CMV therapy. Finally, the recurrence analysis did not account for any differences between treatment groups in either the percentage of patients who had clearance of viremia (a greater proportion with clearance of viremia would mean a greater scope for recurrence) or the incidence of graft-versus-host disease among recipients of hematopoietic-cell transplants. Following this and another trial involving patients with CMV infections that are resistant or refractory to ganciclovir or foscarnet,[31] ongoing clinical trials of maribavir (ClinicalTrials.gov numbers, NCT02931539 and NCT02927067) should address many of these limitations.

In conclusion, maribavir, at doses of at least 400 mg twice daily, had efficacy similar to that of valganciclovir for clearing CMV viremia. The incidence of neutropenia was lower in the maribavir group than in the valganciclovir group. Maribavir was associated with gastrointestinal adverse events, a finding similar to results reported previously.[24,25,27,28,37] With its unique mechanism of action and evidence suggesting a lack of myelosuppression, maribavir should be studied further in patients who have undergone transplantation.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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