Supplement

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

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Supplement 1
Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results from a Phase 3 Randomized Clinical Trial 1
Endpoint Adjudication and Data Monitoring Committees and Investigator List 2
Endpoint Adjudication Committee 2
Data Monitoring Committee 2
Investigators 2
Supplementary Methods 5
Role of the Independent Data Monitoring Committee and Endpoint Adjudication Committee 5
Inclusion and Exclusion Criteria 5
Inclusion Criteria 5
Exclusion Criteria 6
Study Treatment 8
Criteria for Entry into the Rescue Arm 8
Secondary and Exploratory Endpoints 9
Study Assessment Schedule 10
Assessments 10
Statistical Analysis 11
Additional Information 11
Supplementary Results 12
Secondary Endpoints 12
Safety 12
Supplementary Tables 14
Supplementary Figures 25
Supplemental References 26

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Supplementary Methods

Role of the Independent Data Monitoring Committee and Endpoint Adjudication Committee

An independent Data Monitoring Committee was established to act in an expert advisory capacity for periodic assessment of the data to monitor patient safety and to ensure the validity and scientific merit of the trial. An independent Endpoint Adjudication Committee was established to confirm the investigator-assessed diagnosis of cytomegalovirus (CMV) tissue-invasive disease and CMV syndrome for symptomatic patients at baseline and to confirm the change over time, or diagnose new tissue-invasive CMV disease and CMV syndrome.

Inclusion and Exclusion Criteria

Inclusion Criteria

- Provided written informed consent before any study-specific procedures were performed.
- Recipient of hematopoietic-cell or solid-organ transplant.
- Documented CMV infection in whole blood or plasma, with a screening value of ≥2730 IU/mL in whole blood or ≥910 IU/mL in plasma in two consecutive assessments, separated by at least 1 day, as determined by local or central specialty laboratory quantitative polymerase chain reaction (qPCR) or comparable quantitative CMV DNA results. Both samples should be taken within 14 days prior to randomization, with second sample obtained within 5 days prior to randomization. The same laboratory and same sample type (whole blood or plasma) must be used for these assessments.
- Current CMV infection that is refractory to the most recently administered of the four anti-CMV treatment agents. Refractory is defined as documented failure to achieve >1 $\log_{10}$ decrease in CMV DNA level in whole blood or plasma after a 14-day or longer treatment period with intravenous (IV) ganciclovir/oral valganciclovir, IV foscarnet, or IV cidofovir.
    - Patients with documentation of one or more CMV genetic mutations associated with resistance to ganciclovir/valganciclovir, foscarnet, and/or cidofovir must also meet the definition of refractory CMV infection.

- ≥12 years of age at the time of consent.
- Weight ≥35 kg.
- The following results as part of screening laboratory assessments (results from either the central laboratory or a local laboratory can be used for qualification):
  - Absolute neutrophil count ≥1000/mm^3 (1.0 x 10^9/L).
  - Platelet count ≥25,000/mm^3 (25 x 10^9/L).
  - Hemoglobin ≥8 g/dL.
  - Estimated glomerular filtration rate >30 mL/min/1.73 m^2 as assessed by Modification of Diet in Renal Disease formula or Schwartz formula for patients <18 years of age.
- Negative serum β-human chorionic gonadotropin. Female patients had a negative pregnancy test (results from either central or local laboratory as part of screening laboratory assessments).
- Agreed to use an acceptable method of birth control (not solely hormonal contraceptives), as determined by the investigator, during the treatment period and for 3 months thereafter (6 months for foscarnet).
- Able to swallow tablets, or receive tablets crushed and/or dispersed in water via a nasogastric or orogastric tube.
- Life expectancy of ≥8 weeks.
- The patient must be willing and have an understanding and ability to comply fully with study procedures and restrictions defined in the protocol.
- The patient must be willing to provide necessary samples (eg, biopsy) for the diagnosis of end-organ disease at baseline as determined by the investigator.

Exclusion Criteria

- Current CMV infection that is considered refractory or resistant due to inadequate adherence to prior anti-CMV treatment.
- Requiring ganciclovir, valganciclovir, foscarnet, or cidofovir administration for conditions other than CMV when study treatment is initiated or would need a co-administration with

maribavir for CMV infection.

- Receiving leflunomide, letermovir, or artesunate when study treatment is initiated.
  - Patients receiving leflunomide must discontinue the use at least 14 days prior to randomization at Visit 2/Day 0 and the first dose of study treatment. Patients receiving letermovir must discontinue use at least 3 days prior to the first dose of study treatment. Patients receiving artesunate must discontinue the use prior to the first dose of study treatment.
  - Letermovir was added to the exclusion criteria in a protocol amendment on March 26, 2018, following the Food and Drug Administration approval of letermovir for use in prophylaxis of CMV infection in allogeneic hematopoietic-cell transplant recipients [1].
- Severe vomiting, diarrhea, or other severe gastrointestinal illness within 24 hours prior to the first dose of study treatment that would preclude administration of oral/enteral medication.
- Known hypersensitivity to the active substance or to an excipient for a study treatment.
- Tissue-invasive CMV disease with central nervous system involvement, including the retina.
- Serum aspartate aminotransferase (AST) >5 x upper limit of normal (ULN) at screening, or serum alanine aminotransferase (ALT) >5 x ULN at screening, or total bilirubin ≥3.0 x ULN at screening (except for documented Gilbert's syndrome), by local or central laboratory assessment. Patients with biopsy-confirmed CMV hepatitis will not be excluded from study participation despite AST or ALT >5 x ULN at screening.
- Known positive results for human immunodeficiency virus.
- Require mechanical ventilation or vasopressors for hemodynamic support at the time of enrollment.
- Pregnant or breastfeeding.
- Previously received maribavir.
- Received any investigational agent with known anti-CMV activity within 30 days before

initiation of study treatment or investigational CMV vaccine at any time.

- Received any unapproved agent or device within 30 days before initiation of study treatment.
- Active malignancy with the exception of non-melanoma skin cancer.
- Undergoing treatment for acute or chronic hepatitis C.
- Any clinically significant medical or surgical condition that in the investigator's opinion could interfere with the interpretation of study results, contraindicate the administration of the assigned study treatment, or compromise the safety or well-being of the patient.

Study Treatment

Combination therapy with cidofovir and foscarnet was not permitted. For patients in the investigator-assigned therapy (IAT) group, changes to dose or dosing schedule of anti-CMV therapies were permitted, as well as discontinuation of one agent, if two were originally selected. Addition of another anti-CMV therapy was not permitted and only switches between ganciclovir and valganciclovir were allowed. No change to dose or dosing schedule was allowed for patients in the maribavir group. Interruption of therapy for a maximum of 7 consecutive days, or up to two study treatment interruptions for a total of up to 7 days was permitted at the investigator's discretion. Anti-CMV therapy was continued even if patients achieved viremia clearance before Week 8. Reduction or modifying of immunosuppressant drug use was permitted.

Criteria for Entry into the Rescue Arm

Patients treated in the IAT group for ≥3 weeks who met one of the following criteria were eligible for entry into the maribavir rescue arm between study Weeks 3 and 7:

- Increased whole blood or plasma CMV viremia levels of ≥1 $\log_{10}$ from baseline, as measured by the local or central specialty laboratory qPCR assay (results from the same laboratory will be compared). Local specialty laboratory results must be documented.
- Patient with tissue-invasive CMV disease must meet both criteria after being on

treatment for at least 3 weeks:

- Whole blood or plasma CMV DNA has decreased <1 $\log_{10}$ from baseline as measured by the local or specialty laboratory qPCR assay (results from the same laboratory will be compared). Local specialty laboratory results must be documented.
- Symptomatic patients presenting with tissue-invasive CMV disease that did not improve, or worsened, as assessed by the investigator, or patient who was asymptomatic at baseline developed tissue-invasive CMV disease.

- No CMV viremia clearance was achieved (results from the same laboratory will be assessed) necessitating continued anti-CMV treatment *and* the patient has demonstrated intolerance to the investigator-assigned anti-CMV treatment as evidenced by one of the following conditions:
  - Acute increase in serum creatinine, at least 50% increase from the baseline value, attributed to treatment (cidofovir, foscarnet) toxicity.
  - Development of hemorrhagic cystitis when on treatment with cidofovir or foscarnet.
  - Development of neutropenia (absolute neutrophil count <500/mm^3 [0.5 x 10^9/L]) when on treatment with ganciclovir or valganciclovir.

Secondary and Exploratory Endpoints

Secondary efficacy endpoints included:

- Achievement of CMV viremia clearance at the end of Week 8 after completion of 8 weeks of study treatment.
- Achievement of CMV viremia clearance and symptom control at the end of Week 8, and maintenance through Week 12 to Week 20.
- Incidence of recurrence of CMV viremia (plasma CMV DNA concentration greater than or equal to the lower limit of quantification [LLOQ] when assessed by the central laboratory COBAS® AmpliPrep/COBAS® TaqMan® CMV Test [Roche Diagnostics] in two consecutive plasma samples at least 5 days apart, after achieving confirmed viremia

clearance) during the first 8 weeks of the study.

- All-cause mortality.
- Efficacy of maribavir as a rescue treatment.

An exploratory efficacy endpoint was time to first viremia clearance within study Week 8 and recurrence requiring alternate anti-CMV therapy.

Study Assessment Schedule

Patients were evaluated weekly until Week 12, then every 2 weeks through to Week 20. At every visit, blood samples for CMV DNA tests were taken and patients were assessed for symptomatic CMV infection. Treatment-emergent adverse events (TEAEs) were monitored at every visit. Clinical laboratory testing was conducted every 2 weeks until Week 20. 12-lead electrocardiograms (ECGs) were conducted at treatment initiation and at the end of the 8-week treatment period and 12-week follow-up periods. Immunosuppressant drug concentrations were monitored at study treatment initiation, after half a week, after 1 week, and at the end of Weeks 8 and 9.

Patients who prematurely discontinued study treatment completed the planned end of treatment procedures at Week 8; these patients continued a modified schedule of assessments through the remaining weekly visits scheduled for the study treatment phase and the regular schedule of assessments through the 12-week follow-up phase. The end of treatment (Week 8) sample for immunosuppressant drug concentration level was collected at the next visit scheduled 1 week after the study treatment discontinuation.

Assessments

Patients who achieved confirmed CMV viremia clearance and symptom control at the end of Week 8, but these effects were not maintained through Week 16 (including missing virologic data), or who received alternative anti-CMV therapy prior to Week 16 were considered non-responders for the key secondary endpoint.

All-cause mortality on study was assessed for the entire study period regardless of the

use of rescue treatment or alternative anti-CMV treatment.

The time to first CMV viremia clearance by Week 8 was calculated as stop date minus start date plus 1 day, where:

- Start date was the date of randomization
- Stop date was the event (the date of first of two consecutive samples with plasma CMV DNA less than the LLOQ that met the criteria of confirmed CMV viremia clearance) or a censored time (date of last CMV DNA assessment within Week 8 before the initiation of rescue or alternative anti-CMV treatment).

The time to CMV viremia clearance was summarized using Kaplan–Meier method. Patients who did not achieve CMV viremia clearance by Week 8 were censored on the date of last CMV DNA assessment within study Week 8 before initiation of alternative anti-CMV treatment.

Adverse events (AEs) were recorded from the time of informed consent through 30 days after the last dose of study drug. Serious AEs were recorded until the end of study or resolution (whichever was later). Patients were analyzed according to the treatment actually received. An AE (classified by preferred term) with a start date on or after the first dose of study treatment, or a start date before the first dose of study treatment but with increases in severity after the first dose of trial treatment, was considered a treatment-emergent adverse event (TEAE). Analysis of TEAEs was based on TEAEs occurred during the on-treatment observation period. The on-treatment observation period started at the time of study-assigned treatment initiation and continued through 7 days after the last dose of study-assigned treatment or through 21 days if cidofovir was used, until the maribavir rescue treatment initiation, or until the non-study CMV treatment initiation, whichever was earlier.

Statistical Analysis

Additional Information

Based on the results of a phase 2 trial of maribavir in patients with resistant/refractory CMV

infection [2], in the current trial it was estimated that ≥60% of patients in the maribavir group would achieve undetectable plasma CMV DNA at Week 7 and Week 8, and that 40% of patients would achieve undetectable plasma CMV DNA in the IAT group. To demonstrate statistical superiority of maribavir in the reduction of CMV DNA, it was calculated (based on a two-group continuity-corrected Chi-square test of equal proportions) that 315 patients were required (2:1 maribavir:IAT) to provide 90% power in hypothesis testing at an alpha level of 0.05 (two-sided test) to detect a 20% treatment difference. Assuming a dropout rate of 10%, 351 patients (234, maribavir; 117, IAT) were to be enrolled and randomized.

Sensitivity analyses of the primary endpoint were conducted in the Randomized Population using similar methods to those described for the primary endpoint, but without adjustment for multiple comparisons. Efficacy in the rescue arm was conducted in the Rescue Population (all patients who entered the rescue arm and received any dose of maribavir as rescue therapy). Time-to-event endpoints were summarized using Kaplan–Meier estimation.

Supplementary Results

A breakdown of reasons for not achieving the primary endpoint is shown in Figure S2.

Secondary Endpoints

Additional analysis showed that 70.5% (129/183) and 59.5% (22/37) of the subset of patients who had completed 8 weeks of study-assigned maribavir or IAT treatment, respectively, achieved viremia clearance at end of Week 8 (adjusted difference [95% CI]: 10.2 [–7.01 to 27.41]; Supplement Table 3). Recurrence during the first 8 weeks of the study (after the achievement of viremia clearance) occurred in 33/184 (17.9%) patients in the maribavir group and in 8/65 (12.3%) patients in the IAT group.

Safety

In the maribavir group, there was one treatment-related, treatment-emergent serious adverse

event (TESAE) of sudden death (Table S5), potentially due to a cardiac arrhythmia as a result of drug interactions.

Supplementary Tables

Supplementary Table 1. Additional Baseline Characteristics (Randomized Population)

Characteristic	Maribavir (n = 235)	IAT (n = 117)
Ethnicity — no. (%)		
Hispanic or Latino	14 (6.0)	7 (6.0)
Not Hispanic or Latino	198 (84.3)	95 (81.2)
Not reported	19 (8.1)	12 (10.3)
Unknown	4 (1.7)	3 (2.6)
Weight — kg	n = 232	n = 115
Median	74.1	70.0
Range	(36–124)	(39–131)
Region — no. (%)		
North America	134 (57.0)	71 (60.7)
Europe	97 (41.3)	39 (33.3)
Asia	4 (1.7)	7 (6.0)
Underlying disease (HCT recipients) — no. (%)[a]	n = 93	n = 48
Leukemia (acute myeloid)	36 (38.7)	18 (37.5)
Leukemia (chronic myeloid)	2 (2.2)	0
Leukemia (acute lymphocytic)	12 (12.9)	7 (14.6)
Lymphoma (non-Hodgkin’s)	9 (9.7)	4 (8.3)
Myelodysplastic syndrome	11 (11.8)	8 (16.7)
Other myeloid malignancy	2 (2.2)	1 (2.1)
Other	21 (22.6)	10 (20.8)
Type of preparative conditioning regimen[b] — no. (%)[a]	n = 92	n = 48
Myeloablative	47 (51.1)	16 (33.3)
Non-myeloablative	17 (18.5)	12 (25.0)
Reduced-intensity conditioning regimen	28 (30.4)	17 (35.4)
Not applicable	0	1 (2.1)
Missing	0	2 (4.2)
Net immunosuppression use changed prior to the study treatment initiation — no. (%)		
No	181 (77.0)	80 (68.4)
Yes	54 (23.0)	36 (30.8)
Missing	0	1 (0.9)
Lymphocyte depletion therapy[c] — no. (%)	100 (42.6)	49 (41.9)
Renal impairment[d] — no. (%)		
No impairment	81 (34.5)	39 (33.3)

Characteristic	Maribavir (n = 235)	IAT (n = 117)
Mild	71 (30.2)	42 (35.9)
Moderate	60 (25.5)	22 (18.8)
Severe	8 (3.4)	3 (2.6)
Missing	15 (6.4)	11 (9.4)
Hepatic impairment[e] — no. (%)		
No impairment	218 (92.8)	107 (91.5)
Grade 1	9 (3.8)	3 (2.6)
Grade 2	4 (1.7)	3 (2.6)
Grade 3 or 4	0	0
Missing	4 (1.7)	4 (3.4)
Karnofsky Performance Status Scale score — no. (%)		
>80	102 (43.4)	42 (35.9)
>60 to ≤80	82 (34.9)	55 (47.0)
>40 to ≤60	20 (8.5)	6 (5.1)
≤40	9 (3.8)	5 (4.3)
Missing	22 (9.4)	9 (7.7)
CMV DNA level category at randomization, by local laboratory assessment[f] — no. (%)		
Low (<9100 IU/mL)	108 (46.0)	54 (46.2)
Intermediate (≥9100 and <91,000 IU/mL)	99 (42.1)	49 (41.9)
High (≥91,000 IU/mL)	28 (11.9)	14 (12.0)
Prior use of CMV prophylaxis — no. (%)	100 (42.6)	45 (38.5)
Current CMV infection is the first episode post-transplant — no. (%)	162 (68.9)	78 (66.7)
Prior direct-acting anti-CMV agents at any time[g] — no. (%)	n = 234	n = 116
Valganciclovir	178 (76.1)	96 (82.8)
Ganciclovir	147 (62.8)	82 (70.7)
Foscarnet	49 (20.9)	37 (31.9)
Letermovir	12 (5.1)	5 (4.3)
Cidofovir	7 (3.0)	5 (4.3)

Abbreviations: CMV, cytomegalovirus; HCT, hematopoietic-cell transplant; IAT, investigator-assigned therapy; ULN, upper limit of normal.

[a] Percentage was calculated by specified subgroup.

[b] In patients who received allogeneic HCT.

[c] Included ex vivo and in vivo T-cell depletion modalities (anti-lymphocyte globulin or alemtuzumab).

[d] Calculated using the Cockcroft–Gault equation. Levels of impairment: none: creatinine

clearance >80 mL/minute; mild: creatinine clearance 50–80 mL/minute; moderate creatinine clearance 30–<50 mL/minute; severe: creatinine clearance <30 mL/minute.

[e] Defined based on the baseline total bilirubin (aligned with Common Terminology Criteria for Adverse Events version 4.03 for toxicity grading): none: ≤ULN; grade 1: >ULN to <1.5 x ULN; grade 2: ≥1.5 x ULN to <3 x ULN; grade 3 or 4: ≥3 x ULN.

[f] Local eligibility laboratories used for stratification at baseline.

[g] In the Safety Population. Defined as any medication from the date of most recent transplant through the date of randomization, with the start date prior to the date of the first dose of study treatment.

Supplementary Table 2. Concomitant Immunosuppressant and Systemic Corticosteroid Treatment During the On-Treatment Observation Period (Safety Population)

	Maribavir (n = 234)	IAT (n = 116)
	No. of patients (%)	
Any immunosuppressant	216 (92.3)	109 (94.0)
Tacrolimus	178 (76.1)	79 (68.1)
Mycophenolate	104 (44.4)	46 (39.7)
Cyclosporine	31 (13.2)	23 (19.8)
Everolimus	13 (5.6)	8 (6.9)
Sirolimus	13 (5.6)	8 (6.9)
Azathioprine	9 (3.8)	4 (3.4)
Belatacept	3 (1.3)	1 (0.9)
Any systemic corticosteroids	176 (75.2)	84 (72.4)
Prednisone	123 (52.6)	56 (48.3)
Methylprednisolone	41 (17.5)	15 (12.9)
Prednisolone	26 (11.1)	17 (14.7)
Hydrocortisone	20 (8.5)	9 (7.8)
Fludrocortisone	11 (4.7)	1 (0.9)
Dexamethasone	4 (1.7)	2 (1.7)

Abbreviation: IAT, investigator-assigned therapy.

Supplementary Table 3. Sensitivity Analyses of the Primary Endpoint (Randomized Population)

CMV viremia clearance at end of Week 8 (Response)	Maribavir no. (%)	IAT no. (%)	Adjusted difference in proportion of responders (95% CIs)
Randomized patients	235	117	
Based on alternate definitions of response			
Patients who met criteria of confirmed CMV viremia clearance at the time of premature study discontinuation were included as a responder	137 (58.3)	39 (33.3)	26.1 (15.61–36.67)
Patients with confirmed CMV viremia clearance at any time during the treatment phase were included as a responder	174 (74.0)	61 (52.1)	23.6 (13.18–33.93)
Patients with confirmed CMV viremia clearance at Week 8 regardless of initiating alternative anti-CMV treatment before Week 8 in the IAT group, but not in the maribavir group, were included as a responder	131 (55.7)	41 (35.0)	21.7 (11.02–32.48)
Based on stratification used at randomization			
Patients with response	131 (55.7)	28 (23.9)	31.8 (21.86–41.76)
Patients who received 8 weeks of study-assigned treatment	183	37	
Patients with response	129 (70.5)	22 (59.5)	10.2 (–7.01 to 27.41)
Patients on treatment 72 hours after treatment initiation	233	116	
Patients with response	131 (56.2)	28 (24.1)	33.1 (23.08–43.12)
Patients on treatment 7 days after treatment initiation	232	113	
Patients with response	131 (56.5)	28 (24.8)	32.6 (22.47–42.79)
Patients on treatment 14 days after treatment initiation	224	98	
Patients with response	131 (58.5)	28 (28.6)	30.8 (19.87–41.81)
Patients on treatment 21 days after treatment initiation	217	80	
Patients with response	131 (60.4)	27 (33.8)	27.5 (15.34–39.75)
Patients on treatment 28 days after treatment initiation	214	65	

CMV viremia clearance at end of Week 8 (Response)	Maribavir no. (%)	IAT no. (%)	Adjusted difference in proportion of responders (95% CIs)
Patients with response	131 (61.2)	25 (38.5)	23.4 (9.90–36.94)
Randomized patients with baseline CMV DNA >LLOQ per the central laboratory	225	109	
Patients with response	124 (55.1)	27 (24.8)	31.2 (20.85–41.54)
Randomized patients with baseline CMV DNA ≥910 IU/mLper the central laboratory	182	88	
Patients with response	94 (51.6)	22 (25.0)	27.4 (15.86–38.98)

Plasma CMV DNA assessments after starting alternative anti-CMV treatment or rescue treatment were not evaluable for the assessment of study-assigned treatment effect, unless otherwise specified.

Randomized patients with no efficacy data were treated as nonresponders. Patients with confirmed CMV viremia clearance at the end of Week 8 were considered as responders regardless of whether the study-assigned treatment was discontinued before the end of the stipulated 8 weeks of therapy, unless otherwise specified.

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; DNA, deoxyribonucleic acid; IAT, investigator-assigned therapy; IU, international units; LLOQ, lower limit of quantification.

Supplementary Table 4. Causes of All Deaths

Fatal TEAE	Maribavir (n = 234)	IAT (n = 116)
	No. of patients	
CMV encephalitis	2	2[a]
Multiple organ dysfunction syndrome	3	0
Respiratory failure	2	1
Septic shock	2	0
Respiratory tract infection	2	0
Recurrence of leukemia	1	1
Recurrence of acute myeloid leukemia	1	1
Recurrence of Hodgkin's disease	1[b]	0
Recurrence of diffuse B-cell lymphoma	1	0
Recurrence of acute lymphocytic leukemia	1	0
Deep vein thrombosis	1	0
Venous thrombosis	1	0
Hypoxia	1	0
Drug interaction	1[c]	0
CMV syndrome and dyspnea	1	0
Pulmonary embolism	1	0
General physical health deterioration	1	0
CMV enterocolitis	0	1
Myocardial infarction	1	0
Acute GvHD	1	0
Cardiac arrest	1	0
Acute respiratory distress syndrome	0	2
CMV colitis	1	0
CMV pneumonia	0	1
Febrile neutropenia, pneumonia, and tuberculosis	0	1[c]
Pneumonia due to fungus and respiratory syncytial virus	0	1
Neutropenic sepsis	0	1
Post-transplant lymphoproliferative disorder	0	1

Abbreviations: CMV, cytomegalovirus; GvHD, graft-versus-host disease; IAT investigator-assigned therapy; TEAE, treatment-emergent adverse event.

[a] Includes one patient who had onset of fatal TEAE on Day 3 of maribavir rescue therapy.

[b] Relapse of Hodgkin's disease occurred 3 days prior to initiation of study treatment.

[c] TEAE was considered related to study-assigned treatment..

Supplementary Table 5. Treatment-Emergent Adverse Events During the On-Treatment Observation Period (Safety Population)

TEAE	Maribavir (n = 234)	IAT (n = 116)
	No. of patients (%)	
Any TEAE	228 (97.4)	106 (91.4)
Any treatment-related TEAE	141 (60.3)	57 (49.1)
Any TESAE	90 (38.5)	43 (37.1)
Any treatment-related TESAE	12 (5.1)	17 (14.7)
Any severe TEAE[a]	75 (32.1)	44 (37.9)
Any treatment-related severe TEAE	9 (3.8)	24 (20.7)
Any TEAE that led to treatment discontinuation	31 (13.2)	37 (31.9)
Any treatment-related TEAE that led to treatment discontinuation	11 (4.7)	27 (23.3)
Any TESAE that led to treatment discontinuation	20 (8.5)	17 (14.7)
Any treatment-related TESAE that led to treatment discontinuation	5 (2.1)	9 (7.8)
Any TEAE that led to study discontinuation	17 (7.3)	9 (7.8)
Any treatment-related TEAE that led to study discontinuation	3 (1.3)	2 (1.7)
Any TESAE with outcome of death	16 (6.8)	6 (5.2)
Any treatment-related TESAE with outcome of death[b]	1 (0.4)	1 (0.9)

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 non-study CMV treatment initiation, whichever was earlier.

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

[a] Defined as an adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

[b] In the maribavir group, there was one treatment-related TESAE of sudden death, potentially due to a cardiac arrhythmia as a result of drug interactions (per investigator). The patient had multiple comorbidities and received concomitant medications known to interact and prolong QT intervals (domperidone, with the risk markedly increased by the introduction of voriconazole and then posaconazole); the event was assessed by the sponsor as being unrelated to maribavir treatment based on extensive review of the patient's medical history, prior and concomitant medications, and clinical laboratory and electrocardiogram data at screening and baseline visit. In the IAT group, febrile neutropenia, pneumonia, and

tuberculosis (one patient) were reported as fatal TESAEs related to valganciclovir.

Supplementary Table 6. Treatment-Emergent Adverse Events Occurring in ≥5% of Patients in Either Treatment Group or for Individual IAT, Considered Related to Study-Assigned Treatment by the Investigator[a] (Safety Population)

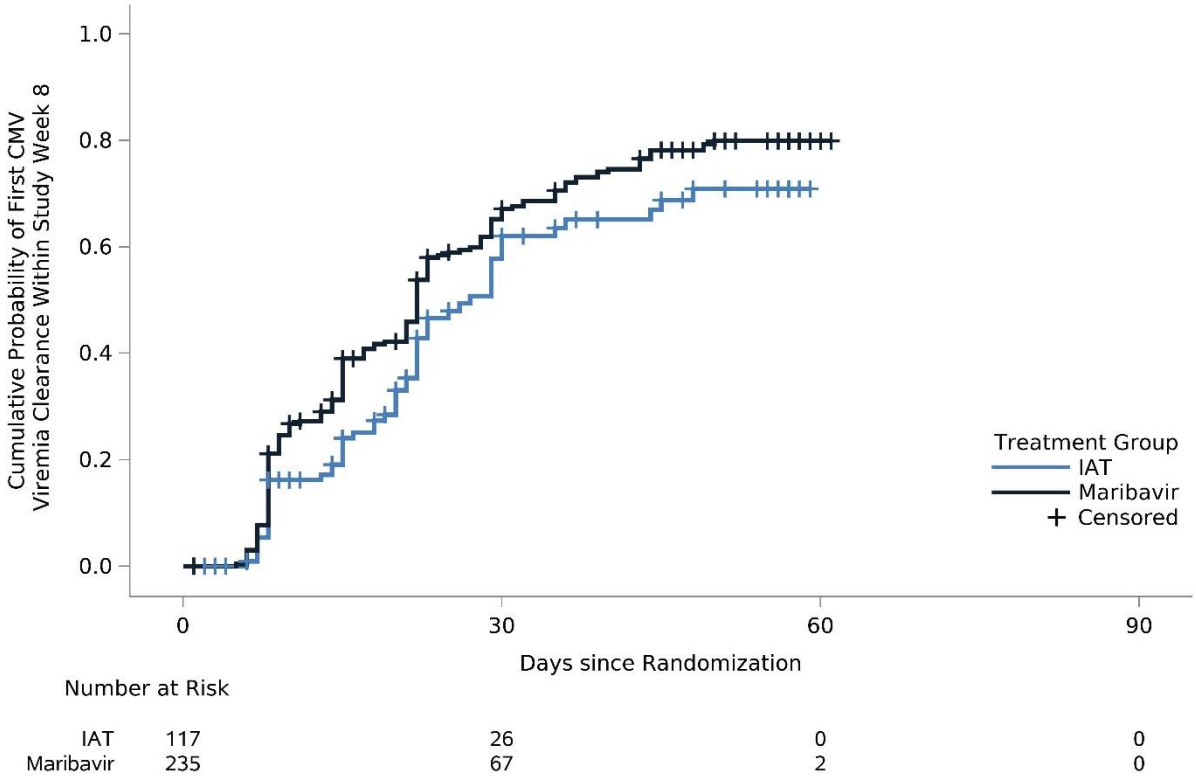
System Organ Class Preferred Term	Maribavir (n = 234)	IAT (n = 116)	IAT Type		
			Ganciclovir/ Valganciclovir (n = 56)	Foscarnet (n = 47)	Cidofovir (n = 6)
	No. of patients (%)				
Any related TEAE	141 (60.3)	57 (49.1)	23 (41.1)	29 (61.7)	2 (33.3)
Blood and lymphatic system disorders					
Anemia	3 (1.3)	9 (7.8)	3 (5.4)	6 (12.8)	0
Febrile neutropenia	0	4 (3.4)	4 (7.1)	0	0
Leukopenia	0	5 (4.3)	4 (7.1)	1 (2.1)	0
Neutropenia	4 (1.7)	16 (13.8)	14 (25.0)	2 (4.3)	0
Thrombocytopenia	0	6 (5.2)	4 (7.1)	2 (4.3)	0
Gastrointestinal disorders					
Diarrhea	9 (3.8)	6 (5.2)	1 (1.8)	4 (8.5)	1 (16.7)
Nausea	20 (8.5)	11 (9.5)	1 (1.8)	8 (17.0)	1 (16.7)
Vomiting	18 (7.7)	5 (4.3)	0	4 (8.5)	1 (16.7)
General disorders and administration site conditions					
Edema peripheral	0	4 (3.4)	0	4 (8.5)	0
Investigations	20 (8.5)	9 (7.8)	2 (3.6)	6 (12.8)	0
Immunosuppressant drug level increased	14 (6.0)	0	0	0	0
Metabolism and nutrition disorders					
Hypocalcemia	0	5 (4.3)	1 (1.8)	4 (8.5)	0
Hypokalemia	1 (0.4)	5 (4.3)	0	4 (8.5)	1 (16.7)
Hypomagnesemia	0	5 (4.3)	1 (1.8)	4 (8.5)	0
Nervous system disorders					
Dysgeusia	84 (35.9)	1 (0.9)	1 (1.8)	0	0
Headache	2 (0.9)	4 (3.4)	0	4 (8.5)	0
Taste disorder	20 (8.5)	1 (0.9)	0	1 (2.1)	0
Renal and urinary disorders					
Acute kidney injury	4 (1.7)	9 (7.8)	0	9 (19.1)	0
Renal impairment	0	3 (2.6)	0	3 (6.4)	0
Proteinuria	1 (0.4)	2 (1.7)	0	1 (2.1)	1 (16.7)
Renal failure	0	2 (1.7)	0	0	1 (16.7)

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

[a] The cidofovir group was not considered in the application of the 5% cutoff due to low patient numbers (n = 6).

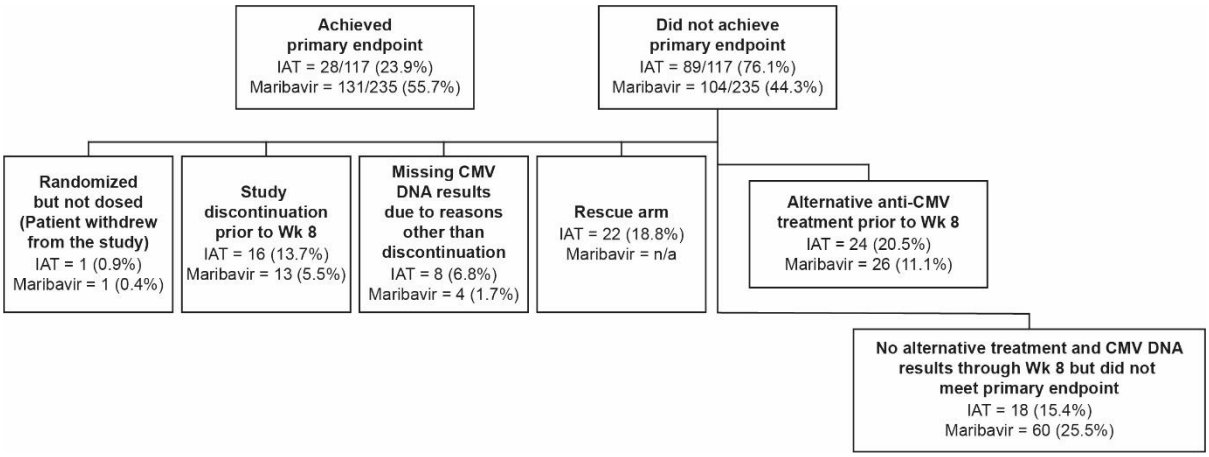
Supplementary Figures

Supplementary Figure 1. Cumulative Probability of First CMV Viremia Clearance Within Study Week 8 by Treatment Group (Randomized Population)



Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned therapy.

Supplementary Figure 2. Breakdown of Reasons for Not Achieving the Primary Endpoint



Percentages are based on number of patients randomized to each treatment group.

A patient was counted only once in one category based on the primary non-responder reason.

Abbreviations: CMV, cytomegalovirus; IAT, investigator-assigned therapy; n/a, not applicable; Wk, week.

Supplemental References

1. Marty FM, Ljungman P, Chemaly RF, et al. Letermovir Prophylaxis for Cytomegalovirus in Hematopoietic-Cell Transplantation. *N Engl J Med.* 2017;377(25):2433–2444.
2. Papanicolaou GA, Silveira FP, Langston AA, et al. Maribavir for Refractory or Resistant Cytomegalovirus Infections in Hematopoietic-cell or Solid-organ Transplant Recipients: A Randomized, Dose-ranging, Double-blind, Phase 2 Study. *Clin Infect Dis.* 2019;68(8):1255–1264.