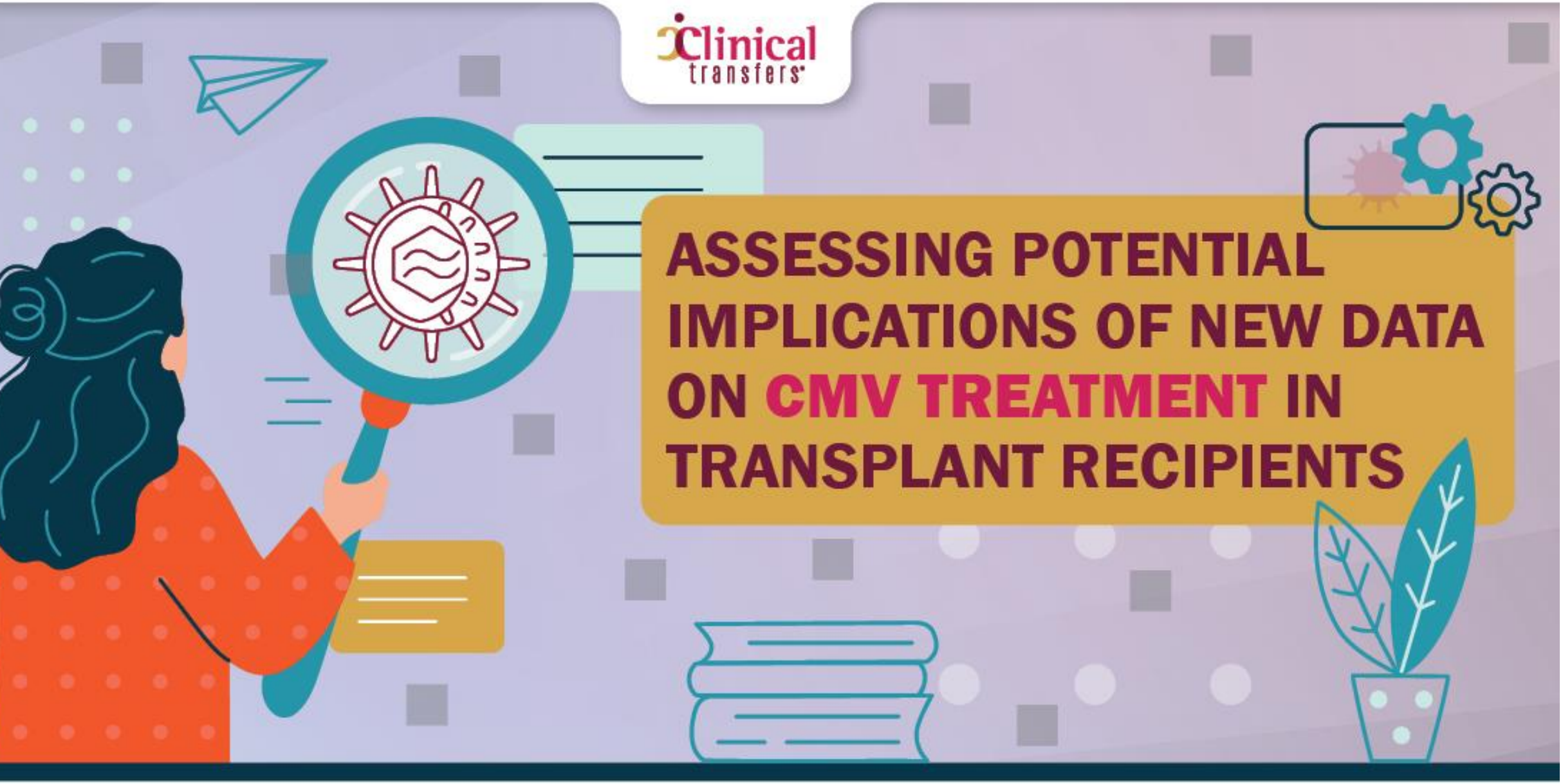

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RMEI MEDICAL EDUCATION FOR BETTER OUTCOMES

This activity is supported by an educational grant from Takeda Pharmaceuticals U.S.A., Inc.

CMV in Transplant: What is it and Why it is Important

Cytomegalovirus

- Frequently observed opportunistic pathogen in transplant recipients
- Establishes life-long latency after initial infection
- CMV infection may be asymptomatic in transplant patients
- Most transplant patients get prophylactic or preemptive therapy to prevent CMV disease

Consequences in SOT Patients

- Tissue invasive disease (GI tract, lung, liver, CNS, and retina)
- Opportunistic co-infections (viral, bacterial, and fungal)
- Higher risk of post-transplant lymphoma
- Higher risk of graft rejection
- Increased mortality

Consequences in HCT Patients

- Tissue invasive disease (GI tract, lung, liver, CNS, and retina)
- Opportunistic co-infections (viral, bacterial, and fungal)
- Higher risk of acute GVHD in recipients of T-cell depleted grafts
- Higher risk of chronic GVHD
- Increased non-relapse and overall mortality

CMV, cytomegalovirus; SOT, solid organ transplant; HCT, hematopoietic cell transplant; GVHD, graft vs. host disease

Kotton CN, et al. *Transplantation.* 2018;102(6):900-931; Hakki M, et al. *Transplant Cell Ther*. 2021;27(9):707-719; Boeckh M, et al. *Blood*. 2009;113(23):5711-5719; Ljungman P, et al. *Lancet Infect Dis*. 2019;19(8):e260-e272.

Taking Stock of Recent Key Learnings About CMV Treatment in Transplantation

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Maribavir Phase 3 SOLSTICE Trial: Treatment of Resistant/Refractory CMV

352 SOT and HCT recipients with R/R CMV were randomized 2:1

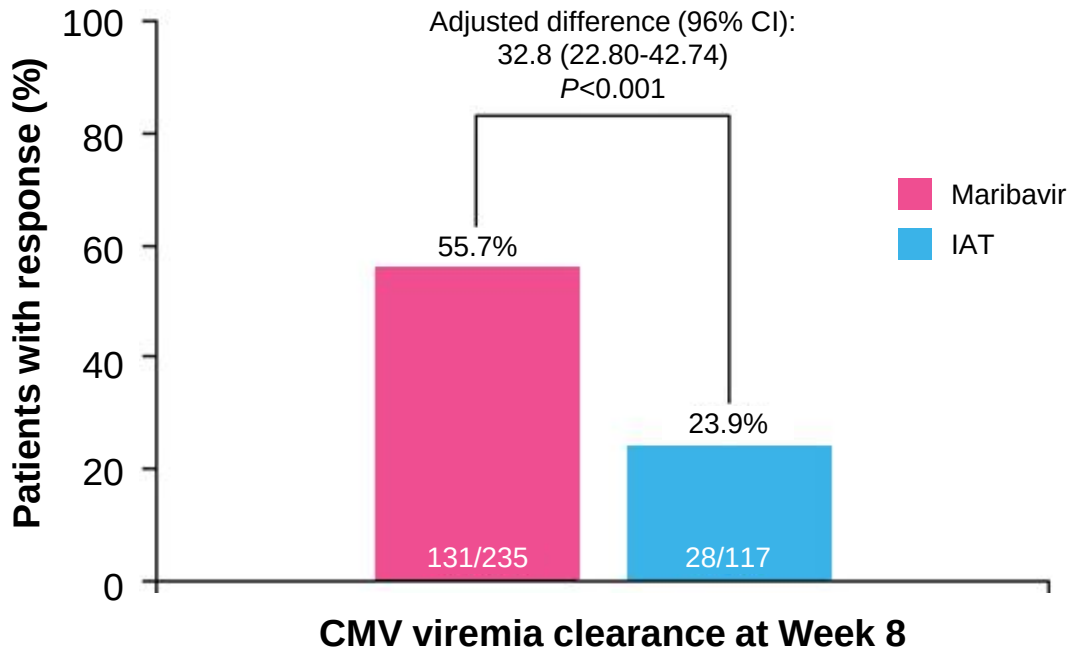
Maribavir (n=235)
400 mg PO twice daily for 8 weeks

IAT
(valganciclovir/ganciclovir, foscarnet, or cidofovir; n=117) for 8 weeks

12 weeks of follow-up after treatment

*Maribavir is the first and only in a new class of antiviral therapies FDA approved for CMV treatment in transplant patients, thus there are no comparison therapies to evaluate.

Primary Endpoint: CMV Viremia Clearance At Week 8



IAT, investigator-assigned therapy; SOT, solid organ transplant; R/R, refractory or resistant

Avery RK, et al. *Clin Infect Dis.* 2022;75(4):690-671.

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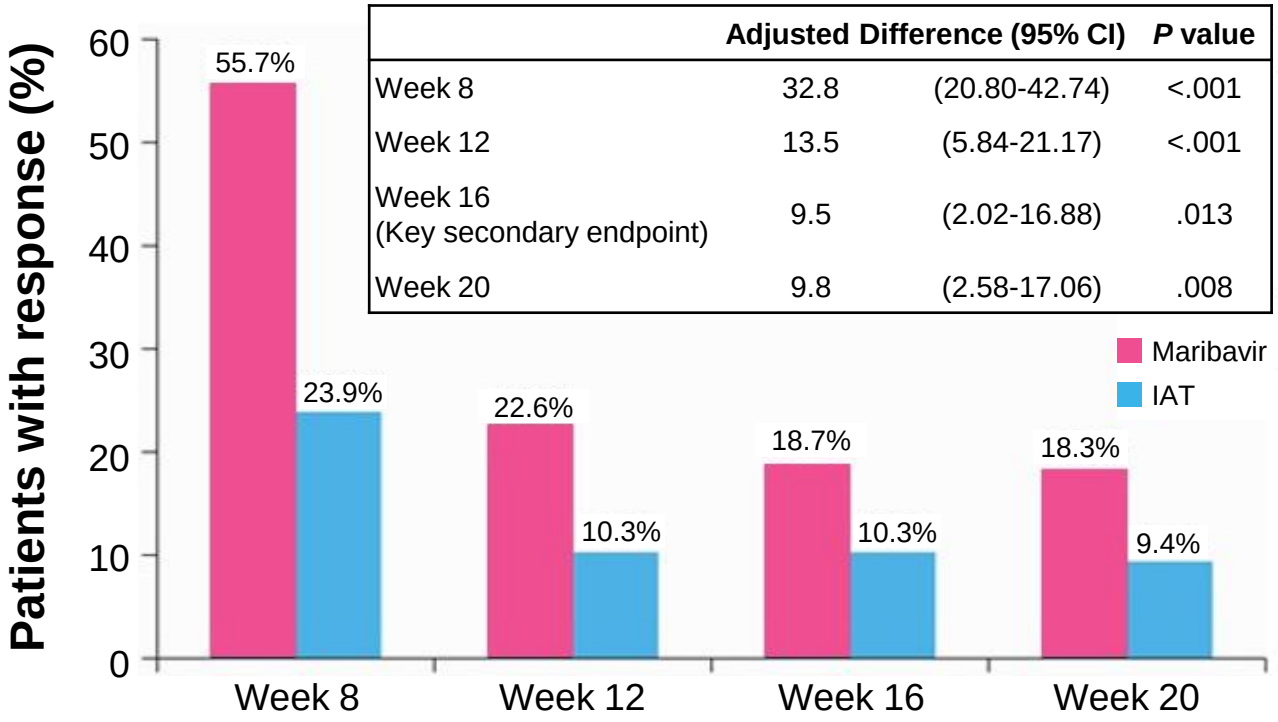
Maribavir Phase 3 Trial: SOLSTICE (*cont'd*)

Secondary Endpoint: Confirmed Viremia Clearance and Symptom Control



	Adjusted Difference (95% CI)		*P* value
Week 8	32.8	(20.80-42.74)	<.001
Week 12	13.5	(5.84-21.17)	<.001
Week 16 (Key secondary endpoint)	9.5	(2.02-16.88)	.013
Week 20	9.8	(2.58-17.06)	.008

- Maribavir was superior to IAT for CMV viremia clearance
- Viremia clearance and symptom control were better through week 20 with maribavir

Avery RK, et al. *Clin Infect Dis.* 2022;75(4):690-671.

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Time to First Cytomegalovirus Viremia Clearance in Transplant Recipients With Refractory Cytomegalovirus Infection With or Without Resistance Receiving Maribavir versus Investigator-Assigned Therapy: Subgroup Analyses of a Phase III Trial

Kaplan–Meier Estimates of Time to First CMV Viremia Clearance Within Study Week 8 in Subgroups (Randomized Population)

	Maribavir (n=235)	IAT (n=117)
Patients with CMV resistance mutations at baseline	n=121	n=69
Patients with viremia clearance – n (%)	88 (72.7)	27 (39.1)
Time to first viremia clearance – days		
Median	27.0	44.0
95% CI	22.0–30.0	29.0–NA
Patients without CMV resistant mutations at baseline	n=96	n=34
Patients with viremia clearance – n (%)	70 (72.9)	22 (64.7)
Time to first viremia clearance – days		
Median	17.0	22.0
95% CI	13.0–22.0	13.0–27.0
Patients with low VL at baseline[a]	n=153	n=85
Patients with viremia clearance – n (%)	127 (83.0)	48 (56.5)
Time to first viremia clearance – days		
Median	15.0	22.0
95% CI	13.0–17.0	20.0–29.0
Patients with intermediate/high VL at baseline[a]	n=82	n=32
Patients with viremia clearance – n (%)	47 (57.3)	13 (40.6)
Time to first viremia clearance – days		
Median	43.0	44.0
95% CI	30.0–49.0	26.0–NA
HCT recipients	n=93	n=48
Patients with viremia clearance – n (%)	70 (75.3)	29 (60.4)
Time to first viremia clearance – days		
Median	15.0	22.0
95% CI	9.0–19.0	15.0–23.0
SOT recipients	n=142	n=69
Patients with viremia clearance – n (%)	104 (73.2)	32 (46.4)
Time to first viremia clearance – days		
Median	25.0	30.0
95% CI	22.0–29.0	25.0–48.0

[a]Viral load by central laboratory CMV DNA levels from plasma were obtained at baseline and categorized as follows: low (<9,100 IU/mL) and intermediate/high VL (≥9,100 IU/mL).

- A post-hoc analysis of the Phase 3 SOLSTICE study examined the time to first CMV viremia clearance in subgroups within study week 8.
- Time to first confirmed CMV clearance was shorter for maribavir than IAT in the randomized set, both for patients with documented resistance and those with refractory disease.

Alain S, et al. Presented at ECCMID; April 23-26, 2022; Abstract 00059.

Assessment of Discontinuations and Anti-Cytomegalovirus Treatment Switching in Post-transplant Refractory/Resistant Cytomegalovirus Infections: Safety and Sensitivity Analyses from a Phase 3 Randomized Trial

System organ class Preferred terms	Maribavir (n=234) n (%)	IAT (n=116) n (%)	IAT type: Val/ganciclovir (n=56) n (%)	IAT type: Foscarnet (n=47) n (%)
Any TEAE leading to discontinuation of study-assigned treatment	31 (13.2)	37 (31.9)	18 (32.1)	17 (36.2)
Blood and lymphatic system	0	13 (11.2)	13 (23.2)	0
Anemia		2 (1.7)	2 (3.6)	
Leukopenia		3 (2.6)	3 (5.4)	
Neutropenia		11 (9.5)	11 (19.6)	
Thrombocytopenia		4 (3.4)	4 (7.1)	
Gastrointestinal disorders	4 (1.7)	3 (2.6)	1 (1.8)	2 (4.3)
Diarrhea	2 (0.9)	1 (0.9)	1 (1.8)	0
Nausea	2 (0.9)	1 (0.9)	0	1 (2.1)
Infections and infestations	17 (7.3)	8 (6.9)	4 (7.1)	3 (6.4)
CMV infection	7 (3.0)	1 (0.9)	0	0
CMV infection reactivation	2 (0.9)	0	0	0
CMV viremia	4 (1.7)	2 (1.7)	2 (3.6)	0
Encephalitis CMV	2 (0.9)	1 (0.9)	0	1 (2.1)
Neoplasms (benign malignant and unspecified)	2 (0.9)	2 (1.7)	1 (1.8)	1 (2.1)
Recurrent acute lymphocytic leukemia	2 (0.9)	0	0	0
Nervous system disorders	3 (1.3)	0	0	0
Dysgeusia	2 (0.9)			
Renal and urinary disorders	0	11 (9.5)	0	10 (21.3)
Acute kidney injury		6 (5.2)		6 (12.8)
Renal failure		2 (1.7)		1 (2.1)
Renal impairment		2 (1.7)		2 (4.3)

- The purpose of this study was to assess the impact of discontinuations or treatment switching on CMV viremia clearance at week 8 in the SOLSTICE trial
- Treatment emergent adverse events (TEAEs) leading to treatment discontinuation were less frequent in the maribavir group (13.2%) than the IAT group (31.9%)
- Neutropenia (MBV 0%; val/ganciclovir 19.6%) and acute kidney injury (MBV 0%; foscarnet 12.8%) were the most frequently reported TEAEs that led to discontinuation

Alain S, et al. Presented at ECCMID; April 23-26, 2022; Abstract 00059.

Healthcare Resource Utilization in Transplant Recipients with Cytomegalovirus Infection Refractory/Resistant to Treatment Receiving Maribavir versus Investigator Assigned Therapy: Exploratory Analysis of a Phase 3 Trial

Hospital admission rates and LOS per patient by treatment

	On-treatment phase[a]		Full study period[b]	
	MBV n=235	IAT n=117	MBV n=235	IAT n=117
Hospitalizations				
Patients with ≥1 admission, n (%)	75 (31.9)	43 (36.8)	125 (53.2)	65 (55.6)
Adjusted incidence rate, admissions/person/year (95% CI)	2.74 (2.22, 3.38)	4.20 (3.12, 5.67)	2.49 (2.12, 2.93)	3.20 (2.48, 4.12)
Adjusted difference in rates of hospital admissions, IRR (95% CI)	0.65 (0.45, 0.94)		0.78 (0.58, 1.05)	
Percent reduction for MBV compared with IAT	34.8% p=0.021		22.1% p=0.102	
LOS				
LOS per patient, mean no. of days (SD)	3.1 (7.1)	3.5 (7.6)	9.6 (16.1)	9.7 (22.7)
Adjusted duration of LOS, days/person/year (95% CI)	13.27 (8.89, 19.82)	28.73 (16.34, 50.52)	34.29 (25.89, 45.42)	48.88 (32.77, 72.92)
Adjusted difference in LOS, IRR (95% CI)	0.46 (0.23, 0.92)		0.70 (0.43, 1.14)	
Percent reduction for MBV compared with IAT	53.8% p=0.029		29.8% p=0.155	

[a]On-treatment adjusted rates and LOS are adjusted for duration of time on treatment (52 days for maribavir, 35.7 days for IAT). [b]Adjusted rates and LOS for the full-study period are adjusted for duration of time in study (132.1 days for maribavir, 92.9 days for IAT).
SD, standard deviation.

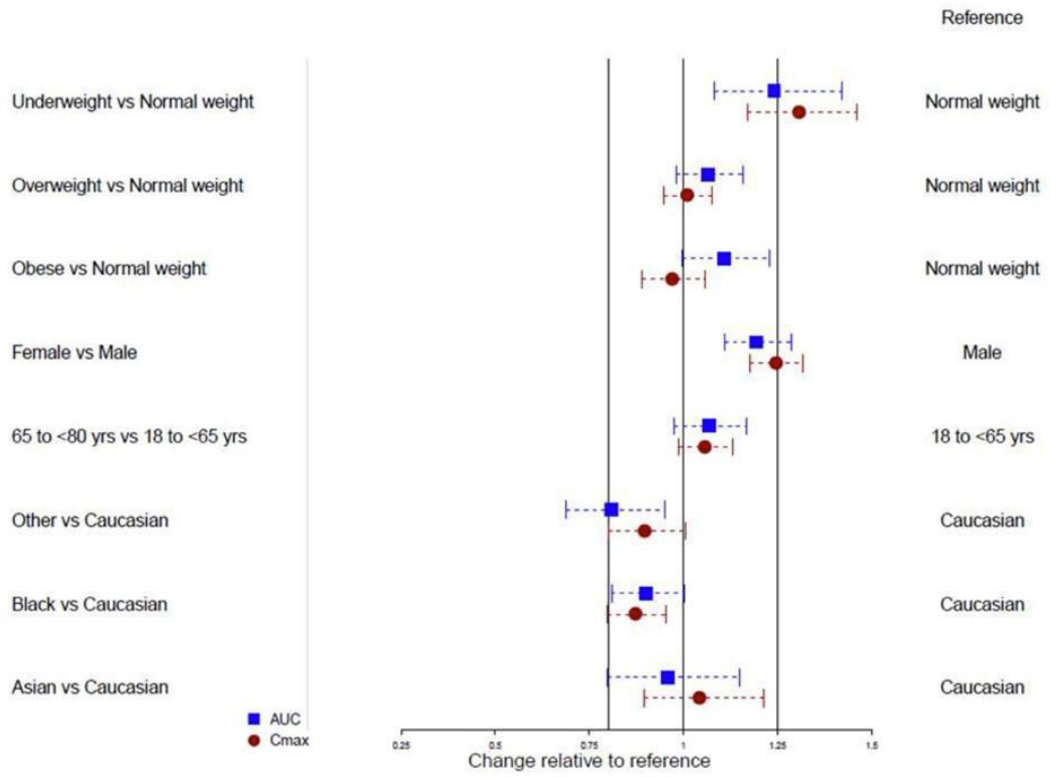
- This study evaluated HCRU for the maribavir and IAT arms in an exploratory analysis of SOLSTICE
- Patients on maribavir versus IAT had reductions of 34.8% in hospitalizations and 53.8% in LOS
- The hospitalization rate in the IAT group pre-rescue with maribavir was 2.54 times higher than on or after rescue with maribavir
- Foscarnet patients tended to have higher hospitalizations (5.5 admissions/person/year) and longer LOS (51.7 days/person/year) on treatment
- **Maribavir may help to reduce hospitalizations, which can reduce HCRU**

HCRU, healthcare resource utilization; LOS, length of stay

Hirji I, et al. Presented at the Transplantation and Cellular Therapy Meetings; April 23-26, 2022. Abstract 52.

Population Pharmacokinetics and Exposure: Response Relationships of Maribavir in Transplant Recipients With Cytomegalovirus Infections

Geometric mean ratios and 90% CIs for comparisons versus reference of steady-state AUC_{0-t} and C_{max} for MBV in transplant recipients with CMV by patient characteristics of weight, sex, age, and race



- This study used population pharmacokinetic (PK) and pharmacodynamic (PD) models to characterize the time course of plasma maribavir concentrations and the exposure-response (E-R) relationships for selected efficacy and safety clinical trial assessments
- Maribavir plasma concentration–time data from hematopoietic cell or solid organ transplant (HCT/SOT) recipients with CMV infection were used to develop a population PK model
- PK/PD models were developed using analyses of the primary and key secondary efficacy endpoints of the SOLSTICE trial and safety assessments
- E-R analyses indicated there were no clinically meaningful relationships between MBV exposure and the probability of achieving primary or key secondary efficacy endpoints or the probability of dysgeusia, fatigue, increase in immunosuppressant drug concentration, or serious adverse event, as the odds ratios were all close to 1
- **Based on PK/PD modeling, dose adjustment of MBV will not be required in adult transplant recipients for the treatment of CMV infection regardless of age, body weight, sex, race, transplant type, baseline plasma CMV DNA, or presence of CMV mutations**

Song I, et al. Presented at the Transplantation and Cellular Therapy Meetings; April 23-26, 2022; Abstract 470.

Taking Stock of Recent Key Learnings About CMV Prevention in Transplantation

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Safety and Efficacy of Letermovir versus Valganciclovir for Prevention of Cytomegalovirus Disease in Kidney Transplant Recipients: A Phase 3 Randomized Study

- This study evaluated CMV prophylaxis with LET versus VGCV in 601 adult CMV D+/R- kidney transplant recipients (KTRs)
- Adult CMV D+/R- KTRs were randomized 1:1 within 7 days post-kidney transplant (KT) to receive either LET 480 mg QD (PO/IV) with acyclovir (400 mg PO BID, adjusted for renal function), or VGCV (900 mg PO QD, adjusted for renal function), through week 28 post-KT and followed up through week 52 post-KT
- The proportion of patients with CMV disease through week 52 post-KT was 10.4% with LET vs 11.8% with VGCV

Parameter, n (%)	LET[b] (N = 289)	VGCV[c] (N = 297)	Stratum-adjusted treatment difference (LET – VGCV), % (95% CI)[d]
Primary endpoint			
CMV disease[e] through Week 52 post-KT	30 (10.4)	35 (11.8)	-1.4 (-6.5, 3.8) Non-inferior[f]
Secondary endpoint			
CMV disease[e] through Week 28 post-KT	0	5 (1.7)	-1.7 (-3.4, 0.1)
Exploratory endpoints			
CMV DNAemia[g] through Week 28 post-KT	6 (2.1)	26 (8.8)	–
All-cause mortality through Week 52 post-KT	4 (1.4)	3 (1.0)	–

CI, confidence interval; CMV, cytomegalovirus; KT, kidney transplant; LET, letermovir; pts, participants; VGCV, valganciclovir.
[a]The efficacy (full analysis set) population was defined as all donor CMV-seropositive/recipient CMV-seronegative randomized pts who received ≥1 dose of study medication and had no detectable CMV viral DNA on Day 1.
[b]Co-administered with acyclovir.
[c]Co-administered with placebo for acyclovir.

*As of November 2022, letermovir is not FDA approved for prophylaxis of CMV infection or disease in solid organ transplant recipients.

Limaye AP, et al. Presented at IDWeek; October 19-23, 2022; Abstract LB2307.

Safety and Efficacy of Letermovir versus Valganciclovir for Prevention of Cytomegalovirus Disease in Kidney Transplant Recipients: A Phase 3 Randomized Study (*cont'd*)

Parameter, n (%)	LET[a] (N = 292)	VGCV[b] (N = 297)	Difference estimate, LET – VGCV, % (95% CI)[c]
Pts in treatment arm			
With ≥1 AE	271 (92.8)	276 (92.9)	-0.1 (-4.4, 4.2)
With no AEs	21 (7.2)	21 (7.1)	0.1 (-4.2, 4.4)
With drug-related AEs[d]	58 (19.9)	104 (35.0)	-15.2 (-22.2, -8.0)
With serious AEs	106 (36.3)	113 (38.0)	-1.7 (-9.5, 6.1)
With serious drug-related AEs	4 (1.4)	15 (5.1)	-3.7 (-7.0, -0.9)
Who died	2 (0.7)	1 (0.3)	0.3 (-1.3, 2.2)
Who discontinued drug due to an AE	12 (4.1)	40 (13.5)	-9.4 (-14.1, -4.9)
Who discontinued drug due to a drug-related AE[d]	8 (2.7)	26 (8.8)	-6.0 (-10.1, -2.4)
Who discontinued drug due to a serious AE	6 (2.1)	14 (4.7)	-2.7 (-5.9, 0.3)
Who discontinued drug due to a serious drug-related AE	2 (0.7)	7 (2.4)	-1.7 (-4.2, 0.4)
Pts with ≥1 leukopenia or neutropenia (preferred term or laboratory criteria) events[e]	76 (26.0)	190 (64.0)	-37.9 (-45.1, -30.3) P < 0.0001

AE, adverse event; CI, confidence interval; KT, kidney transplant; LET, letermovir; pts, participants; VGCV, valganciclovir.

[a]Co-administered with acyclovir.

[b]Co-administered with a placebo for acyclovir.

- Drug-related adverse events (AEs) were reported in 19.9% of patients with LET and 35.0% of patients with VGCV through week 28 post-KT
- The rate of discontinuations due to an AE was 4.1% in the LET arm and 13.5% in the VGCV arm
- The incidence of neutropenia (absolute neutrophil count <1000/µL) during the treatment phase was lower with LET than with VGCV
- **LET was non-inferior to VGCV in preventing CMV disease in high-risk (CMV D+/R-) KTRs through week 52 post-KT and led to a lower rate of myelotoxicity than VGCV**

*As of November 2022, letermovir is not FDA approved for prophylaxis of CMV infection or disease in solid organ transplant recipients.

Limaye AP, et al. Presented at IDWeek; October 19-23, 2022. Abstract LB2307.

Viral Resistance and Neutropenia/Leukopenia with Letermovir versus Valganciclovir as Cytomegalovirus Prophylaxis in Adult Kidney Transplant Recipients: A Phase 3 Randomized Study

- Examined exploratory secondary endpoints:
  - Viral resistance
  - Neutropenia/leukopenia

- The proportion of participants requiring ≥1 use of granulocyte colony stimulating factor during the treatment period was lower with LET (1.7%) vs VGCV (7.1%)

- The rate of discontinuation due to myelotoxicity was lower in the LET arm

- **The prevalence of viral resistance associated mutations was lower in the LET arm (0%) vs the VGCV arm (12.1%)**

	LET Arm		VGCV Arm	
	n=52	(%)	n=66	(%)
With any known LET resistance substitution	0	(0.0)	0	(0.0)
pUL51	0	(0.0)	0	(0.0)
pUL56	0	(0.0)	0	(0.0)
pUL89	0	(0.0)	0	(0.0)
With any known VGCV resistance substitution	2	(3.8)	8	(12.1)
pUL54	0	(0.0)	2	(3.0)
pUL97	2	(3.8)	7	10.6)

Next generation sequencing was performed for each indicated gene and number participants with known resistance-associated substitutions detected at a frequency of ≥5% are shown.

Vincenti F, et al. Presented at the American Society of Nephrology Kidney Week; November 3-6, 2022. Abstract TH-PO995.

Interim Results From a Phase 2, Randomized, Observer-blind, Placebo-controlled, Dose-finding Trial of an mRNA-Based Cytomegalovirus Vaccine in Healthy Adults

- In this Phase 2, randomized, placebo-controlled, observer-blind, dose-finding trial, safety and immunogenicity of mRNA-1647 was evaluated in healthy CMV seropositive and CMV seronegative adults aged 18 to 40 years
- The mRNA-based vaccine against CMV, mRNA-1647, consists of 6 mRNA sequences encoding 2 CMV antigens (glycoprotein B and the pentameric glycoprotein complex) in a lipid nanoparticle formulation

	Part 1	Part 2
Randomization 3:1 CMV-seronegative and CMV-seropositive men and women	mRNA-1647 (doses of 50, 100, or 150 µg) or placebo at months 0, 2, and 6	mRNA-1647 100 µg or placebo at months 0, 2, and 6
Results 1 month after dose 3	100 µg was generally well-tolerated, induced robust antibody responses in CMV-seronegative participants, and boosted antibody titers in CMV-seropositive participants	No notable differences in the safety profile compared with Part 1

Panther L, et al. Presented at IDWeek; October 19-23, 2022. Abstract 112.

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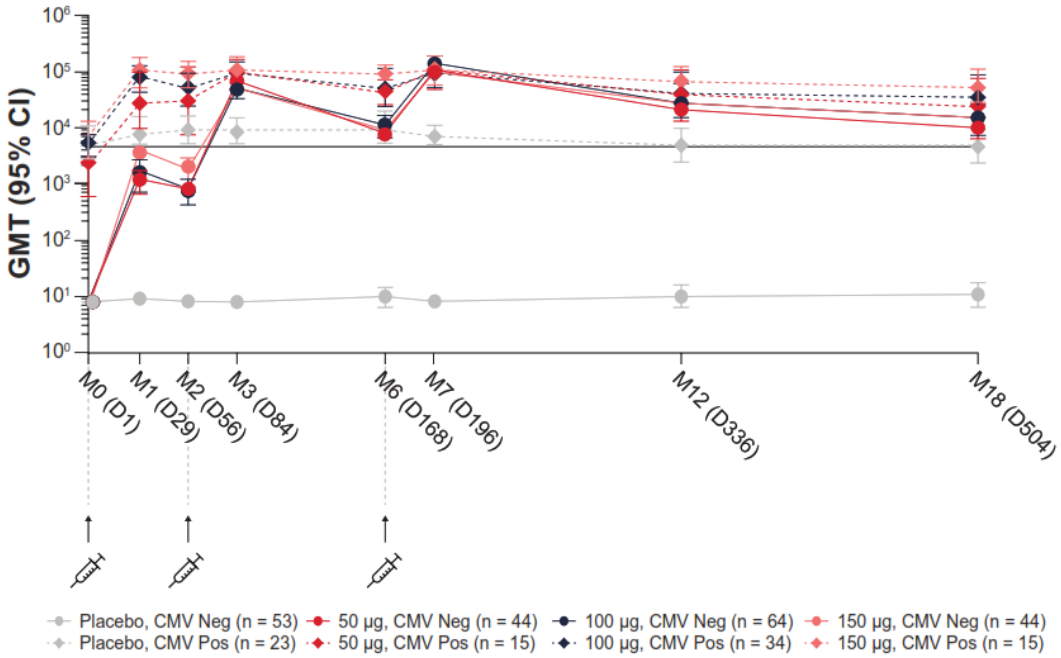
Immunogenicity in mRNA-1647 Treatment Groups

- CMV-seronegative participants
  - Neutralizing antibody (nAB) geometric mean titers (GMTs) against epithelial cell infection increased above baseline after dose 1 and continued to increase after doses 2 and 3
- CMV-seropositive participants
  - nAB GMTs against epithelial cell infection increased over baseline in a dose-related manner after dose 1, and GMTs after doses 2 and 3 were comparable to or exceeded GMTs observed after dose 1
- **mRNA-1647 was well-tolerated and immunogenic at all dose levels assessed**

Figure 3. nAb GMTs Against Epithelial Cell Infection by CMV Serostatus and Dose Level[a]



CI, confidence interval; CMV, cytomegalovirus; D, day; GMT, geometric mean titer; M, month; nAb, neutralizing antibody; Neg, negative; Pos, positive.

[a]The solid black line indicates the baseline nAb GMT against epithelial cell infection of all CMV-seropositive participants at baseline (GMT = 4575.7). Doses 1, 2, and 3 were administered at Months 0, 2, and 6, respectively, as represented by an arrow and syringe. n is the number of participants with non-missing data at baseline and the corresponding time point.

Panther L, et al. Presented at IDWeek; October 19-23, 2022. Abstract 112.

Summary

- Recent data suggest that letermovir and maribavir have fewer drug-related adverse events and fewer discontinuations than conventional antiviral prophylaxis and treatment for resistant/refractory disease
- As a result, maribavir may offer advantages over conventional antiviral treatment for resistant/refractory disease
- Await full data on letermovir as prophylaxis for kidney transplant; it may offer interesting alternative agent for prophylaxis
- Clinical trials of an mRNA CMV vaccine are underway; initial data appears promising
- More effective and/or tolerable prevention and treatment options may decrease the burden of CMV infection in transplant recipients by reducing healthcare resource utilization and costs