Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial

Robin K. Avery,[1] Sophie Alain,[2] Barbara D. Alexander,[3] Emily A. Blumberg,[4] Roy F. Chemaly,[5] Catherine Cordonnier,[6] Rafael F. Duarte,[7] Diana F. Florescu,[8] Nassim Kamar,[9] Deepali Kumar,[10] Johan Maertens,[11] Francisco M. Marty,[12,a] Genovefa A. Papanicolaou,[13,14] Fernanda P. Silveira,[15] Oliver Witzke,[16] Jingyang Wu,[17] Aimee K. Sundberg,[18] and Martha Fournier[18]; for the SOLSTICE Trial Investigators[b]

[1]Division of Infectious Diseases, Johns Hopkins University, Baltimore, Maryland, USA; [2]Department of Virology and National Reference Center for Herpesviruses, Limoges University Hospital, UMR Inserm 1092, University of Limoges, Limoges, France; [3]Division of Infectious Diseases and International Health, Duke University, Durham, North Carolina, USA; [4]Department of Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, Pennsylvania, USA; [5]Department of Infectious Diseases, Infection Control, and Employee Health, University of Texas MD Anderson Cancer Center, Houston, Texas, USA; [6]Haematology Department, Henri Mondor Hospital and University Paris-Est-Créteil, Créteil, France; [7]Department of Haematology, Hospital Universitario Puerta de Hierro Majadahonda, Madrid, Spain; [8]Infectious Diseases Division, University of Nebraska Medical Center, Omaha, Nebraska, USA; [9]Department of Nephrology and Organ Transplantation, Toulouse Rangueil University Hospital, INFINITY-Inserm U1291-CNRS U5051, University Paul Sabatier, Toulouse, France; [10]Transplant Centre, University Health Network, Toronto, Ontario, Canada; [11]Haematology Department, University Hospitals Leuven, KU Leuven, Leuven, Belgium; [12]Department of Infectious Disease, Brigham and Women's Hospital and Dana-Farber Cancer Institute, Boston, Massachusetts, USA; [13]Infectious Disease Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York, USA; [14]Department of Medicine, Weill Cornell Medicine, New York, New York, USA; [15]Department of Medicine, Division of Infectious Diseases, University of Pittsburgh and University of Pittsburgh Medical Center, Pittsburgh, Pennsylvania, USA; [16]Department of Infectious Diseases, West German Centre of Infectious Diseases, University Medicine Essen, University Duisburg-Essen, Essen, Germany; [17]Biostatistics, Takeda Development Center Americas, Inc, Lexington, Massachusetts, USA; and [18]Clinical Sciences, Takeda Development Center Americas, Inc, Lexington, Massachusetts, USA

Background. Therapies for refractory cytomegalovirus infections (with or without resistance [R/R]) in transplant recipients are limited by toxicities. Maribavir has multimodal anti-cytomegalovirus activity through the inhibition of UL97 protein kinase.

Methods. In this phase 3, open-label study, hematopoietic-cell and solid-organ transplant recipients with R/R cytomegalovirus were randomized 2:1 to maribavir 400 mg twice daily or investigator-assigned therapy (IAT; valganciclovir/ganciclovir, foscarnet, or cidofovir) for 8 weeks, with 12 weeks of follow-up. The primary endpoint was confirmed cytomegalovirus clearance at end of week 8. The key secondary endpoint was achievement of cytomegalovirus clearance and symptom control at end of week 8, maintained through week 16.

Results. 352 patients were randomized (235 maribavir; 117 IAT). Significantly more patients in the maribavir versus IAT group achieved the primary endpoint (55.7% vs 23.9%; adjusted difference [95% confidence interval (CI)]: 32.8% [22.80–42.74]; $P < .001$) and key secondary endpoint (18.7% vs 10.3%; adjusted difference [95% CI]: 9.5% [2.02–16.88]; $P = .01$). Rates of treatment-emergent adverse events (TEAEs) were similar between groups (maribavir, 97.4%; IAT, 91.4%). Maribavir was associated with less acute kidney injury versus foscarnet (8.5% vs 21.3%) and neutropenia versus valganciclovir/ganciclovir (9.4% vs 33.9%). Fewer patients discontinued treatment due to TEAEs with maribavir (13.2%) than IAT (31.9%). One patient per group had fatal treatment-related TEAEs.

Conclusions. Maribavir was superior to IAT for cytomegalovirus viremia clearance and viremia clearance plus symptom control maintained post-therapy in transplant recipients with R/R cytomegalovirus. Maribavir had fewer treatment discontinuations due to TEAEs than IAT.

Clinical Trials Registration. NCT02931539 (SOLSTICE).

Keywords. cytomegalovirus; transplant recipients; antiviral agents; drug resistance; maribavir.

Graphical Abstract

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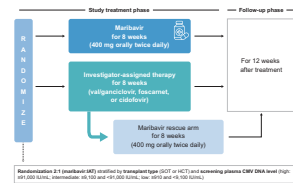
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Graphical abstract — Introduction, Study Design, Study Endpoints, Results, Safety, and Conclusions.

Cytomegalovirus (CMV) infection, a serious post-transplantation complication [1], significantly increases the risk of morbidity and mortality [2–5], particularly among transplant recipients with resistant or refractory infection [6–8]. Transplant recipients with resistant or refractory CMV often require prolonged anti-CMV therapy [6, 7], and treatment options are suboptimal due to limited efficacy [9, 10], toxicities, and possible resistance or cross-resistance among currently available anti-CMV agents [11, 12]. Treatment-limiting toxicities associated with available antiviral agents include myelosuppression with valganciclovir/ganciclovir and nephrotoxicity with foscarnet or cidofovir [5, 13–15]. Thus, there is an unmet need for new, effective agents with improved safety profiles.

Maribavir, a benzimidazole riboside, has multimodal anti-CMV activity, inhibiting CMV DNA replication, encapsidation, and nuclear egress of viral capsids via inhibition of the UL97 protein kinase and its natural substrates [16–19]. Maribavir is active in vitro and in vivo against CMV, including strains resistant to ganciclovir, foscarnet, or cidofovir [20, 21]. In 2 phase 2 studies of maribavir (400 mg, 800 mg, and 1200 mg twice daily [BID]) in solid-organ (SOT) and hematopoietic-cell transplant (HCT) recipients, maribavir was efficacious in clearing viremia within 6 weeks in patients with refractory CMV infection (with or without resistance [R/R]) [22], as well as in patients without R/R CMV infection or CMV organ disease [23]

This phase 3 trial compared the efficacy and safety of maribavir versus investigator-assigned therapy (IAT) for treatment of R/R CMV infection in SOT and HCT recipients.

METHODS

The roles of the independent Data Monitoring Committee and the Endpoint Adjudication Committee (EAC) are described in the Supplementary Methods.

Trial Design and Patients

In this phase 3, randomized, open-label, multicenter, active-controlled trial, HCT and SOT recipients (aged ≥12 years) were eligible if they had documented CMV infection in plasma (DNAemia, referred to as viremia), with a CMV DNA screening value of 910 IU/mL or greater in 2 consecutive tests separated by 1 or more day determined by local/central specialty laboratory quantitative polymerase chain reaction (qPCR). The detailed trial design is shown in Figure 1. The patient's CMV infection must have been refractory to the most recent treatment, defined as failure to achieve a more than 1-$\log_{10}$ decrease in CMV DNA after 14 days or more of anti-CMV treatment [22]. Patients with resistant CMV infection, defined as 1 or more genetic mutation associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir, were also included if they met refractory criteria. Key exclusion criteria included resistant or
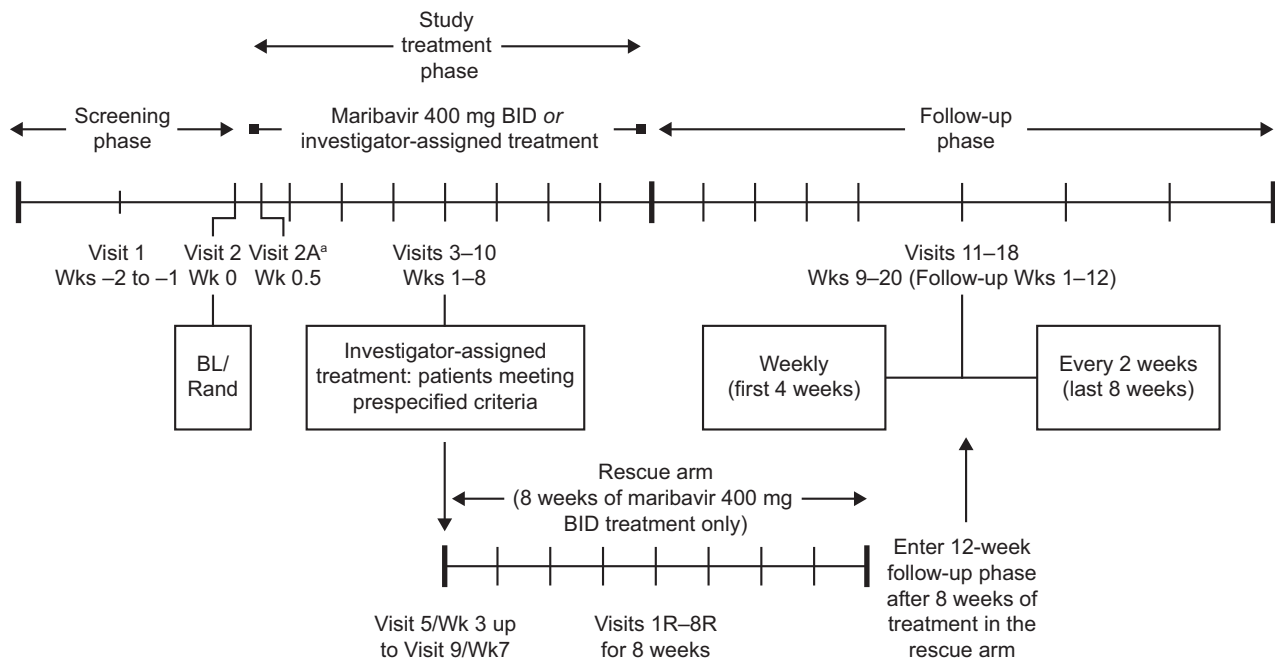
Figure 1. Trial design. [a]Visit 2A/2A(R) was only required for patients receiving tacrolimus, cyclosporine, everolimus, or sirolimus at visit 2/2R. Abbreviations: BID, twice daily; BL, baseline; R, rescue; Rand, randomization; Wk, week.

refractory CMV infection due to inadequate adherence to prior anti-CMV treatment; CMV disease with central nervous system involvement or retinitis; and concomitant need for leflunomide, letermovir, or artesunate (Supplementary Methods).

Eligible patients were randomized 2:1 to receive maribavir (400 mg orally BID) or IAT for 8 weeks (Figure 1) through a centralized interactive response technology system. Randomization was stratified by transplant type (HCT/SOT) and CMV DNA level (using the most recent local/central laboratory qPCR screening results available; high, ≥91 000 IU/mL; intermediate, ≥9100 to <91 000 IU/mL; low, <9100 to ≥910 IU/mL). The treatment phase was followed by 12 weeks of follow-up, in which patients were off study-assigned therapy.

The choice of specific IAT was at the investigators' discretion and could include mono- or combination therapy (≤2 drugs) with intravenous (IV) ganciclovir, oral valganciclovir, IV foscarnet, or IV cidofovir (Supplementary Methods). Switching between ganciclovir and valganciclovir was permitted. A maribavir rescue arm was an option for patients originally assigned IAT after 3 or more weeks of treatment upon medical monitor confirmation of meeting 1 of 3 prespecified criteria (Supplementary Methods).

The study was conducted in accordance with International Conference on Harmonisation of Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. Institutional review boards/independent ethics committees at each center approved the trial. All patients/legal guardians provided written informed consent.

Endpoints and Assessments

The primary endpoint was confirmed CMV viremia clearance at the end of week 8 (regardless of premature treatment discontinuation). Confirmed viremia clearance was defined as plasma CMV DNA level below the lower limit of quantification (<137 IU/mL) in 2 consecutive post-baseline samples, separated by 5 or more days, performed at the central laboratory using COBAS AmpliPrep/COBAS TaqMan CMV Test (Roche Diagnostics). Patients who received maribavir rescue or alternative anti-CMV treatment before the end of week 8, or who failed to achieve confirmed CMV viremia clearance at week 8 (including missing virologic data), were considered nonresponders.

The key secondary endpoint was a composite of confirmed CMV viremia clearance and symptom control at the end of week 8, maintained through week 16 (8 weeks beyond the treatment phase) after receiving exclusively study-assigned treatment. Symptom control was defined as resolution/improvement of CMV disease/syndrome for patients symptomatic at baseline or absence of the development of CMV disease/syndrome for patients asymptomatic at baseline. Cytomegalovirus disease/syndrome was assessed by the investigator using the classification in Ljungman et al [24, 25]; assessments were adjudicated by an independent, blinded EAC. Additional secondary and exploratory endpoints and study assessment details are within the Supplementary Methods.

Safety endpoints included treatment-emergent adverse events (TEAEs) and serious TEAEs (TESAEs).

Statistical Analysis

Sample size determination details are described within the Supplementary Methods. Analyses of the primary and key secondary endpoints were conducted in the treatment group to which patients were randomized (Randomized Population). Difference in the proportion of patients achieving the primary endpoint between treatment groups was obtained using Cochran–Mantel–Haenszel weighted average across strata of baseline central laboratory CMV viral load (low, <9100 IU/mL; intermediate/high, ≥9100 IU/mL) and transplant type (SOT, HCT). If the difference in the proportion of patients achieving clearance at the end of week 8 with maribavir was higher than IAT ($P \le .05$), maribavir was superior to IAT. The key secondary endpoint was analyzed using the same method. The primary endpoint was also evaluated in prespecified subgroups in the randomized population using similar methods, including any applicable stratification factors, and in multiple prespecified sensitivity analyses (Supplementary Methods). Additionally, an analysis of the primary endpoint in the subset of patients who completed 8 weeks of treatment was conducted. Hypothesis testing of primary and key secondary endpoints was adjusted for multiple comparisons using a fixed-sequence testing procedure to control the family-wise type 1 error rate at a 2-sided 5% level. Other analyses did not control for multiplicity of inferences (Supplementary Methods). Safety data were analyzed descriptively in all patients who received a dose of study drug (Safety Population).

RESULTS

Patients

The study was conducted between December 2016 and August 2020. A total of 415 patients were screened (101 sites, 12 countries) and 352 were randomized (maribavir, n = 235; IAT, n = 117) (Figure 2); 1 patient per group did not receive the study drug. The median age of patients was 55 (range, 19–79) years and baseline characteristics were balanced between treatment groups (Table 1; Supplementary Tables 1 and 2); 40.1% of patients had undergone HCT and 59.9% SOT. Overall, 257 patients (73.0%) completed the study (maribavir, 199 [84.7%]; IAT, 58 [49.6%]), and 22 patients received maribavir as rescue treatment (Figure 2).

Efficacy

Primary Endpoint

A significantly higher proportion of patients in the maribavir group achieved confirmed CMV viremia clearance at week 8 than in the IAT group (55.7% [131/235] vs 23.9% [28/117]; adjusted difference: 32.8%; 95% confidence interval [CI]: 22.80–42.74%; $P < .001$) (Figure 3A). Across prespecified subgroups, results remained generally consistent, including transplant type (Figure 3B). A greater proportion of patients with baseline genotypic resistance to IAT achieved viremia clearance at the end

of week 8 in the maribavir versus IAT group (62.8% vs 20.3%; adjusted difference: 44.1%; 95% CI: 31.33–56.94%). A numeric treatment difference between maribavir and IAT was also observed among patients with refractory (nonresistant) CMV infection (43.8% vs 32.4%; adjusted difference: 12.6%; 95% CI: −6.24 to 31.43%). Reasons for primary endpoint nonresponders are provided in the Supplementary Methods. Multiple sensitivity analyses were conducted, and the results were consistent with the primary analysis results (Supplementary Table 3).

Secondary Endpoints

A higher proportion of patients randomized to maribavir versus IAT demonstrated CMV viremia clearance and symptom control at the end of week 8, maintained through week 16 (key secondary endpoint; 18.7% vs 10.3%; adjusted difference: 9.5%; 95% CI: 2.02–16.88%; $P = .01$) (Figure 4). This effect was consistent at weeks 12 (22.6% vs 10.3%; $P < .001$) and 20 (18.3% vs 9.4%; $P = .008$). Viremia clearance after 8 weeks of study-assigned treatment and recurrence during the first 8 weeks of the study are described in the Supplementary Results.

Overall, 40 deaths were reported (Supplementary Table 4); 8 deaths were due to CMV disease (maribavir: 4 [1.7%]; IAT: 4 [3.4%]). All-cause mortality was 11.5% with maribavir and 11.1% with IAT.

Exploratory Evaluations

Kaplan–Meier median (95% CI) time to first confirmed CMV viremia clearance (within study week 8) occurred earlier in the maribavir versus IAT groups (22.0 [21.0–23.0] vs 27.0 [22.0–30.0] days; $P = .04$, log-rank test) (Supplementary Figure 1).

Clinically relevant recurrence (ie, recurrence among responders, after week 8, who received alternative anti-CMV treatment) occurred less frequently in patients randomized to maribavir (26.0%) than IAT (35.7%). Among the 22 patients who initially received IAT and subsequently received maribavir rescue treatment due to lack of response, 11 (50.0%) achieved confirmed CMV viremia clearance at week 8 of the maribavir rescue treatment phase.

Safety

Median (range) duration of exposure was 57 (2–64) days with maribavir and 34 (4–64) days with IAT. At least 1 TEAE was reported in 97.4% and 91.4% of patients in the maribavir and IAT groups, respectively (Table 2). Fewer patients discontinued maribavir than IAT due to TEAEs (13.2% and 31.9%) (Supplementary Table 5).

Dysgeusia was the most frequently reported TEAE in the maribavir group (maribavir: 37.2%; IAT: 3.4%) (Table 2); this was reported as mostly mild, and usually resolved either on treatment or shortly after the last dose of maribavir (Kaplan–Meier median time to resolution off treatment: 7 days), and
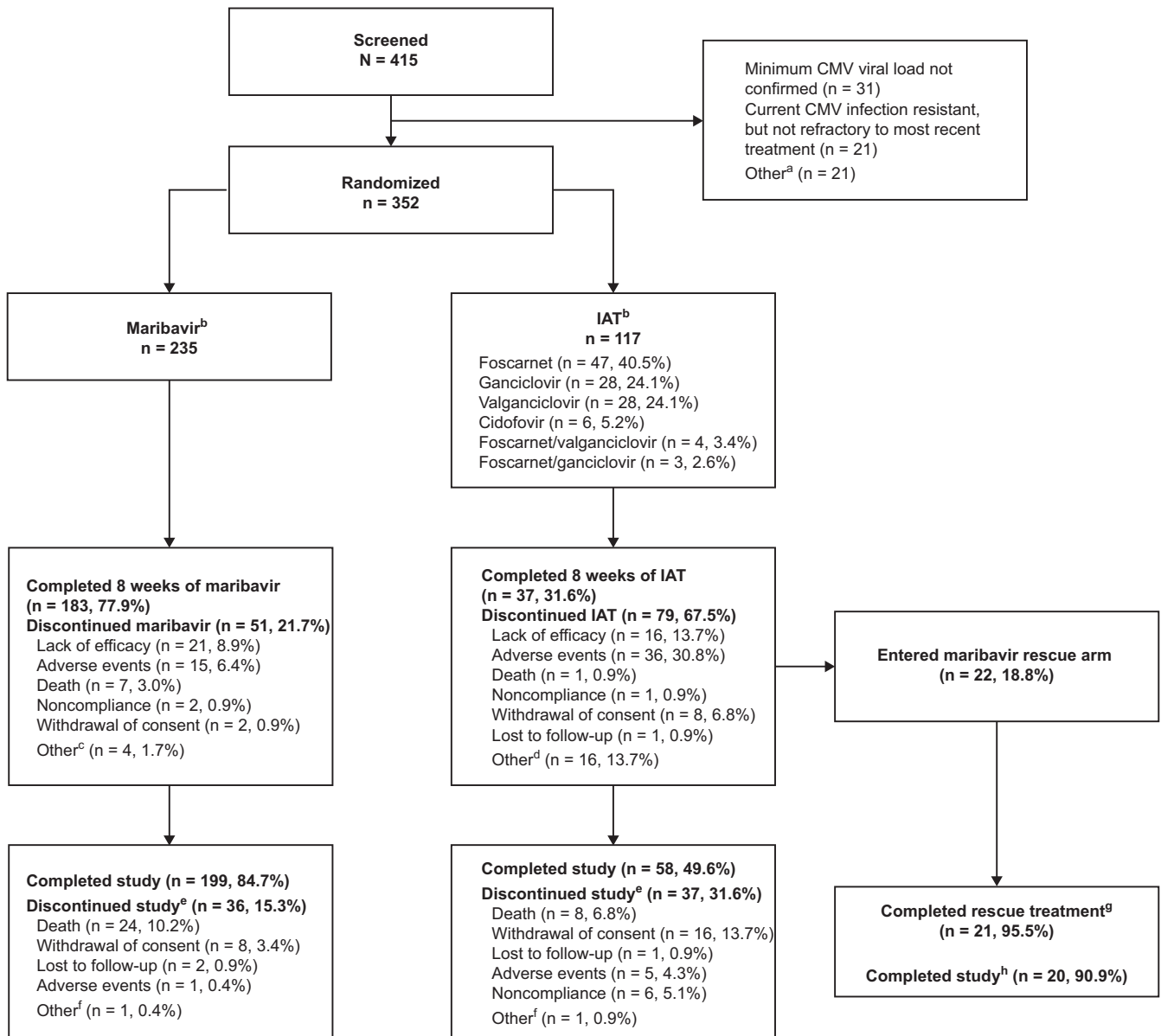
Figure 2. Patient disposition at enrollment, randomization, and follow-up. Percentages were calculated based on the number of patients randomized to each treatment group. Percentages may not total to 100% due to rounding. Serious AEs were recorded until the end of trial participation or resolution (whichever was later); median on-study duration was 141.0 days in each group. [a]Patients could have multiple reasons for not being randomized. Other reasons were: patient did not receive an HCT or SOT (n = 1); CMV infection not confirmed refractory to most recent treatment (n = 2); investigator not willing to treat the patient with ganciclovir, valganciclovir, foscarnet, or cidofovir (n = 2); platelet count <25 000/mm^3 (n = 5); hemoglobin <8 g/dL (n = 1); eGFR ≤30 mL/min/1.73 m^2 (n = 1); pregnancy (n = 1); patient was not willing/not able to comply fully with study procedures/restrictions (n = 3); current refractory or resistant CMV infection due to inadequate adherence to prior treatment (n = 2); serum aspartate aminotransferase >5 × ULN at screening, or serum alanine aminotransferase >5 × ULN at screening, or total bilirubin ≥3.0 × ULN at screening (n = 1); received any investigational agent with known anti-CMV activity within 30 days before initiation of study treatment or investigational CMV vaccine at any time (n = 1); and active malignancy (n = 1). [b]One patient per group was randomized but did not receive trial medication. Percentage for each IAT type was calculated based on n = 116. [c]Other reasons for treatment discontinuation in the maribavir group included investigator decision to switch to letermovir, CMV detected in patient's cerebrospinal fluid, nothing-by-mouth status with mental status change with risk for aspiration, and disease progression (in 1 patient each). [d]Other reasons for treatment discontinuation in the IAT group were: low viral load/CMV clearance (with concern of toxicity with continued administration of IAT (n = 9), patient safety (n = 3), patient/investigator request (n = 2), no efficacy and patient ineligible for rescue therapy (n = 1), and peripherally inserted central catheter issues (n = 1). [e]These results are based on investigator determination for the primary reason for study discontinuation. [f]Other reasons for study discontinuation in maribavir or IAT group included investigator discretion to discontinue 1 patient before dosing with maribavir, and no efficacy with IAT for a patient who was not eligible for rescue therapy. [g]Per protocol, maribavir rescue arm treatment was discontinued in 1 patient due to CMV encephalitis. [h]One patient was unable to complete follow-up visits in the study due to hospitalization in a different city and therefore did not complete the maribavir rescue study period. Abbreviations: AE, adverse event; CMV, cytomegalovirus; eGFR, estimated glomerular filtration rate; HCT, hematopoietic-cell transplant; IAT, investigator-assigned therapy; SOT, solid-organ transplant; ULN, upper limit of normal.

Table 1. Patient Characteristics at Baseline (Randomized Population)

Characteristics	Maribavir (n = 235)	IAT (n = 117)
Age, years		
Median	57.0	54.0
Range	(19–79)	(19–77)
Male sex, n (%)	148 (63.0)	65 (55.6)
Race, n (%)		
White	179 (76.2)	87 (74.4)
Black or African American	29 (12.3)	18 (15.4)
Asian	9 (3.8)	7 (6.0)
Other	16 (6.8)	5 (4.3)
Missing	2 (0.9)	0
Solid-organ transplant,[a] n (%)	142 (60.4)	69 (59.0)
Kidney[b]	74 (52.1)	32 (46.4)
Lung[b]	40 (28.2)	22 (31.9)
Heart[b]	14 (9.9)	9 (13.0)
Multiple[b]	5 (3.5)	5 (7.2)
Liver[b]	6 (4.2)	1 (1.4)
Pancreas[b]	2 (1.4)	0
Intestine[b]	1 (0.7)	0
Hematopoietic-cell transplant,[c] n (%)	93 (39.6)	48 (41.0)
Allogeneic[d]	92 (98.9)	48 (100.0)
Donor type[e]		
HLA identical sibling	13 (14.1)	2 (4.2)
HLA matched other relative	12 (13.0)	10 (20.8)
HLA mismatched relative	11 (12.0)	7 (14.6)
Unrelated donor	56 (60.9)	29 (60.4)
Stem cell source[e]		
Peripheral blood stem cell	71 (77.2)	30 (62.5)
Bone marrow	16 (17.4)	13 (27.1)
Cord blood	5 (5.4)	5 (10.4)
Presence of acute GvHD confirmed for HCT recipients[f]	23 (25.0)	8 (17.0)
Presence of chronic GvHD confirmed for HCT recipients[f]	6 (6.5)	5 (10.6)
CMV DNA levels by central laboratory at baseline, IU/mL		
Median (IQR)[g]	3377.0 (1036.0–12 544.0)	2869.0 (927.0–11 636.0)
CMV DNA levels category as reported by central laboratory at baseline, n (%)		
Low (<9100 IU/mL)	153 (65.1)	85 (72.6)
Intermediate (≥9100 and <91 000 IU/mL)	68 (28.9)	25 (21.4)
High (≥91 000 IU/mL)	14 (6.0)	7 (6.0)
Symptomatic CMV infection by Endpoint Adjudication Committee,[h] n (%)	21 (8.9)	8 (6.8)
CMV syndrome in SOT recipients	10 (47.6)	7 (87.5)
CMV disease[i]	12 (57.1)	1 (12.5)
CMV serostatus for SOT recipients, n (%)	n = 142	n = 69
Donor +/recipient +	11 (7.7)	8 (11.6)
Donor –/recipient +	3 (2.1)	1 (1.4)
Donor +/recipient –	120 (84.5)	56 (81.2)
Donor –/recipient –	7 (4.9)	3 (4.3)
Missing	1 (0.7)	1 (1.4)
CMV serostatus for HCT recipients, n (%)	n = 93	n = 48
Donor +/recipient +	42 (45.2)	17 (35.4)
Donor –/recipient +	39 (41.9)	26 (54.2)
Donor +/recipient –	6 (6.5)	3 (6.3)
Donor –/recipient –	5 (5.4)	1 (2.1)
Missing	1 (1.1)	1 (2.1)
Patients with or without CMV mutations known to confer resistance to ganciclovir, foscarnet, and/or cidofovir,[j] n (%)		
Refractory CMV infection with resistance	121 (51.5)	69 (59.0)
Refractory CMV infection without resistance	96 (40.9)	34 (29.1)
Missing resistance results	18 (7.7)	14 (12.0)

Table 1. Continued

Characteristics	Maribavir (n = 235)	IAT (n = 117)
Most recent anti-CMV agent prior to randomization,[k] n (%)		
Ganciclovir/valganciclovir	204 (86.8)	98 (83.8)
Foscarnet	27 (11.5)	18 (15.4)
Cidofovir	4 (1.7)	1 (0.9)

Maribavir, n = 235, and IAT, n = 117, unless otherwise specified. All CMV DNA levels reported by central laboratory were based on plasma concentration.

Abbreviations: CMV, cytomegalovirus; GvHD, graft-versus-host disease; HCT, hematopoietic-cell transplant; HLA, human leukocyte antigen; IAT, investigator-assigned therapy; IQR, interquartile range; LLOQ, lower limit of quantification; SOT, solid-organ transplant.

[a]Based on most recent transplant type. Those classed as "multiple" had multiple organs transplanted at once.

[b]The denominator is the number of patients who received SOT within each treatment arm.

[c]There was 1 (1.1%) autologous HCT in the maribavir group.

[d]The denominator is the number of patients who received HCT within each treatment arm.

[e]The denominator is the number of patients who received allogenic HCT within each treatment arm.

[f]Based on the safety population.

[g]Half of the LLOQ value (ie, 137/2 = 68.5) was imputed for those who had <LLOQ.

[h]Patients were not stratified by symptomatic infection at randomization. One patient had both CMV disease and syndrome at baseline.

[i]Most patients had CMV gastrointestinal disease: 10/12 for the maribavir arm and 1/1 for the IAT arm.

[j]Per central laboratory results.

[k]Defined as the most recent anti-CMV agent, used to confirm refractory eligibility criteria.

rarely led to treatment discontinuation (0.9% of patients in the maribavir group). Neutropenia was the most frequently reported TEAE in the IAT group (maribavir: 9.4%; IAT: 22.4%), with highest frequency in patients treated with valganciclovir/ganciclovir (33.9%). Rates of nausea (21.4% vs 21.6%), vomiting (14.1% vs 16.4%), and diarrhea (18.8% vs 20.7%) were similar between treatment groups. In the maribavir group, leukopenia occurred less frequently versus valganciclovir/ganciclovir (3.0% vs 12.5%). Hypokalemia and acute kidney injury (AKI) occurred less frequently in the maribavir group versus foscarnet (3.4% vs 19.1% and 8.5% vs 21.3%, respectively). For treatment-related TEAEs, neutropenia was less frequent with maribavir versus valganciclovir/ganciclovir (1.7% vs 25.0%), and AKI was less frequent with maribavir versus foscarnet (1.7% vs 19.1%) (Supplementary Table 6). There were no cases of treatment-related neutropenia or AKI leading to discontinuation in the maribavir group; 19.6% of patients discontinued valganciclovir/ganciclovir due to treatment-related neutropenia and 12.8% discontinued foscarnet due to treatment-related AKI.

There was 1 treatment-related TESAE of sudden death on study day 7 in the maribavir group, possibly due to cardiac arrhythmia resulting from drug interactions according to the investigator. The patient received concomitant medications known to interact and prolong QT intervals (domperidone and posaconazole); the event was assessed by the sponsor as being unrelated to maribavir. One patient in the IAT group had fatal TESAEs on study day 73 (febrile neutropenia, pneumonia, and tuberculosis) related to valganciclovir. Further details are described in the Supplementary Results.

Increased blood immunosuppressant drug levels were reported as TEAEs in 21 (9.0%) patients in the maribavir group (tacrolimus: n = 19; sirolimus: n = 2) and in 1 (0.9%) patient in the IAT (valganciclovir/ganciclovir) group.

DISCUSSION

This phase 3 trial in transplant recipients with R/R CMV infection demonstrated that maribavir was superior to IAT (ganciclovir, valganciclovir, foscarnet, or cidofovir) for CMV viremia clearance at week 8. Patients in the maribavir group had a lower treatment discontinuation rate than those with IAT and also had reduced frequency of neutropenia versus valganciclovir/ganciclovir and AKI versus foscarnet (treatment-limiting toxicities frequently associated with available therapies). The inclusion of a rescue arm within the study design (Figure 1) addressed the antecedent possibility of poor outcomes with IAT.

The benefit with respect to viremia clearance at week 8 of maribavir over IAT was consistent across key subpopulations including HCT and SOT recipients, and patients with resistant CMV infection. This benefit was also maintained in analyses limited to patients completing 8 weeks of study-assigned treatment, included patients in the IAT group who switched to alternative (nonstudy) anti-CMV treatment before week 8 as responders (if meeting criteria of viremia clearance at week 8) or controlled for early treatment discontinuations in the IAT group. Cytomegalovirus viremia clearance appeared earlier with maribavir versus IAT. Notably, CMV viremia persistence in patients with refractory or resistant CMV may be the harbinger of clinical deterioration [26]. The CMV Consensus Forum recently concluded that treatment of viremia prevented disease, viral load kinetics predicted progression to disease, and viral load is an appropriate surrogate endpoint in CMV clinical trials [26]. Thus, the results reported here show that maribavir enables CMV viremia clearance (including drug-resistant strains) with an improved safety profile, illustrating the potential of maribavir to change CMV infection management.

Significantly more patients in the maribavir versus IAT group achieved viremia clearance and symptom control at week 8,
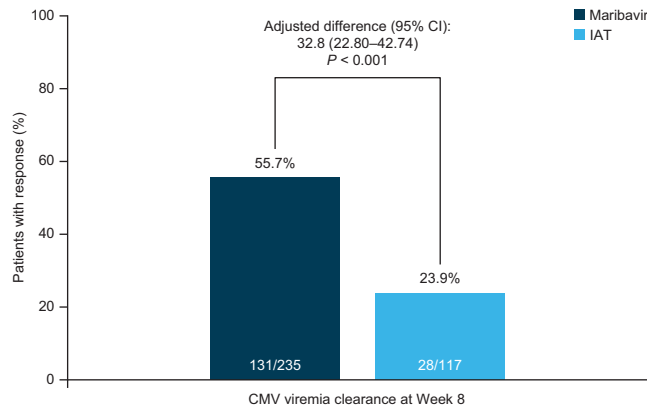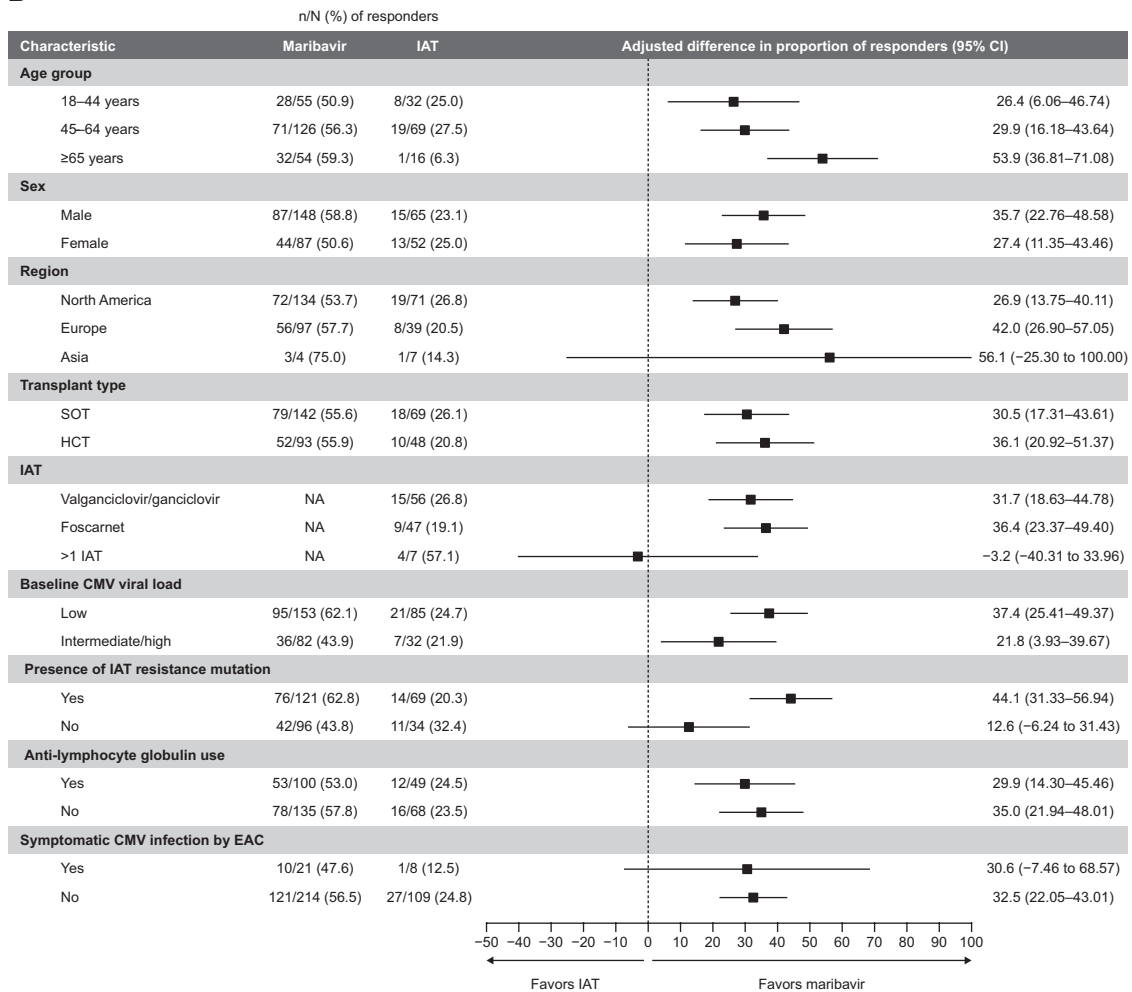
Figure 3. *A*, CMV viremia clearance at week 8 overall (primary endpoint). *B*, CMV viremia clearance at week 8 in subgroups (randomized population). Between-group differences adjusted for applicable stratification factor(s) of baseline CMV DNA level (low or intermediate/high) and SOT/HCT. Six patients received cidofovir as IAT (data not shown); 1 patient did not receive a dose of IAT. Symptomatic CMV infection at baseline was determined by an independent and blinded EAC. Abbreviations: CI, confidence interval; CMV, cytomegalovirus; EAC, Endpoint Adjudication Committee; HCT, hematopoietic-cell transplant; IAT, investigator-assigned therapy; NA, not applicable as adjusted between-group differences used the full maribavir group; SOT, solid-organ transplant.
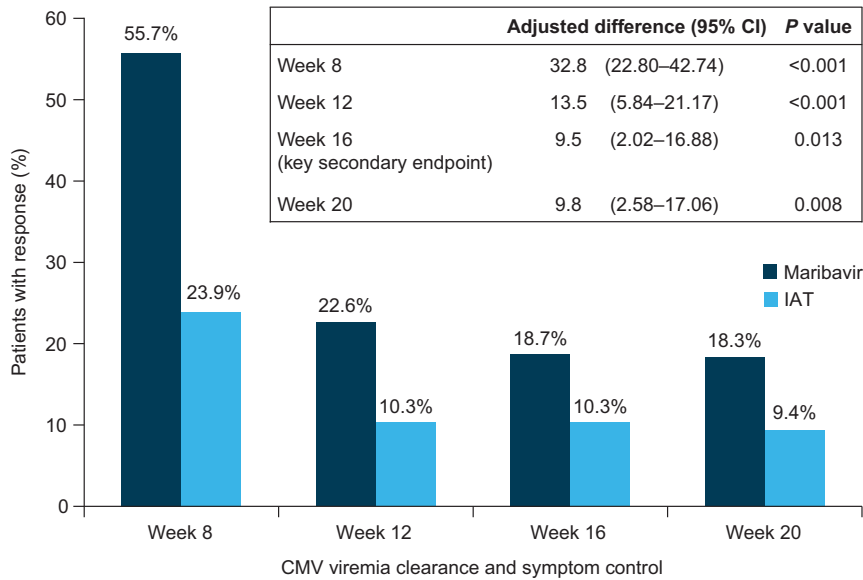
Figure 4. Secondary endpoints: confirmed viremia clearance and symptom control at week 8 and maintained through week 12, week 16 (key secondary endpoint), and week 20 (randomized population). Symptom control was defined as resolution/improvement of CMV disease/syndrome for patients symptomatic at baseline or absence of the development of CMV disease/syndrome for patients asymptomatic at baseline. Abbreviations: CI, confidence interval; CMV, cytomegalovirus; IAT, investigator-assigned therapy.

Table 2. Treatment-Emergent Adverse Events Occurring in ≥10% of Patients in Either Treatment Group or for Individual Investigator-Assigned Therapy (Safety Population)

| System Organ Class Preferred Term | Maribavir (n = 234) | IAT (n = 116) | IAT Type[a] | | |
			Ganciclovir/Valganciclovir (n = 56)	Foscarnet (n = 47)	Cidofovir (n = 6)
Any TEAE	228 (97.4)	106 (91.4)	51 (91.1)	43 (91.5)	5 (83.3)
Blood and lymphatic system disorders					
Anemia	29 (12.4)	14 (12.1)	4 (7.1)	9 (19.1)	0
Leukopenia	7 (3.0)	8 (6.9)	7 (12.5)	1 (2.1)	0
Neutropenia	22 (9.4)	26 (22.4)	19 (33.9)	7 (14.9)	0
Gastrointestinal disorders					
Diarrhea	44 (18.8)	24 (20.7)	13 (23.2)	9 (19.1)	1 (16.7)
Nausea	50 (21.4)	25 (21.6)	8 (14.3)	14 (29.8)	1 (16.7)
Vomiting	33 (14.1)	19 (16.4)	7 (12.5)	8 (17.0)	2 (33.3)
General disorders and administration site conditions					
Fatigue	28 (12.0)	10 (8.6)	7 (12.5)	3 (6.4)	0
Edema peripheral	17 (7.3)	9 (7.8)	3 (5.4)	5 (10.6)	0
Pyrexia	24 (10.3)	17 (14.7)	6 (10.7)	9 (19.1)	2 (33.3)
Infections and infestations					
CMV viremia[b]	24 (10.3)	6 (5.2)	4 (7.1)	1 (2.1)	0
Metabolism and nutrition disorders					
Hypokalemia	8 (3.4)	11 (9.5)	1 (1.8)	9 (19.1)	1 (16.7)
Hypomagnesemia	9 (3.8)	10 (8.6)	2 (3.6)	7 (14.9)	1 (16.7)
Hypophosphatemia	4 (1.7)	5 (4.3)	0	5 (10.6)	0
Nervous system disorders					
Dysgeusia	87 (37.2)	4 (3.4)	2 (3.6)	0	1 (16.7)
Headache	19 (8.1)	15 (12.9)	6 (10.7)	8 (17.0)	0
Paresthesia	4 (1.7)	5 (4.3)	0	5 (10.6)	0
Renal and urinary disorders					
Acute kidney injury	20 (8.5)	11 (9.5)	1 (1.8)	10 (21.3)	0
Vascular disorders					
Hypertension	9 (3.8)	8 (6.9)	1 (1.8)	6 (12.8)	0

Data are presented as n (%). The cidofovir group was not considered in the application of the 10% cutoff due to low patient numbers (n = 6). The on-treatment observation period started at the time of study-assigned treatment initiation through 7 days after the last dose of study-assigned treatment or through 21 days if cidofovir was used, or until the maribavir rescue treatment initiation or until the nonstudy CMV treatment initiation, whichever was earlier. Adverse events were coded using the *Medical Dictionary for Regulatory Activities*, version 23.0.

Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned therapy; TEAE, treatment-emergent adverse event.

[a]Overall, 7 patients received a combination of valganciclovir/ganciclovir and foscarnet (not included in the table).

[b]Events such as worsening of CMV viremia were coded to the preferred term of CMV viremia.

with maintenance to week 16, although the percentage of patients achieving this endpoint was low in both groups. As CMV is a latent virus, in the setting of continued immunosuppression and simultaneous cessation of effective antiviral therapy CMV viremia recurrence off treatment was expected. Among patients meeting the primary endpoint, CMV recurrence necessitating additional anti-CMV treatment in the follow-up period occurred less frequently with maribavir than IAT. The results raise important questions about the current treatment paradigm for these patients, as available agents have limitations for prolonged use. The availability of an orally bioavailable therapy without the tolerability issues associated with current therapies may confer patient management benefits.

Despite shorter drug exposure with IAT than maribavir in this study, as treatment discontinuations were more than 2-fold higher with IAT than maribavir, the incidence of TESAEs was similar between groups and treatment-related TESAEs occurred less frequently with maribavir than IAT. Dysgeusia, while common with maribavir, only led to discontinuation in 0.9% of patients in the maribavir group. Importantly, consistent with previous studies [22, 23], maribavir-treated patients had substantially lower rates of neutropenia and renal impairment compared with valganciclovir/ganciclovir and foscarnet, respectively. Safety data from this phase 3 study were consistent with those from a phase 2 study of maribavir in R/R CMV infections in HCT/SOT recipients, wherein 400–1200-mg BID doses of maribavir were administered for up to 24 weeks [22]. In the current study, the TEAE of immunosuppressant drug concentration level increase was more common in patients receiving maribavir than IAT. Increased immunosuppressant levels have been previously observed in patients treated with maribavir (particularly at the highest [1200 mg BID] dose) [22, 23], and maribavir is known to inhibit P-gp, a transporter involved in distribution and disposition of standard immunosuppression medications [27]. During the trial, immunosuppressant drug concentration levels were frequently monitored throughout maribavir treatment, particularly following initiation and discontinuation of maribavir, and immunosuppressants were dose adjusted as needed.

All-cause mortality was low and comparable between maribavir and IAT groups (~11%), and was lower than previously reported in some studies of patients with resistant or refractory CMV infection (31–50%) [5, 13]. These differences may be due to the study design (Figure 1) and the exclusion of patients from the trial at high risk of death due to underlying disease; these factors may also account for the similarities in all-cause mortality between treatment groups in this study.

With regard to the patients who died due to CMV encephalitis, it is important to note that limited preclinical data suggest that maribavir does not cross the blood–brain barrier [28]. Patients with CMV encephalitis were excluded from the study, and patients who developed new-onset encephalitis while on treatment with maribavir were required to discontinue maribavir per protocol.

Management of resistance and cross-resistance to anti-CMV therapies is challenging. Currently approved therapies inhibit CMV DNA polymerase (UL54) [29]. Valganciclovir/ganciclovir requires activation by viral UL97 protein kinase [29]. Therefore, specific mutations in the CMV genes coding for UL54 DNA polymerase or UL97 protein kinase can confer resistance to approved therapies [29]. Maribavir has a multimodal mechanism of action [16–18], does not require intracellular processing by UL97 protein kinase [30], and targets a different location on UL97 from valganciclovir/ganciclovir. Due to its unique mechanism of action, maribavir remains active against CMV strains resistant to ganciclovir, foscarnet, or cidofovir due to UL54 or UL97 viral kinase mutations [20, 21]. Therefore, maribavir may be well positioned to satisfy the high unmet need associated with resistant CMV infections. As maribavir directly inhibits UL97 protein kinase, maribavir cannot be co-administered with valganciclovir/ganciclovir.

Maribavir was previously investigated for CMV prophylaxis, with prior phase 3 studies showing that the treatment (administered at 100 mg BID) failed to prevent CMV disease in transplant recipients [31–33]. However, findings from the current phase 3 and phase 2 studies [22, 23] using a higher maribavir dose (400 mg BID) all show maribavir efficacy in clearing CMV viremia among transplant recipients with CMV infection.

Currently, there is no consensus on a CMV viral load cutoff for initiation of therapy [12, 34, 35]; while the CMV DNA cutoff for study inclusion may have excluded some patients, this threshold was selected following discussions with regulatory authorities and in careful consideration towards including patients with clinically significant CMV viremia.

The current study has limitations, including an open-label design, which may have introduced bias. Blinding was not feasible due to the need for individualized IAT drug selection/dosing adjustments and the different routes of treatment administration for IAT compared with maribavir. While this study was designed to include pediatric patients aged 12 years and older, no pediatric patients were enrolled. The benefit of maribavir over IAT was consistent across key subpopulations, including a numerically greater response in patients with refractory CMV without genotyped resistance. However, this study was not powered to detect differences between treatments in this patient subgroup. Further, as patients were not stratified by refractory or resistant CMV at randomization, more patients with refractory-only CMV were included in the maribavir group. Nevertheless, a numerical trend for maribavir versus IAT was observed for this patient subgroup, in alignment with overall study results. A higher study discontinuation rate before week 8 in the IAT group was also observed in the study. These discontinuations were primarily due to adverse events and toxicities known to be associated with available anti-CMV agents. Sensitivity analyses

([Supplementary Table 2](#)) were performed to address this potential bias. Finally, the study-specified treatment duration may have necessitated patients with residual CMV at the end of the 8-week treatment phase to receive an alternative treatment during the follow-up phase and who were therefore considered nonresponders to the key secondary endpoint.

In conclusion, maribavir was superior to IAT with respect to CMV clearance in transplant recipients with R/R CMV infection, and sensitivity analyses demonstrated that a benefit of maribavir over IAT with respect to CMV clearance at week 8 was observed regardless of early discontinuations or the need for alternative treatment. Maribavir demonstrated an improved safety profile versus valganciclovir/ganciclovir with respect to neutropenia and versus foscarnet with respect to AKI, which are treatment-limiting toxicities frequently associated with these conventional therapies. Maribavir represents a promising treatment for R/R CMV infections.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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