Administration of maribavir

ICD-10 Coordination and Maintenance Committee meeting

March 8, 2022

Better Health, Brighter Future

Cytomegalovirus (CMV) epidemiology - post-transplant CMV infections are common and serious threat

CMV is highly prevalent in the general population and can cause infection in transplant recipients[1–3]

Annual transplant numbers in the US	Incidence rates	
39,000 SOT performed yearly[4]	**8–75%*** CMV infection in SOT recipients[6]	**High risk** • Serological mismatch • Intense immunosuppression • Lung transplant
23,800 HSCT performed yearly[5]	**5–30%** CMV infection in HSCT recipients[6]	**High risk** • Serological mismatch • GvHD • Cord blood • ATG

*Incidence of CMV infection varies depending on type of SOT. Incidence of CMV infections are: 50–75% in lung transplant, 50% in pancreas transplant, 9–23% in heart transplant, 22–29% in liver transplant, and 8–32% in kidney transplant.
ATG: anti-thymocyte globulin; CMV: cytomegalovirus; GvHD: graft-versus-host disease; HSCT: hematopoietic stem cell transplant; SOT: solid organ transplant.

[1]Bulka CM, et al. Environmental Epidemiology. 2020;4:e100; [2]Cho S-Y, et al. Int J Mol Sci. 2019;20:2666; [3]Kotton CN, et al. Transplantation. 2018;102:900–31; [4]Organ Procurement and Transplantation Network (OPTN). National Data. Accessed April 28, 2021. Available at: https://optn.transplant.hrsa.gov/; [5]Center for International Blood & Marrow Transplant Research (CIBMTR). 2020 summary slides. Accessed April 28, 2021. https://www.cibmtr.org/; [6]Azevedo LS, et al. Clinics (Sao Paulo). 2015;70:515–23.

Overview of maribavir

Maribavir

- **Approval date:** November 23, 2021, pursuant to a New Drug Application (NDA)
- **Trade name:** LIVTENCITY™
- **Generic name:** maribavir
- **Chemical name:** 5,6-Dichloro-*N*-(1-methylethyl)-1-β-L-ribofuranosyl-1*H*-benzimidazol-2-amine
- **Description:** LIVTENCITY™ tablets contain maribavir, a benzimidazole riboside CMV pUL97 protein kinase inhibitor
- **Indication:** LIVTENCITY is a cytomegalovirus (CMV) pUL97 kinase inhibitor indicated for the treatment of adults and pediatric patients (12 years of age and older and weighing at least 35 kg) with post-transplant CMV infection/disease that is refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet.
- **Adverse reactions:** The most common adverse events (all grades, >10%) in subjects treated with LIVTENCITY were taste disturbance, nausea, diarrhea, vomiting, and fatigue.
- **Designations:**
  - Breakthrough Therapy Designation as a treatment for CMV infection and disease in transplant patients resistant or refractory to prior therapy.
  - Priority Review for post-transplant recipients with CMV infection in those resistant/refractory to prior anti-CMV treatment.
  - Orphan Drug Designation for treatment of clinically significant CMV viremia and disease in at-risk patients.

LIVTENCITY™ (maribavir) Prescribing information, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215596lbl.pdf; https://www.takeda.com/newsroom/newsreleases/2021/phase-3-clinical-trial-subgroup-analysis-across-sot-types-supports-efficacy-of-maribavir-over-conventional-therapies-in-post-transplant-recipients-with-cmv-infection/

Overview of maribavir, continued

- **Dosing**
  - The recommended dosage in adults and pediatric patients (12 years of age and older and weighing at least 35 kg) is 400 mg (two 200 mg tablets) taken orally twice daily with or without food
  - If Maribavir is co-administered with carbamazepine, increase the dosage of Maribavir to 800 mg twice daily. If Maribavir is co-administered with phenytoin or phenobarbital, increase the dosage of Maribavir to 1,200 mg twice daily
- **Route of Administration**
  - Oral (by mouth)
  - In addition, a Phase 1 study was conducted to evaluate the relative bioavailability of whole versus crushed tablets of oral Livtencity (Canas et al. 2009). No differences were observed for the pharmacokinetic parameters between whole tablets and crushed tablets in solution
- **Site of Care**
  - Maribavir is expected to be provided in both the inpatient and outpatient settings
- **Medical record documentation**
  - Maribavir is expected to be listed in the **Medication Administration Record (MAR)**, which includes:
    - A column that lists the names of medications that are prescribed
    - The times and dates the medication is to be taken
    - The initials of the person assisting with the medication
    - A start date should be noted (a stop date is noted when known)
    - Identifying information about the individual, including date of birth, allergies, diagnoses, and names of medical providers

Warnings and precautions

Risk of Reduced Antiviral Activity When Co-administered with Ganciclovir and Valganciclovir

Maribavir may antagonize the antiviral activity of ganciclovir and valganciclovir by inhibiting human CMV pUL97 kinase, which is required for activation/phosphorylation of ganciclovir and valganciclovir. Coadministration of maribavir with ganciclovir or valganciclovir is not recommended.

Virologic Failure During Treatment and Relapse Post-Treatment

Virologic failure due to resistance can occur during and after treatment with maribavir. Virologic relapse during the posttreatment period usually occurred within 4-8 weeks after treatment discontinuation. Some maribavir pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir. Monitor CMV DNA levels and check for maribavir resistance if the patient is not responding to treatment or relapses.

Risk of Adverse Reactions or Loss of Virologic Response Due to Drug Interactions

The concomitant use of maribavir and certain drugs may result in potentially significant drug interactions, some of which may lead to reduced therapeutic effect of maribavir or adverse reactions of concomitant drugs. Consider the potential for drug interactions prior to and during maribavir therapy; review concomitant medications during maribavir therapy and monitor for adverse reactions. Refer to the full prescribing information of maribavir for important drug interactions.

Maribavir is primarily metabolized by CYP3A4. Drugs that are strong inducers of CYP3A4 are expected to decrease maribavir plasma concentrations and may result in reduced virologic response; therefore, coadministration of maribavir with these drugs is not recommended, except for selected anticonvulsants.

Use With Immunosuppressant Drugs

Maribavir has the potential to increase the drug concentrations of immunosuppressant drugs that are CYP3A and/or P-gp substrates where minimal concentration changes may lead to serious adverse events (including tacrolimus, cyclosporine, sirolimus and everolimus). Frequently monitor immunosuppressant drug levels throughout treatment with maribavir especially following initiation and after discontinuation of maribavir and adjust immunosuppressant dose, as needed.

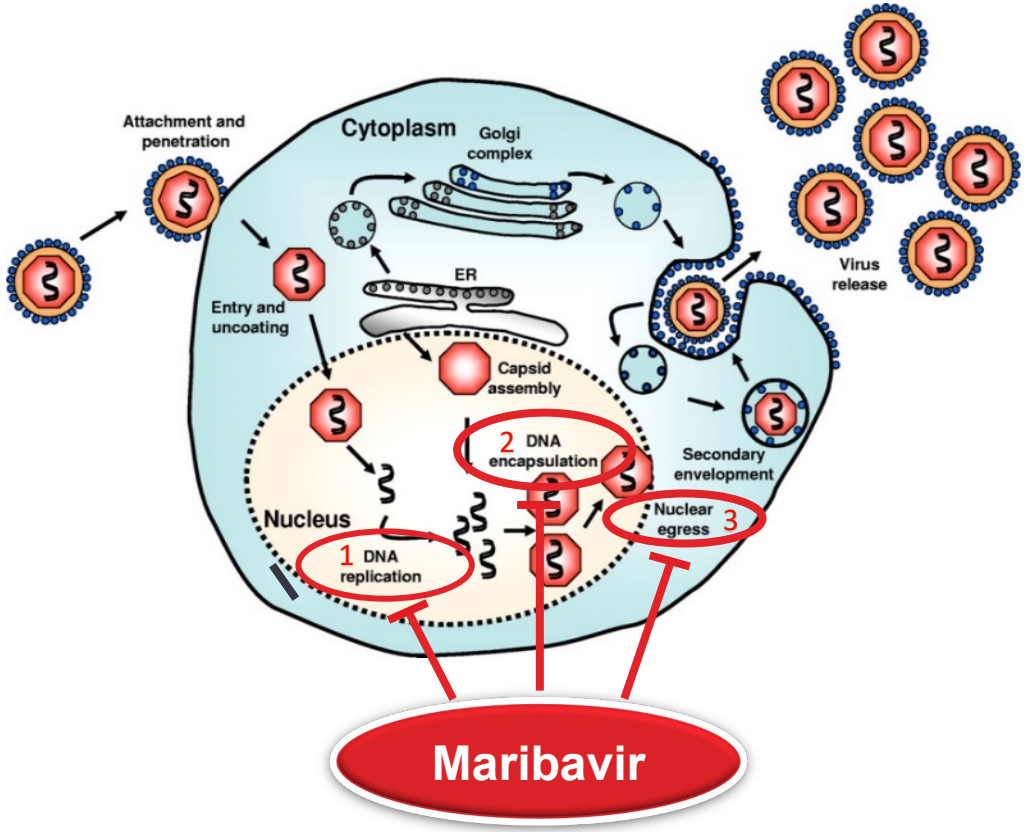
LIVTENCITY™ (maribavir) Prescribing information, available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215596lbl.pdf

Maribavir's mechanism of action

Overview

- Maribavir attaches to the pUL97 encoded serine/threonine kinase at the adenosine triphosphate (ATP) binding site, abolishing phosphotransferase required for a variety of essential viral processes such as DNA replication, encapsidation, and nuclear egress.
- This mechanism enables activity against strains of CMV with viral DNA polymerase mutations.

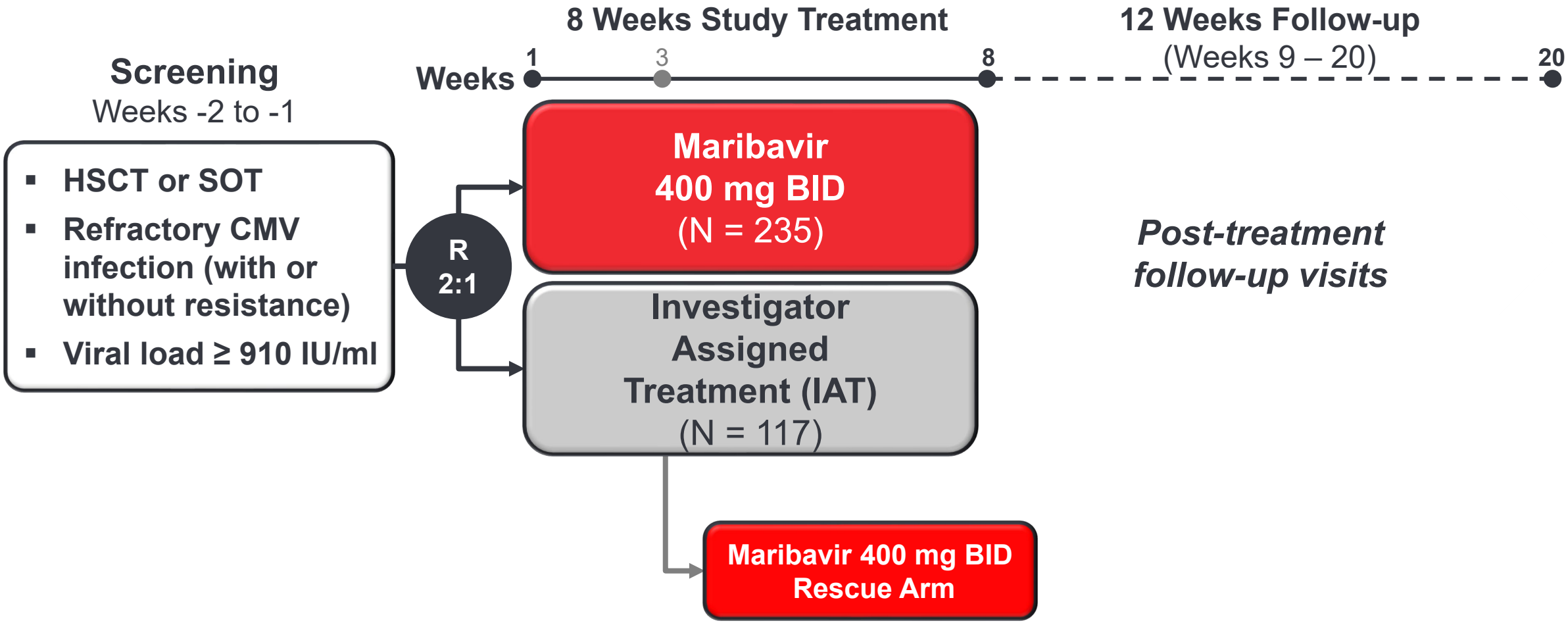
CMV-Infected Cell



CMV: cytomegalovirus; DNA: deoxyribonucleic acid.

Krosky PM, et al. *J Virol.* 2003 Jan;77(2):905-14; Biron KK, et al. *Antimicrob Agents Chemother*. 2002;46(8):2365-2372; Prichard MN. *Rev Med Virol.* 2009 Jul;19(4):215-29; Shannon-Lowe CD, Emery VC. *Herpesviridae*. 2010;1(1):4. Published 2010 Dec 7. doi:10.1186/2042-4280-1-4; Wolf DG, Courcelle CT, Prichard MN, Mocarski ES. *Proc Natl Acad Sci U S A*. 2001;98(4):1895-1900.

Study 303: phase 3 randomized controlled study in adult transplant recipients with R/R CMV



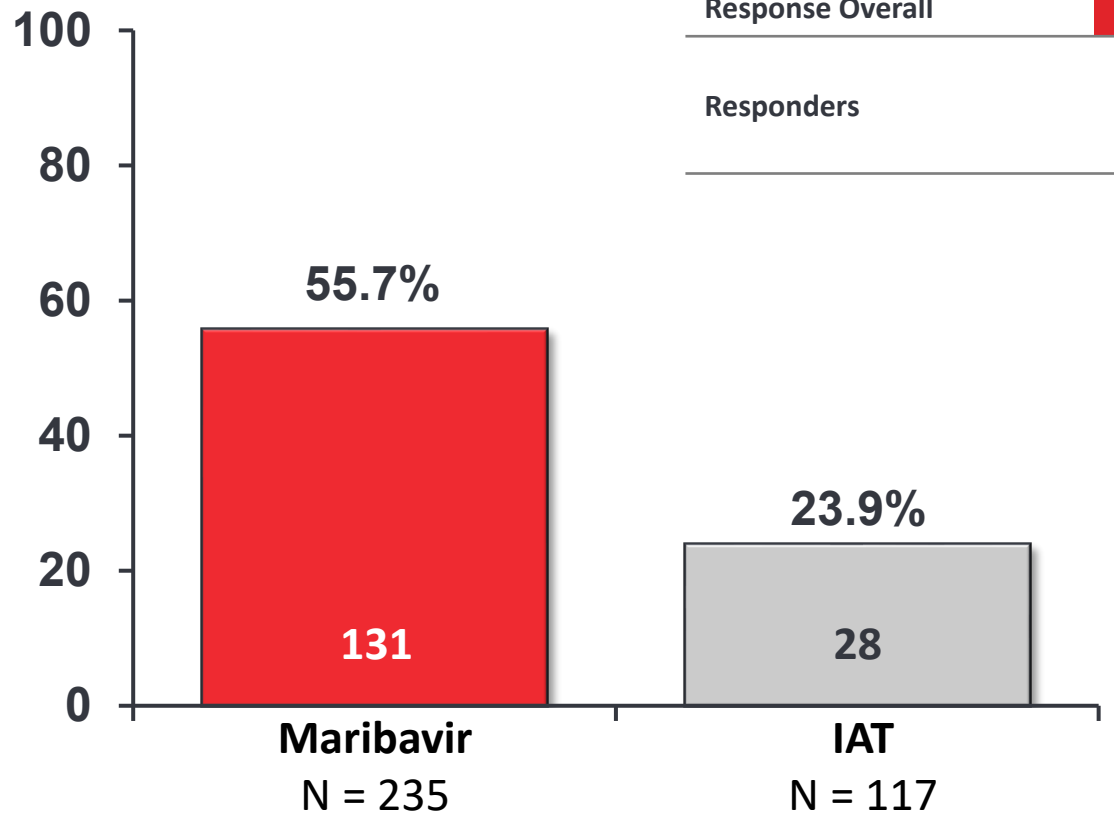
For the comparator (IAT) arm, investigators could choose one or two of the four available CMV antivirals: ganciclovir, valganciclovir, foscarnet, and cidofovir.

BID: two times a day; CMV: cytomegalovirus; IAT: investigator-assigned treatment; HSCT: hematopoietic stem cell transplant; IU: international unit; SOT: solid organ transplant; R/R: refractory, with or without resistance.

Avery RK, et al. In: ATC Virtual Connect; 2021; Takeda DOF. VV-SUP-81025. SOLSTICE CSR.

Study 303: primary endpoint – maribavir demonstrated statistically superior CMV clearance vs IAT

CMV Viremia Clearance Response Overall	Maribavir (N 235)	IAT (N = 117)	Adjusted Difference % (95% CI)	p-value
Responders	131 (55.7%)	28 (23.9%)	32.8 (22.8, 42.7)	< 0.001



A significantly higher proportion of MBV-treated patients achieved confirmed CMV clearance with a 32.8% difference between the two groups in transplant patients with refractory CMV (with or without resistance)

Confirmed CMV clearance (plasma CMV DNA <137 IU/mL in 2 consecutive tests ≥5 days apart at central laboratory)

Between-group difference among all randomized patients, adjusted for baseline CMV viral load (low, <9,100 IU/mL; intermediate/high, ≥9,100 IU/mL [plasma]; central laboratory COBAS CAP/CTM assay), and SOT/ HCT was compared with Cochran–Mantel–Haenszel tests (p≤0.0 significant).

CI: confidence interval; CMV: cytomegalovirus; IAT: investigator-assigned treatment; HSCT: hematopoietic stem cell transplant; MBV: maribavir; SOT: solid organ transplant.

Avery RK, Alain S, Alexander BD, et al. Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial (supplement). *Clin Infect Dis*. Published online December 2, 2021. doi.org/10.1093/cid/ciab988.

Study 303: treatment-related TEAEs in ≥5% of patients

System Organ Class Treatment-related TEAE[a], n (%)	MBV (N=234)	IAT (N=116)	Val/Ganciclovir (N=56)	Foscarnet (N=-47)
Blood and lymphatic system disorders/myelosuppression[b]	7 (3.0)	25 (21.6)	17 (30.4)	8 (17.0)
Anemia	3 (1.3)	9 (7.8)	3 (5.4)	6 (12.8)
Febrile Neutropenia	0	4 (3.4)	4 (7.1)	0
Leukopenia	0	5 (4.3)	4 (7.1)	1 (2.1)
Neutropenia	4 (1.7)	16 (13.8)	14 (25.0)	2 (4.3)
Thrombocytopenia	0	6 (5.2)	4 (7.1)	2 (4.3)
Gastrointestinal disorders	37 (15.8)	15 (12.9)	2 (3.6)	11 (23.4)
Diarrhea	9 (3.8)	6 (5.2)	1 (1.8)	4 (8.5)
Nausea	20 (8.5)	11 (9.5)	1 (1.8)	8 (17)
Vomiting	18 (7.7)	5 (4.3)	0	4 (8.5)
General disorders and administration site conditions	7 (3.0)	9 (7.8)	0	9 (19.1)
Peripheral edema	0	4 (3.4)	0	4 (8.5)
Investigations	20 (8.5)	9 (7.8)	2 (3.6)	6 (12.8)
Immunosuppressant drug level increased	14 (6.0)	0	0	0
Metabolism and nutrition disorders	6 (2.6)	11 (9.5)	12 (3.6)	8 (17.0)
Hypocalcemia	0	5 (4.3)	1 (1.8)	4 (8.5)
Hypokalemia	1 (0.4)	5 (4.3)	0	4 (8.5)
Hypomagnesemia	0	5 (4.3)	1 (1.8)	4 (8.5)
Nervous system disorders	104 (44.4)	9 (7.8)	1 (1.8)	8 (17.0)
Taste disturbance[c]				
Dysgeusia	84 (35.9)	1 (0.9)	1 (1.8)	0
Taste disorder	20 (8.5)	1 (0.9)	0	1 (2.1)
Headache	2 (0.9)	4 (3.4)	0	4 (8.5)
Renal and urinary disorders/Nephrotoxicities[d]	4 (1.7)	15 (12.9)	0	13 (27.7)
Acute kidney injury	4 (1.7)	9 (7.8)	0	9 (19.1)
Renal impairment	0	3 (2.6)	0	3 (6.4)

IAT: investigator assigned treatment; MBV: maribavir; TEAE: treatment-emergent adverse event

[a]Treatment-related TEAEs were defined as any adverse event occurring during the on-treatment observation period considered to be related to the assigned therapy; [b]Myelosuppression includes preferred terms of anemia, leukopenia, neutropenia, febrile neutropenia and thrombocytopenia; [c]Taste disturbance includes preferred terms of dysgeusia, ageusia, hypogeusia and taste disorder; [d]Nephrotoxicities includes preferred terms of AKI, toxic nephropathy, renal failure and renal impairment.

Avery RK, Alain S, Alexander BD, et al. Maribavir for Refractory Cytomegalovirus Infections With or Without Resistance Post-Transplant: Results From a Phase 3 Randomized Clinical Trial (supplement). *Clin Infect Dis*. Published online December 2, 2021. doi.org/10.1093/cid/ciab988.

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