Supplementary Online Content

Limaye AP, Stapleton RD, Peng L, et al. Effect of ganciclovir on IL-6 levels among cytomegalovirus-seropositive adults with critical illness: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.10569

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eAppendix 2. Missing Data

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Methods and Results

Definitions

Sepsis was defined as a documented or suspected infection together with at least 2 of the following 4 clinical findings present: Temperature greater than 38°C (100.4°F) or less than 36°C (96.8°F), Heart rate (HR) greater than 90 beats per minute (bpm), Respiratory rate (RR) greater than 20 breaths per minute or arterial carbon dioxide tension (PaCO2) lower than 32 mm Hg, white blood cell (WBC) count higher than 12,000/μL or lower than 4000/μL, or 10% immature (band) forms. Infection was defined as a documented or a suspected infection. Suspected infection was evidenced by one or more of the following: white cells in a normally sterile body fluid; perforated viscus; radiographic evidence of pneumonia in association with the production of purulent sputum; a syndrome associated with a high risk of infection (e.g., ascending cholangitis) and empiric antibiotic treatment.

Trauma was defined as having respiratory failure and an ISS score > 15 within a 24 hour time period, and within the 120 hour window (where mechanical ventilation was not due solely to a head injury)

Data Collection

An electronic case report form was used to collect data. Chart abstraction for demographic, laboratory, and physiologic data occurred at study entry, daily until the intervention was discontinued, weekly for the remainder of the hospitalization, and again at hospital discharge or death. Review of the hospital records occurred daily throughout the hospitalization (to Day 35) to identify any adverse events.

Results

A total of 33/90 (37%) subjects of the ITT received oral study drug during the study before the protocol was amended due to expiration of the oral study drug supply. The median duration [IQR] of the oral study drug was 6.5 days [3-9]. The proportion of the placebo and ganciclovir recipients who received oral study drug is as shown in the table below.

	Placebo	**Ganciclovir**
ITT, No./Total No. (%)	20/33 (61)	13/33 (39)
Sepsis, No./Total No. (%)	16/25 (64)	9/25 (36)
Septic Shock, No./Total No. (%)	3/4 (75)	1/4 (25)

eTable 1. Days on Mechanical Ventilation by Day 28

	Placebo	Ganciclovir	Absolute Risk Reduction (95% CI)	P-value
Survived over 28 days				
ITT[a]				
No./Total No. (%)	61/72 (85)	74/84 (88)		
Days on MV[b], median [IQR]	7 [3-13]	5 [3-8]	-2 (-5, 0)	0.02
Sepsis				
No./Total No. (%)	56/66 (85)	62/71 (83)		
Days on MV[b], median [IQR]	6.5 [3-12.25]	4 [2.25-7]	-3 (-4, 0)	0.006
Died before day 28				
ITT[a]				
No./Total No. (%)	11/72 (15)	10/84(11)		
Days on MV[b], median [IQR]	5 [3-6]	8.5 [4.25-13.25]	3.5 (-2, 6)	0.08
Sepsis				
No./Total No. (%)	10/66 (15)	9/71 (13)		
Days on MV[b], median [IQR]	5.5 [3-6]	8 [4-11]	2.5 (-5.5, 6)	0.17

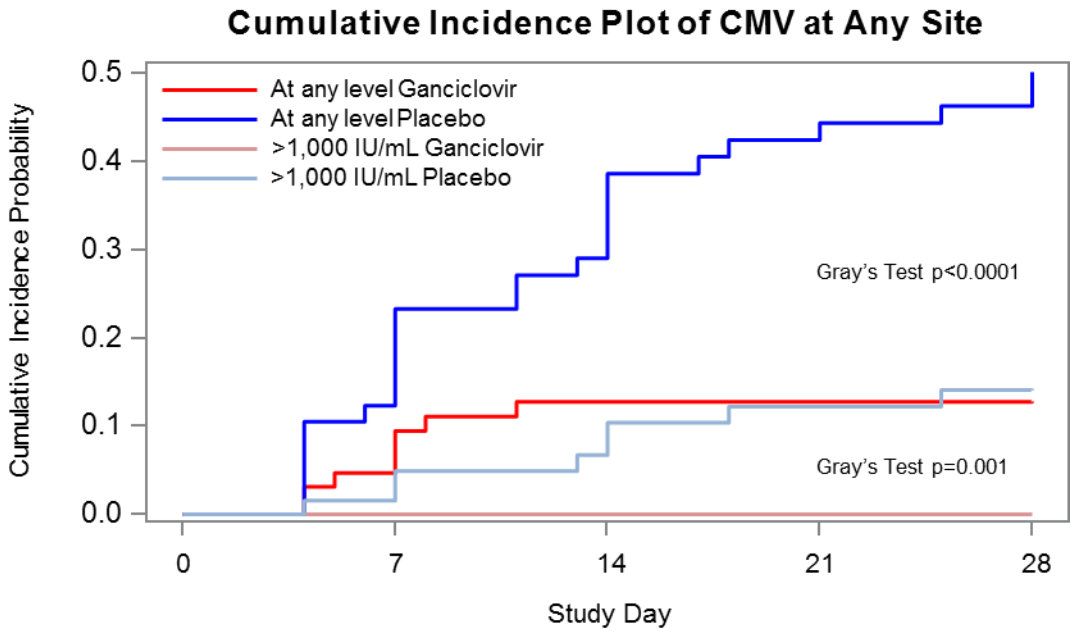
[a] ITT stands for intent-to-treat

[b] MV stands for mechanical ventilation

eFigure 1. Cumulative incidence of CMV reactivation by DNA detection (any level, >1,000 IU/mL) excluding baseline positive DNA detection until day 28 in a) at any site, b) ET aspirate or BAL sample[a], and c) throat

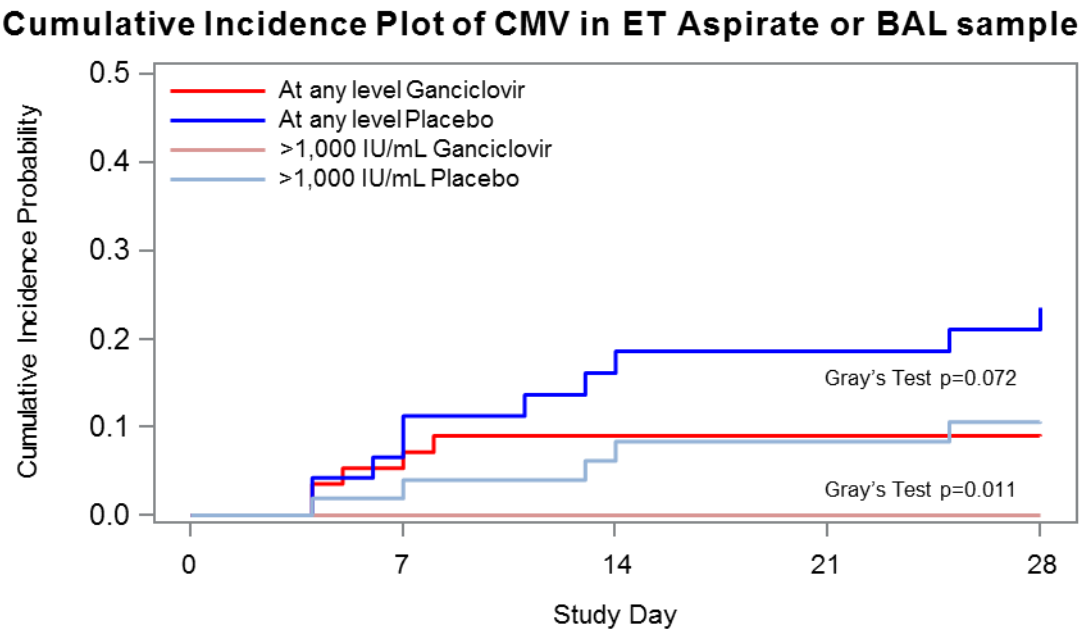
[a] From March 10, 2011 until July 9, 2012, a study-related bronchoscopy/bronchoalveolar lavage was performed on day 1 and day 7. This study procedure was eliminated on July 9, 2012 because of logistical difficulties after the first 10 study participants were enrolled.

a)



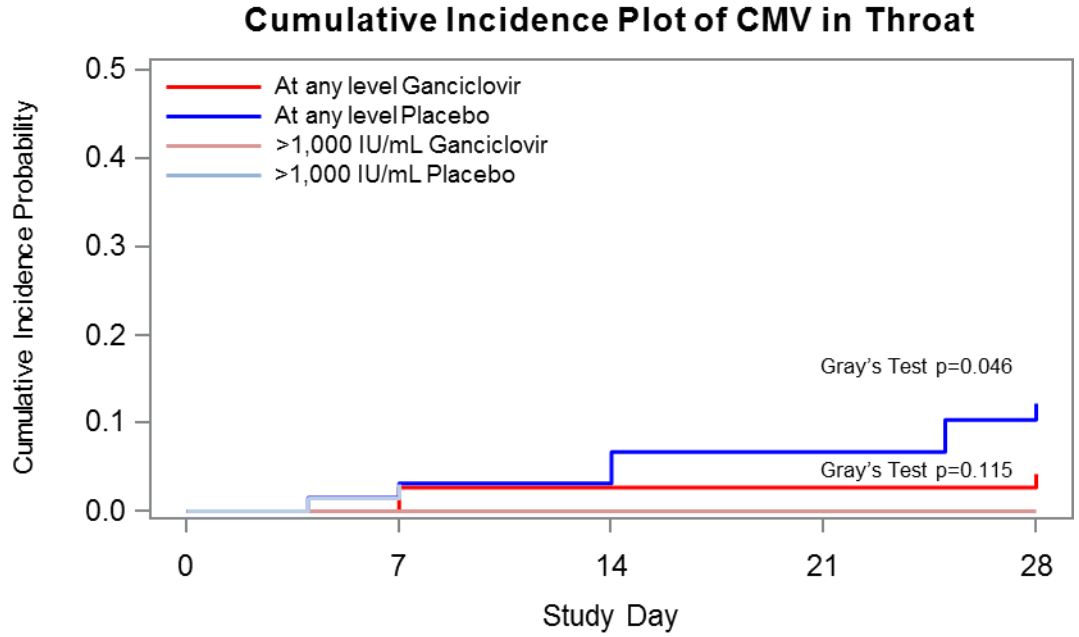
CMV at any level Ganciclovir	66	60	50	50	50
CMV at any level Placebo	59	48	37	30	28
CMV >1,000 IU/mL Ganciclovir	77	74	67	65	64
CMV >1,000 IU/mL Placebo	67	59	51	48	45

b)



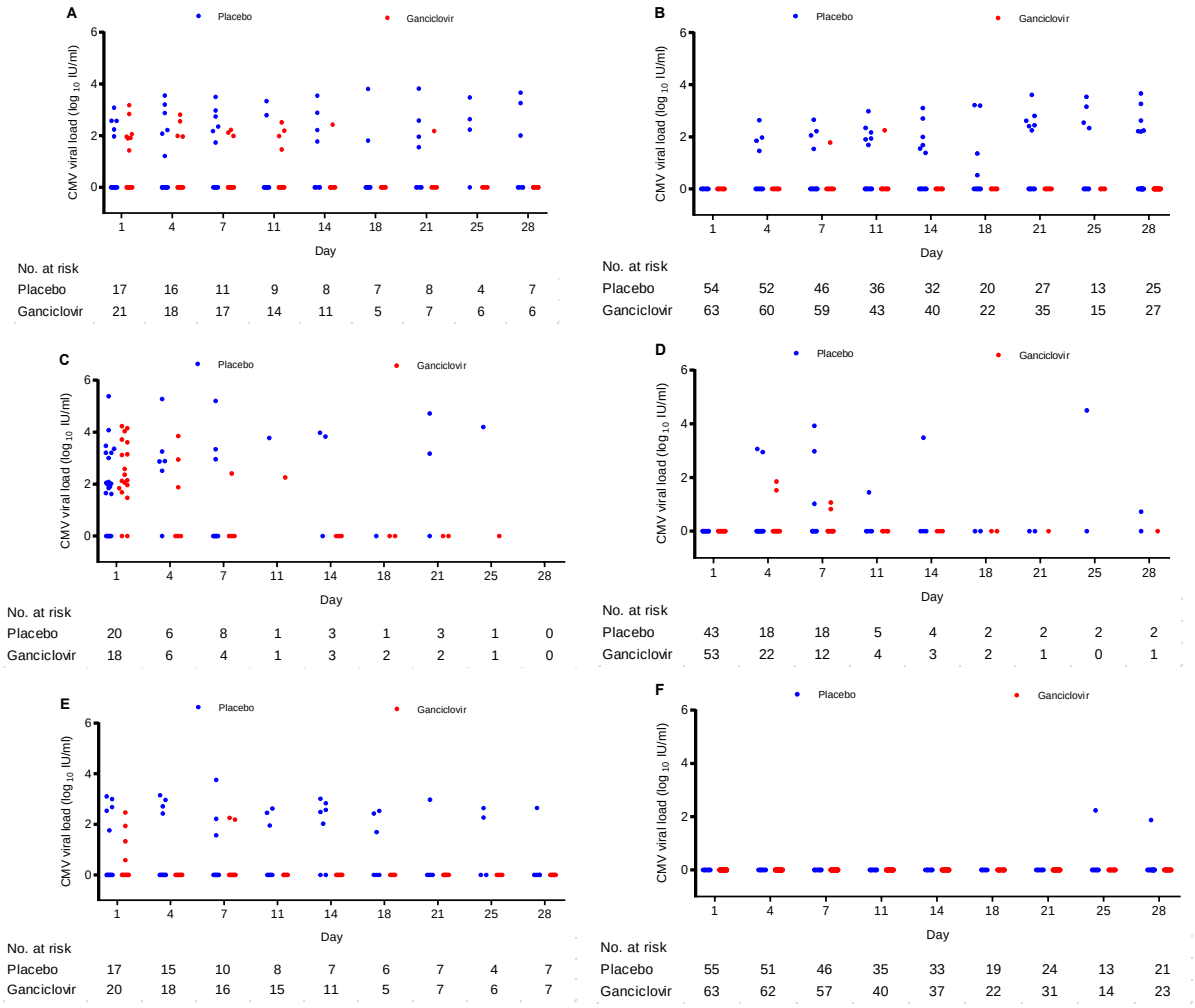
CMV at any level Ganciclovir	57	52	46	46	46
CMV at any level Placebo	49	40	34	33	32
CMV >1,000 IU/mL Ganciclovir	65	63	57	55	55
CMV >1,000 IU/mL Placebo	55	47	43	42	39

c)



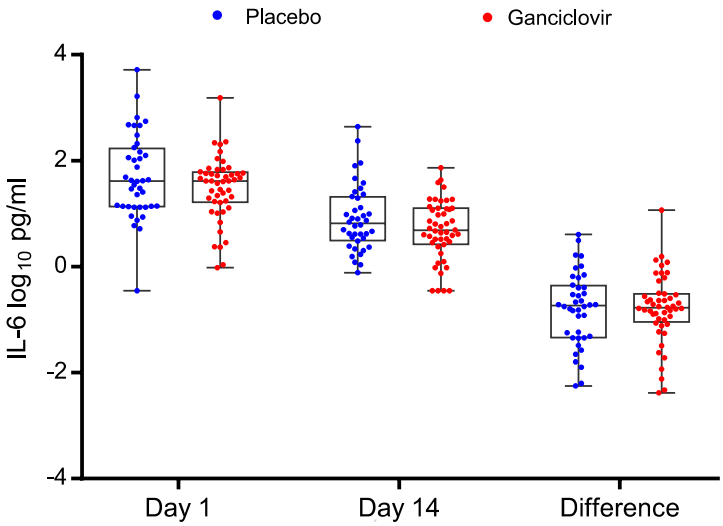
CMV at any level Ganciclovir	80	75	65	63	63
CMV at any level Placebo	68	60	54	52	49
CMV >1,000 IU/mL Ganciclovir	84	79	70	68	67
CMV >1,000 IU/mL Placebo	71	62	56	56	54

eFigure 2. Viral load by test time point in ganciclovir and placebo recipients by site with and without baseline CMV DNA detection at any site: a) viral load in plasma with baseline CMV DNA detection at any site, b) viral load in plasma without baseline CMV DNA detection at any site, c) viral load in ET/BAL with baseline CMV DNA detection at any site, d) viral load in ET/BAL without baseline CMV DNA detection at any site, e) viral load in throat with baseline CMV DNA detection at any site, and f) viral load in throat without CMV detection at any site



eFigure 3. Box-and-whisker plot[a] of plasma IL-6 levels (log10) at day1, day 14, and difference between day 1 and 14 among day 14 survivors.

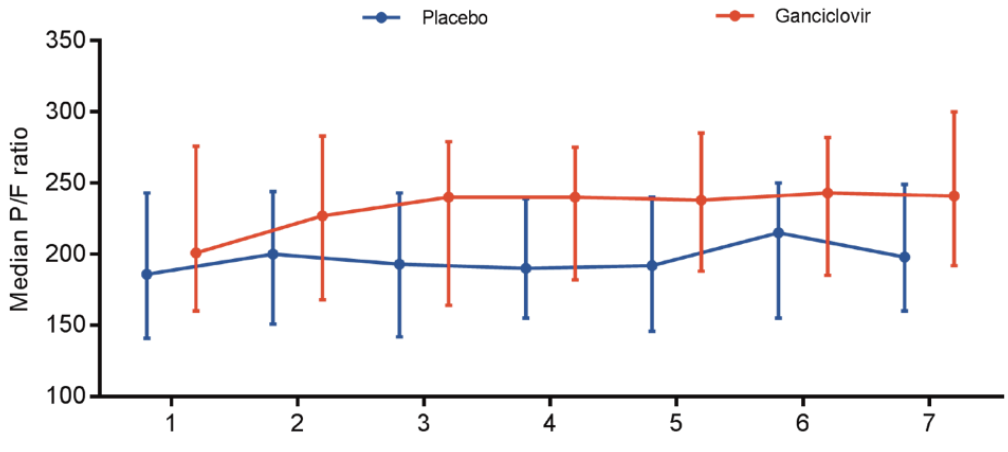
[a] Error bars indicate minimum and maximum values. Limits of the boxes indicate the first and third quartile, and the inner line represents the second quartile (median)



N	
Placebo	40
Ganciclovir	48

eFigure 4. Median PaO2 to FiO2 ratio over first 7 days of mechanical ventilation between ganciclovir and placebo groups (ITT population)[a]

[a] Error bars indicate first and third quartiles



N							
Placebo	71	70	65	55	49	44	38
Ganciclovir	84	81	75	69	58	51	42

eAppendix 2. Missing data

A detailed assessment of missing values for the primary endpoint (which required patient samples at both day1 and day 14) is shown in the table below. Of the 156 dosed participants, 88 (48 ganciclovir, 40 placebo) had paired samples assessable for the primary endpoint. 68 patients (156 minus 88) did NOT have paired d1 and d14 samples, for the reasons shown below.

Reason	n	Cumulative frequency
Early Termination	27	27
- **Death**	17	
- **Refused to further participation**	6	
- **Other**	4	
Missed visit on day 14	23	50
Sample not collected	5	55
- **Unable to process – specimen lab off site**	1	
- **Specimens processed on wrong blood tube – had to discard**	1	
- **Insufficient sample, poor venous access, difficult blood draw**	2	
- **Miscommunication with lab**	1	
Sample collected, not received by lab – possible database entry error	2	57
Discharged before obtaining sample	3	60
Refusal	3	63
Other	4	67
Unknown	1	68