Supplementary Online Content

Luyt C-E, Forel J-M, Hajage D, et al. Acyclovir for mechanically ventilated patients with herpes simplex virus oropharyngeal reactivation: a randomized clinical trial. *JAMA Intern Med*. Published online December 16, 2019. doi:10.1001/jamainternmed.2019.5713

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

eTable 1. Microorganisms Responsible for Bacteremia/Fungemia Post-Randomization According to Study Group.

Parameter	Acyclovir group (N=119)	Placebo group (N=119)
Bacteremia	38 (32)	47 (39)
Enterobacteriaceae	9 (8)	17 (14)
Pseudomonas aeruginosa	7 (6)	5 (4)
Stenotrophomonas maltophilia	3 (3)	3 (3)
Acinetobacter spp.	2 (2)	0
Enterococcus spp.	8 (7)	5 (4)
Coagulase-negative staphylococci	6 (5)	10 (8)
Staphylococcus aureus	1 (1)	1 (1)
Other cocci	2 (2)	6 (5)
Fungemia	5 (4)	5 (4)
Candida spp.	5 (100)	3 (60)
Other	0	2 (40)

Results are expressed as No. (%).

eTable 2. **Ventilator-Free Days and Mortality at Day 60 According to Subgroup Analysis.**

Outcome	**Acyclovir group**	**Placebo group**	***P* value**
Ventilator-free days at day 60, median (IQR)			
According to number of organ failures; no.			.09*
<2 organ failures at randomization; 114	49 (30–56); 57	44 (0–53); 57	.04
≥2 organ failures at randomization; 124	13 (0–43); 62	12 (0–45); 62	.9
According to MV duration; no.			.67
MV pre-randomization ≤10 days; 130	36 (0–53); 70	40 (0–50); 60	.5
MV pre-randomization >10 days; 108	35 (0–51); 49	31 (0–49); 59	.2
Day-60 mortality, no. (%)			
According to number of organ failures; no			.03*
<2 organ failure at randomization; 114	5/57 (9)	17/57 (30)	.004
≥2 organ failure at randomization; 124	21/62 (34)	22/62 (35)	.8
According to MV duration; no.			.5
MV pre-randomization ≤10 days; 130	16/70 (23)	18/60 (30)	.4
MV pre-randomization >10 days; 108	10/49 (20)	21/59 (36)	.08

MV denotes mechanical ventilation, IQR interquartile range.
* *P* value for interaction

eTable 3. Ventilator-Free Days and Day-60 Mortality According to Time of Randomization

Outcome	Acyclovir group	Placebo group	*P* value
Ventilator-free days at day 60, median (IQR)			
According to time of randomization; no.			.43*
Patients randomized before November 2016; 206	37 (0-52)	37 (0-51)	.35
Patients randomized after November 2016; 32	29 (0-53)	0 (0-42)	.20
Day-60 mortality, n (%)			
According to time of randomization; no.			.67*
Patients randomized before November 2016: 206	23 (22)	33 (32)	.12
Patients randomized after November 2016; 32	3 (19)	6 (38)	.43

IQR denotes interquartile range
* *P* value for interaction

eTable 4. Adverse Events.

Adverse event	Acyclovir group (N=119)	Placebo group (N=119)
Patients with at least 1 serious adverse event [a]	33 (28)	27 (23)
Infection	21 (18)	15 (13)
Acute renal failure	3 (3)	2 (2)
Skin rash	3 (3)	0
Cardiac arrest	2 (2)	0
Ischemic stroke	1 (1)	4 (3)
Intracranial hemorrhage	0	1 (1)
Cardiogenic shock	7 (6)	3 (3)
Hemorrhagic shock	3 (3)	1 (1)
Hepatic cytolysis	2 (2)	0
Gastrointestinal bleeding	2 (2)	2 (2)
Myocardial infarction	1 (1)	0
Herpes zoster infection	0	1 (1)
Pneumothorax	0	1 (1)
ICU re-admission after discharge	1 (1)	1 (1)
Miscellaneous	6 (5)	11 (9)

Results are expressed as No. (%).

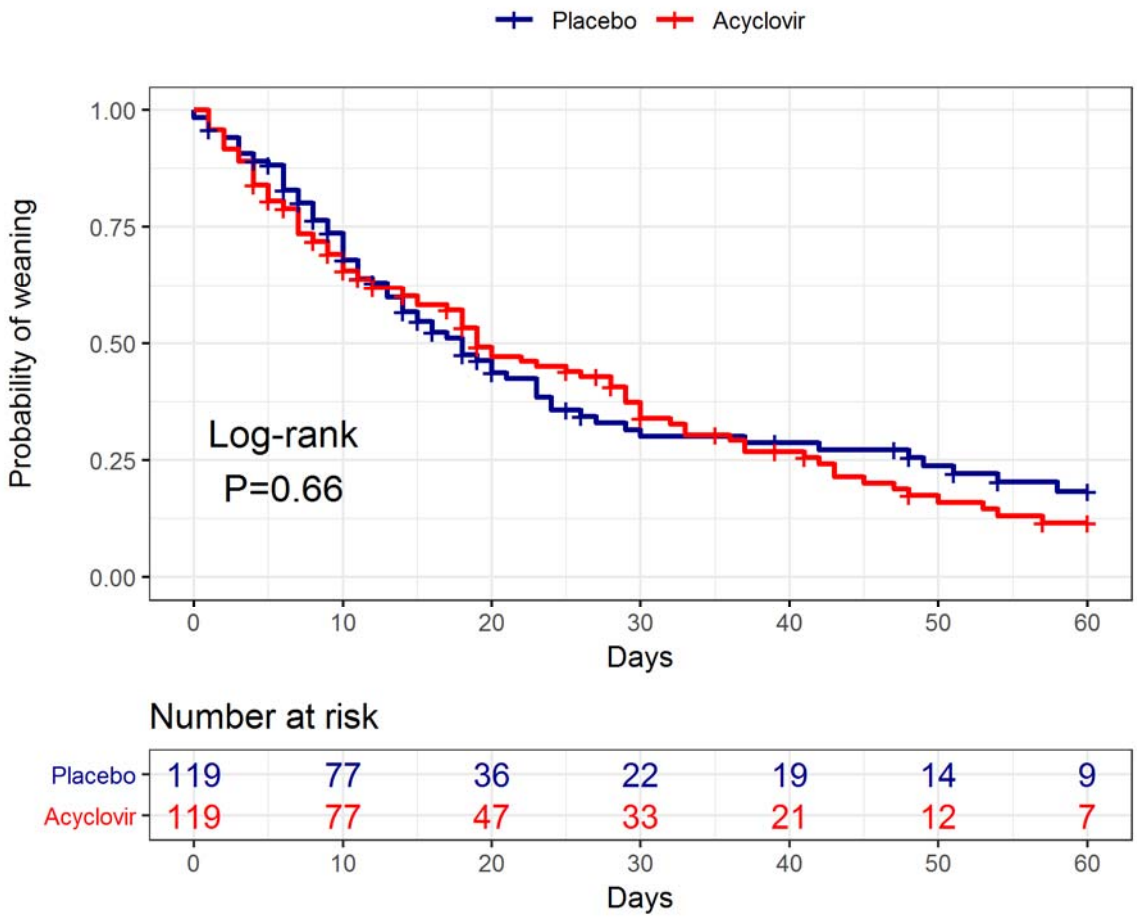
ICU denotes intensive care unit.

[a] P=.4 for between-group comparison.

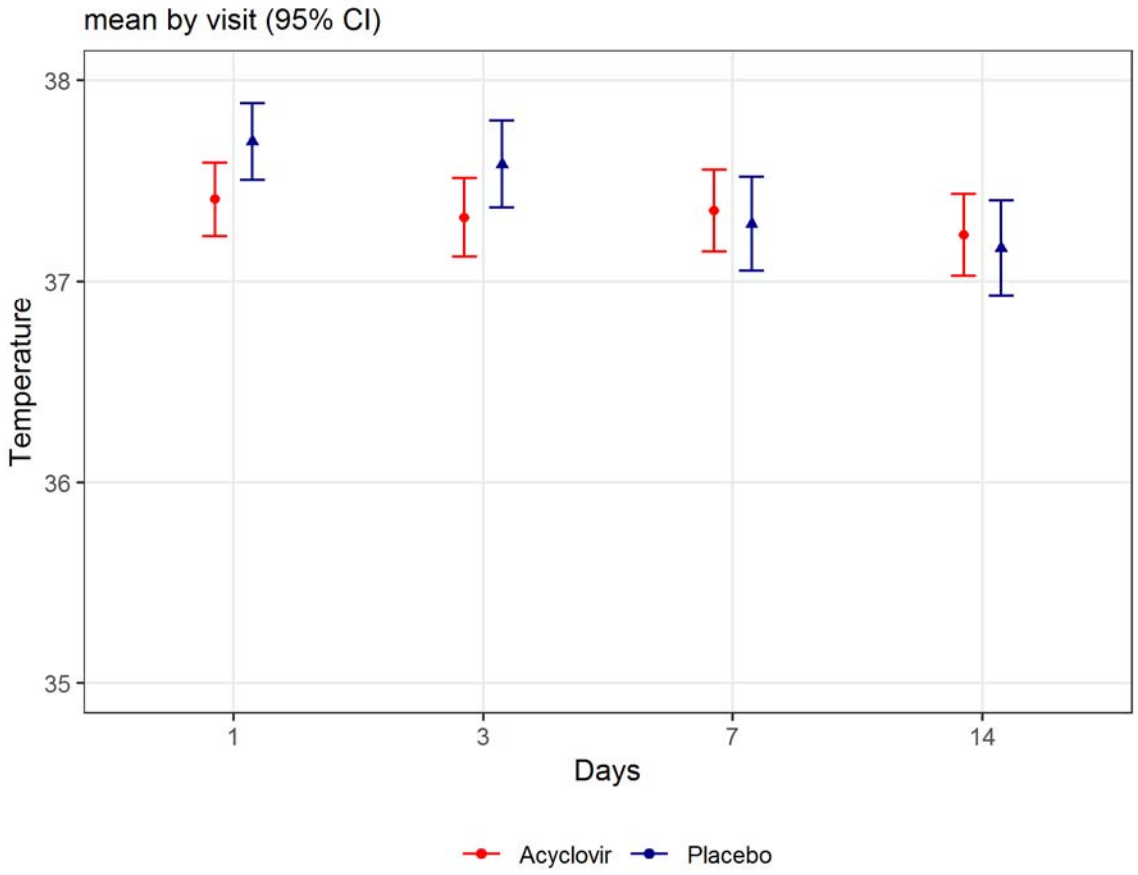
eTable 5. Percentages of Patients Receiving Renal Replacement Therapy According to Study Group from Randomization to Day 21.

Study group	Randomization	Day 3	Day 7	Day 14	Day 21
Acyclovir, no. (%)	36/119 (30)	28/119 (24)	22/115 (19)	21/110 (19)	14/104 (13)
Placebo, no. (%)	29/119 (24)	28/118 (24)	22/111 (20)	20/100 (20)	7/89 (8)

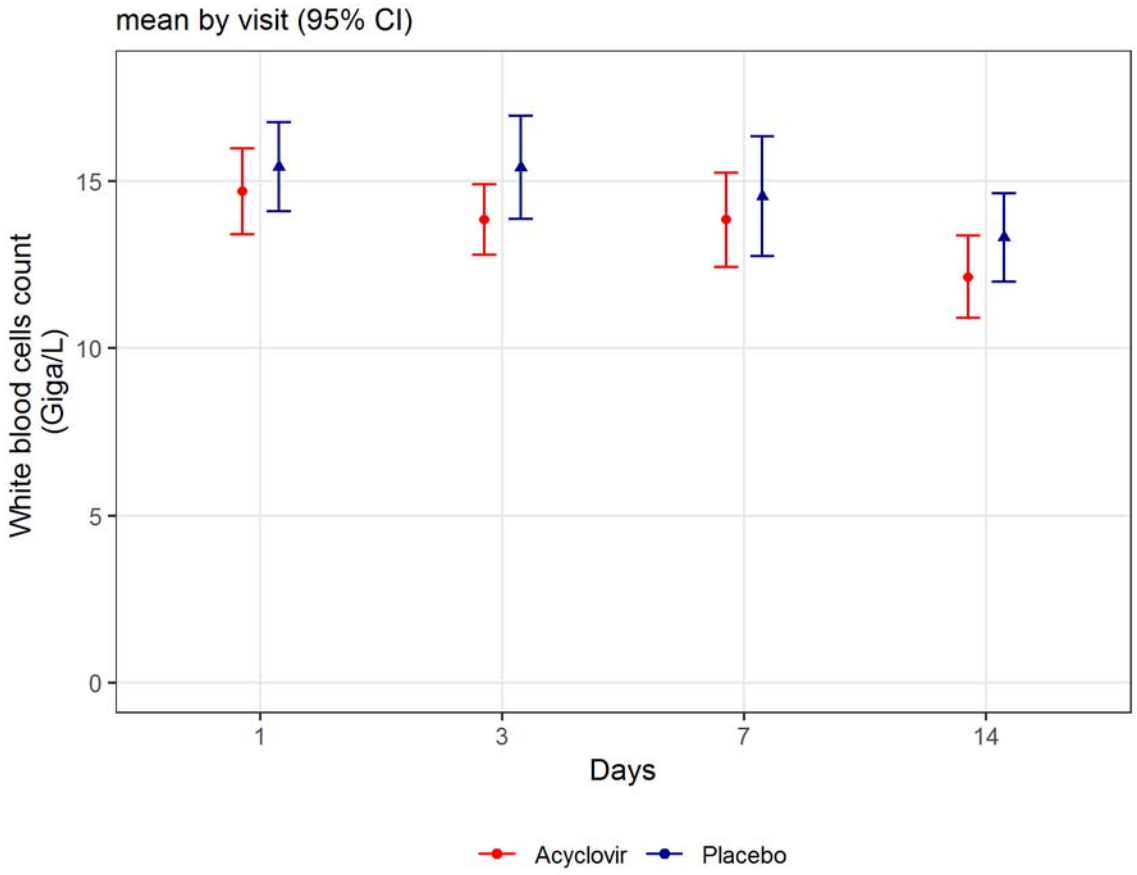
eFigure 1. Time to Weaning off Mechanical Ventilation According to Study Group.



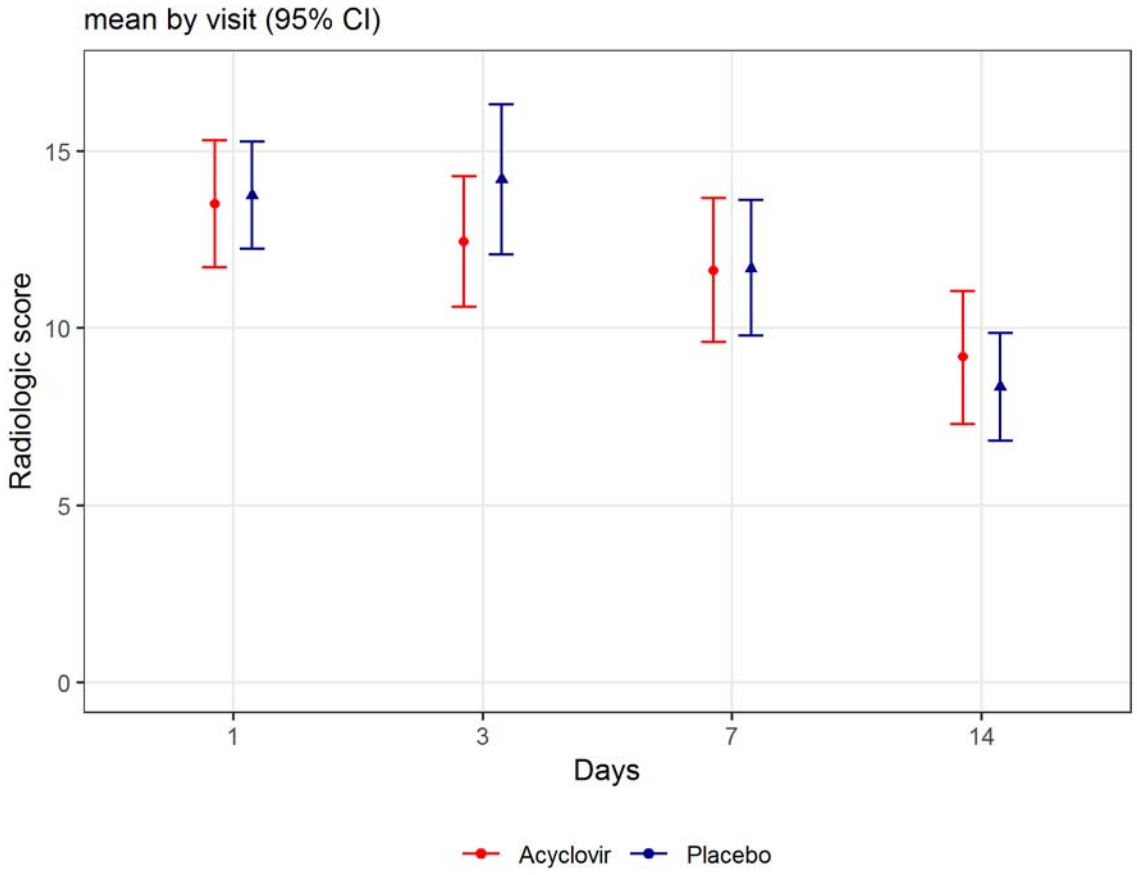
eFigure 2. Temperature Kinetics from Randomization to Day 14 According to Study Group.



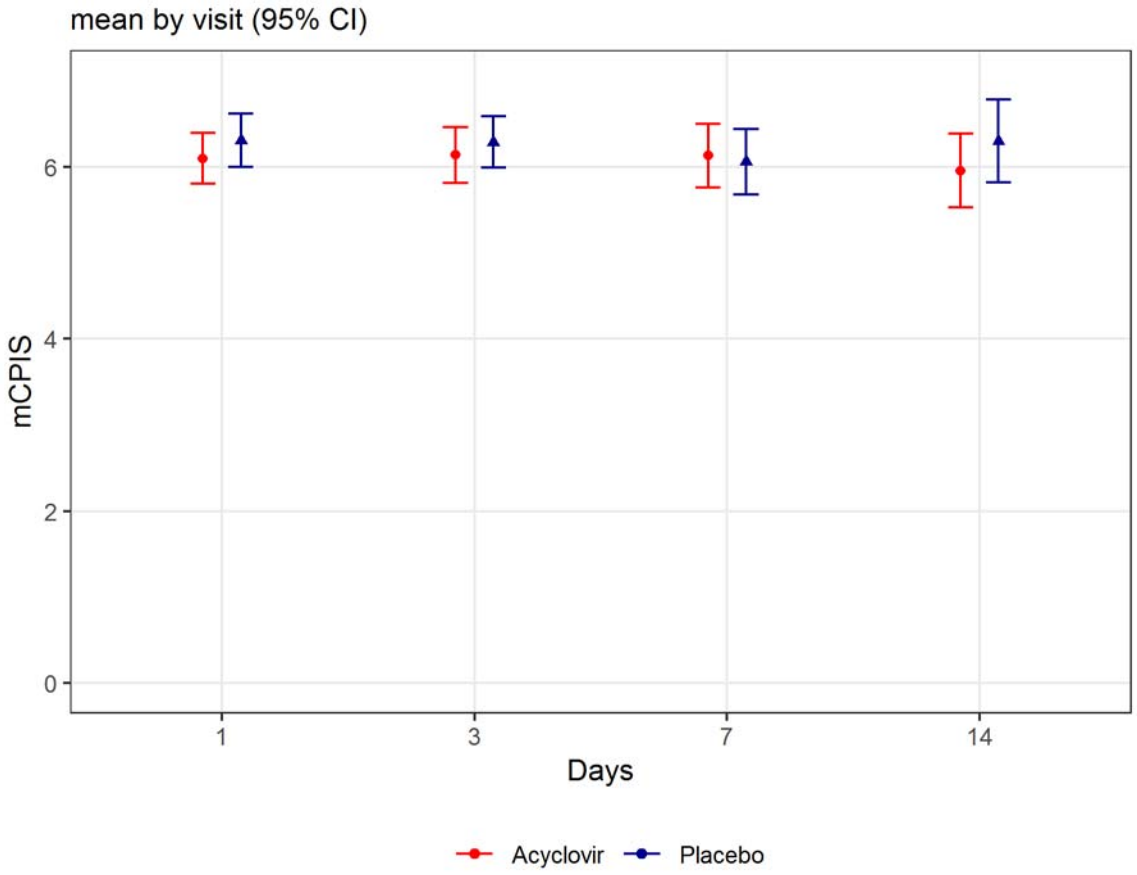
eFigure 3. White Blood-Cell–Count Kinetics from Randomization to Day 14 according to Study Group.



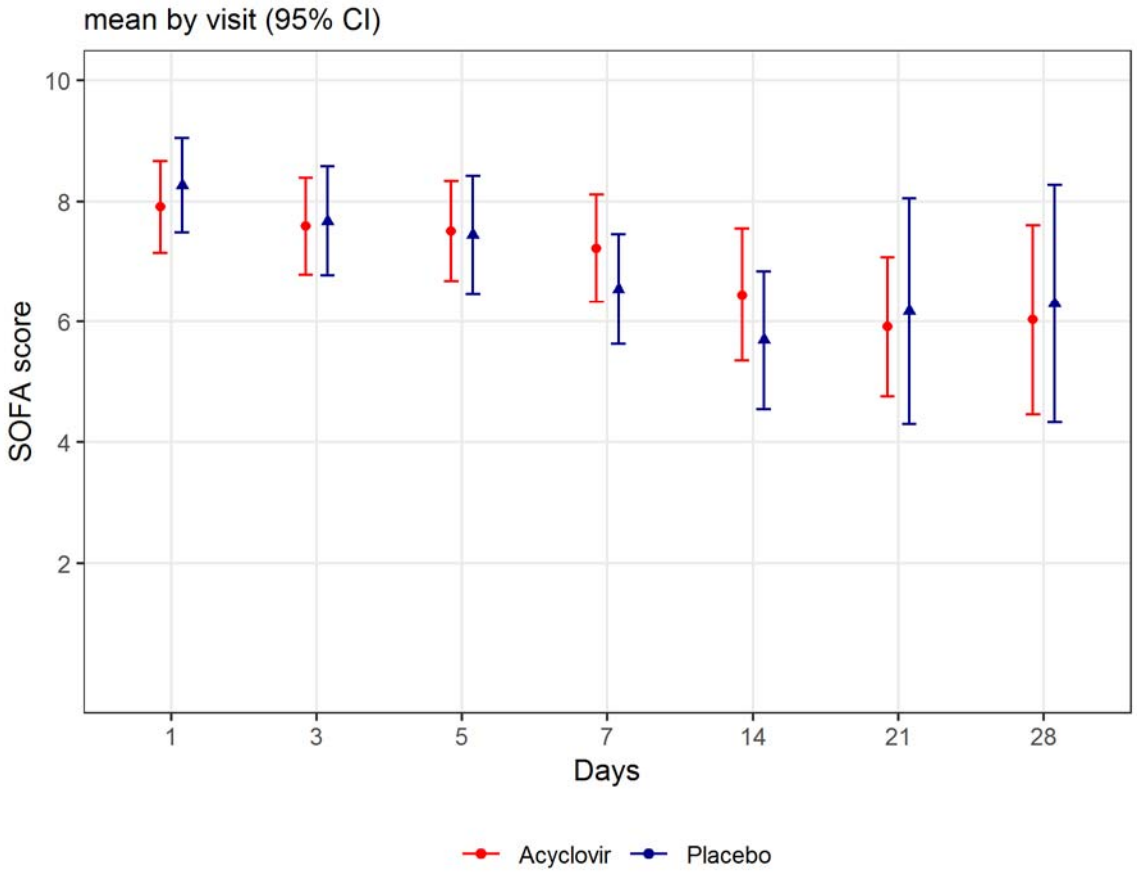
eFigure 4. Kinetics of Radiologic Score[1] from Randomization to Day 14 According to Study Group.



eFigure 5. Evolution of Modified Clinical Pulmonary Infection Score (mCPIS)[2] from Randomization to Day 14 According to Study Group.

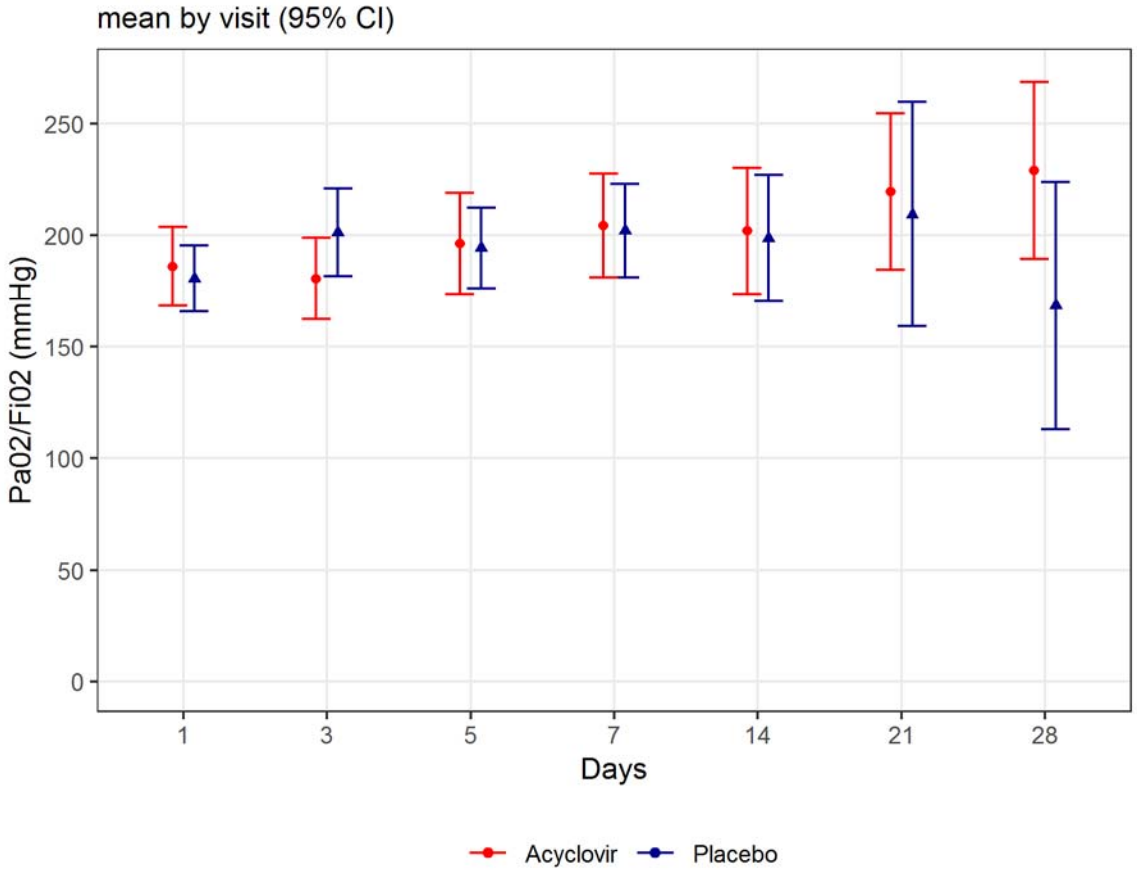


eFigure 6. Kinetics of the Sequential Organ-Failure Assessment (SOFA)[3] Score from Randomization to Day 28 According to Study Group.

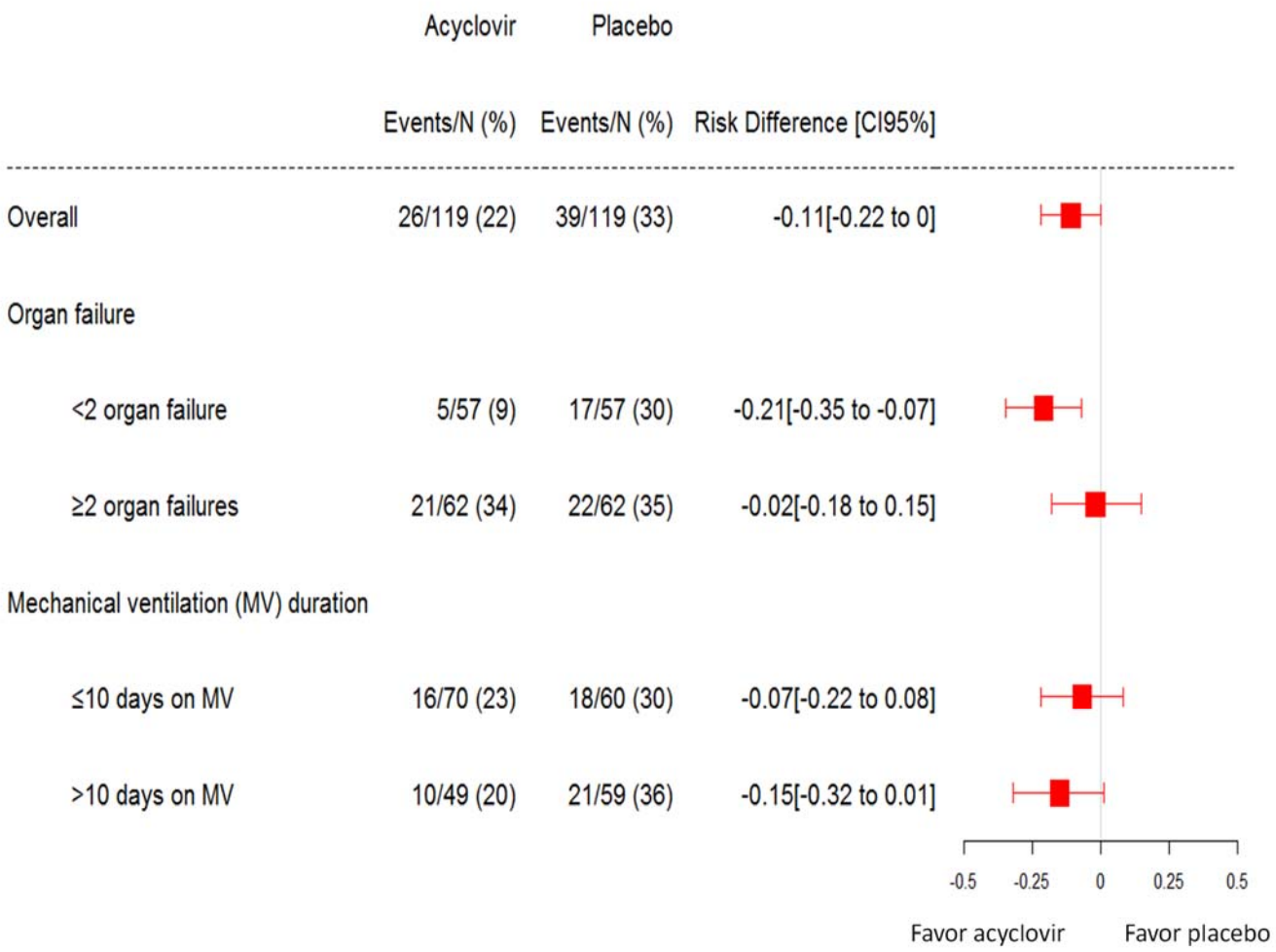


eFigure 7. Evolution of PaO_2/FiO_2 Ratio from Randomization to Day 28 According to Study Group.

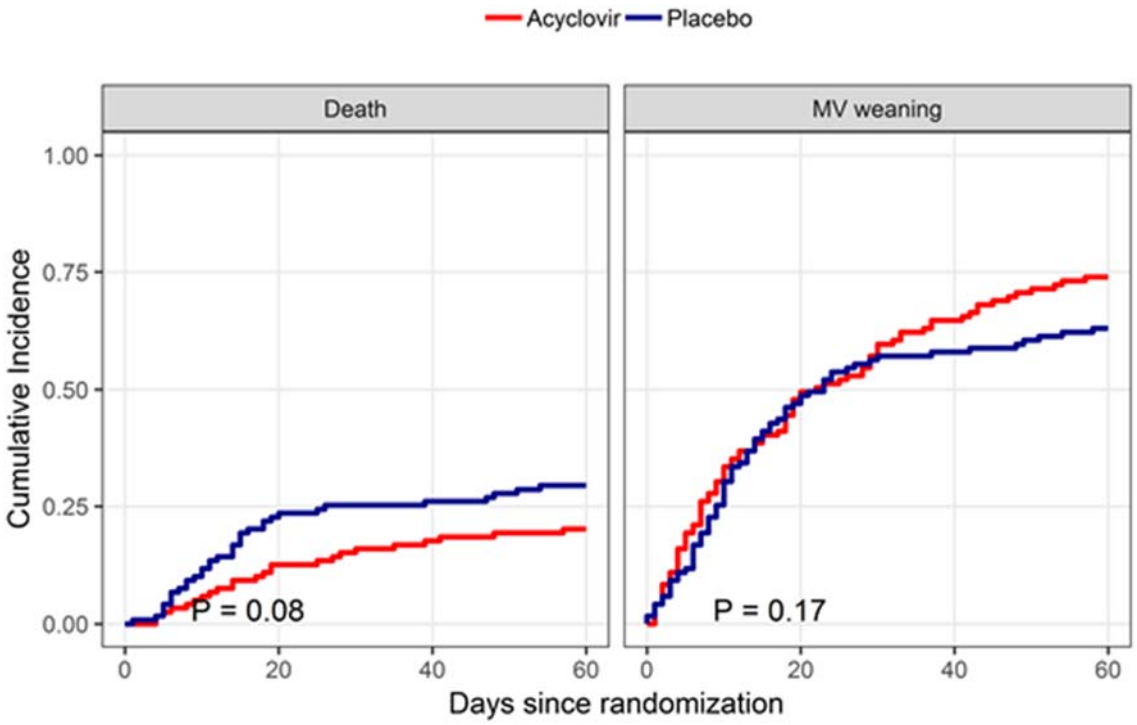
PaO_2/FiO_2 denotes partial oxygen pressure in arterial blood/fraction of inspired oxygen ratio.



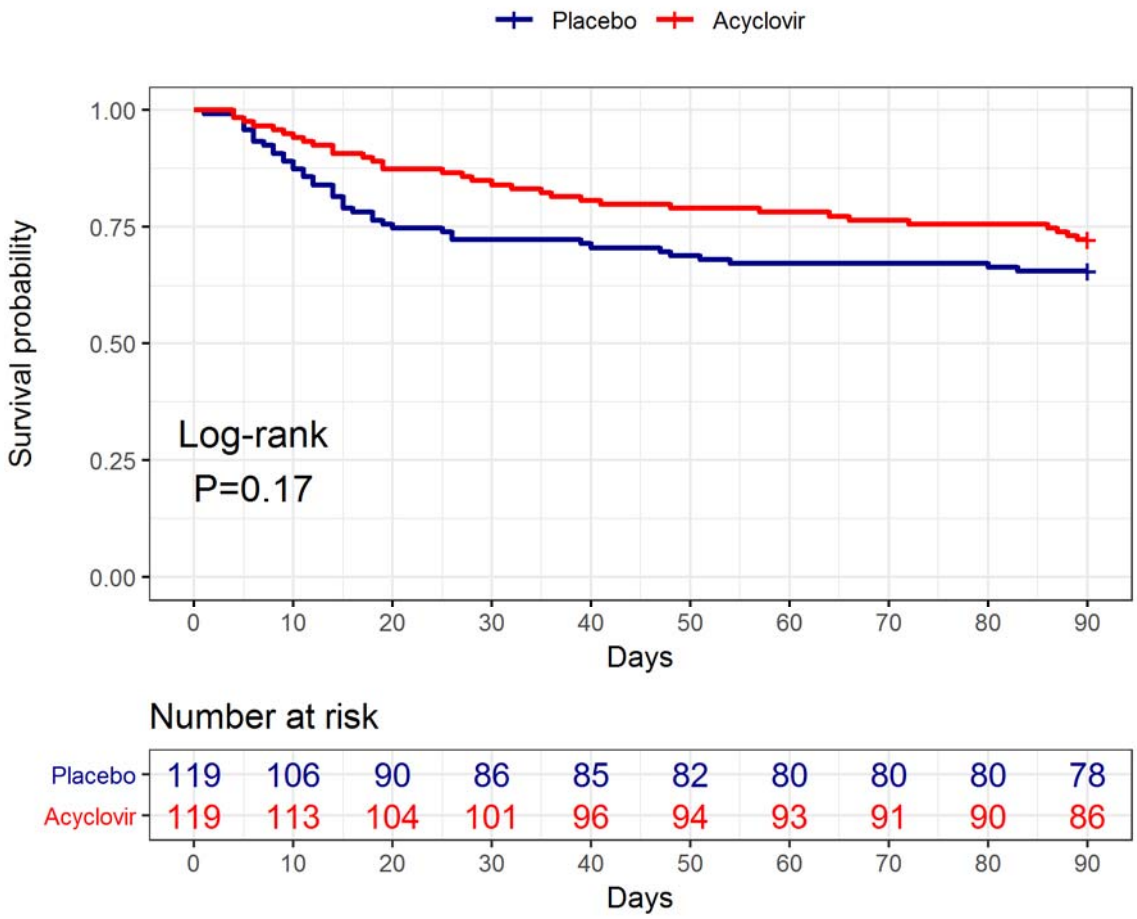
eFigure 8. Subgroup Analyses of Day 60 Mortality.



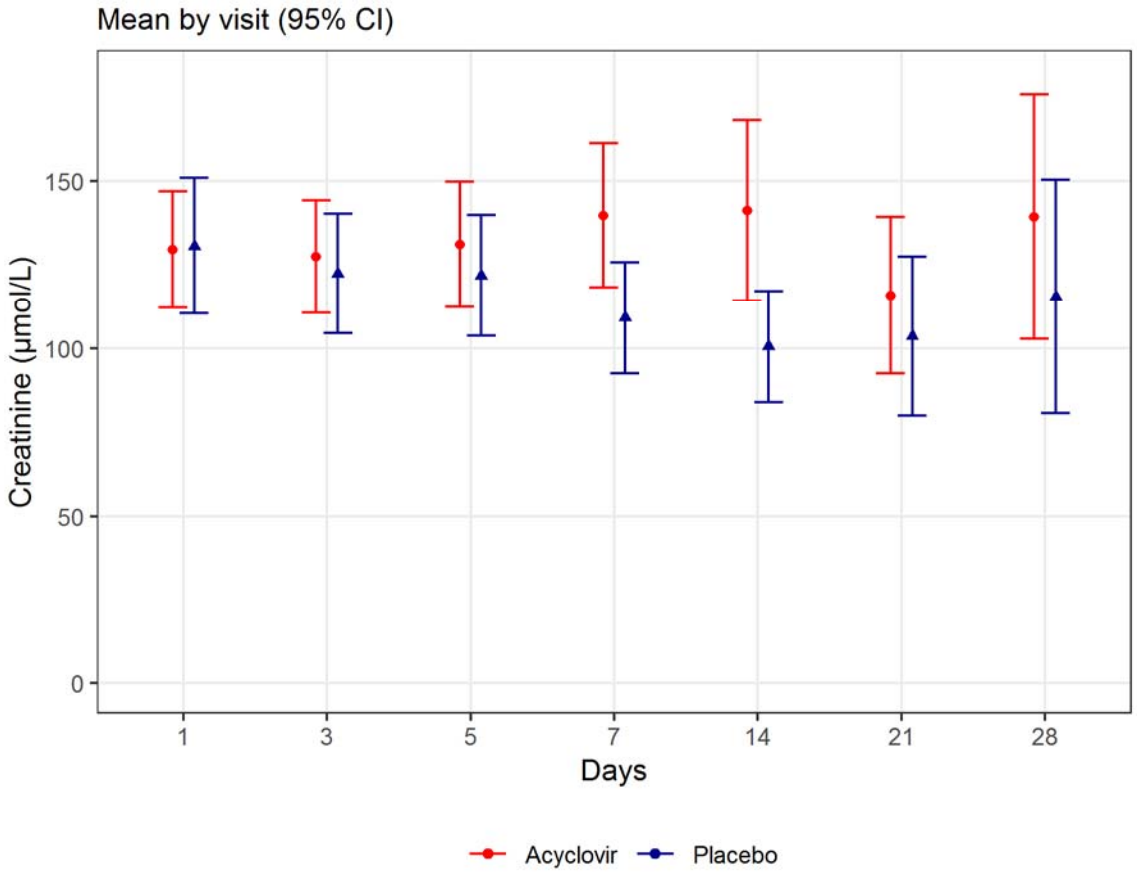
eFigure 9. Sensitivity Analysis Comparing the Cumulative Incidence of Each Event; Weaning of Mechanical Ventilation and Death



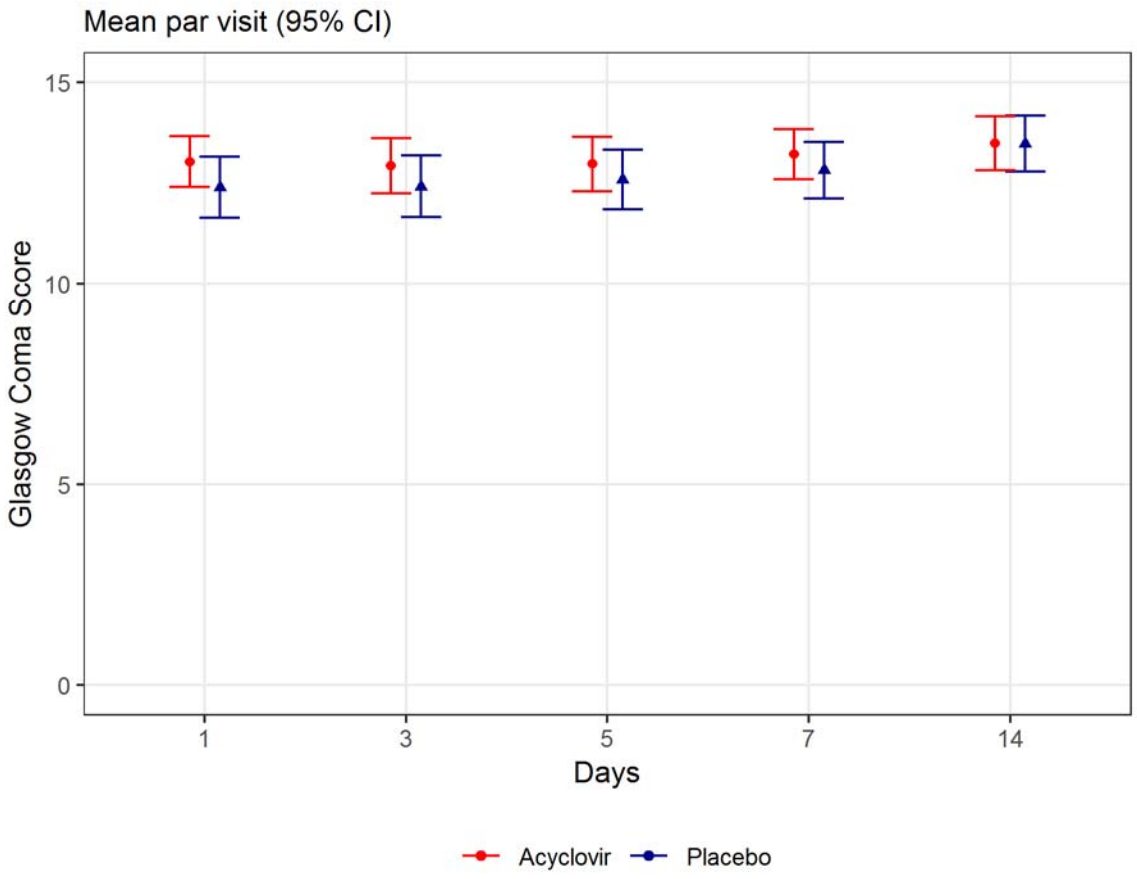
eFigure 10. Kaplan–Meier 90-Day Survival Estimates for the Intention-To-Treat Population.



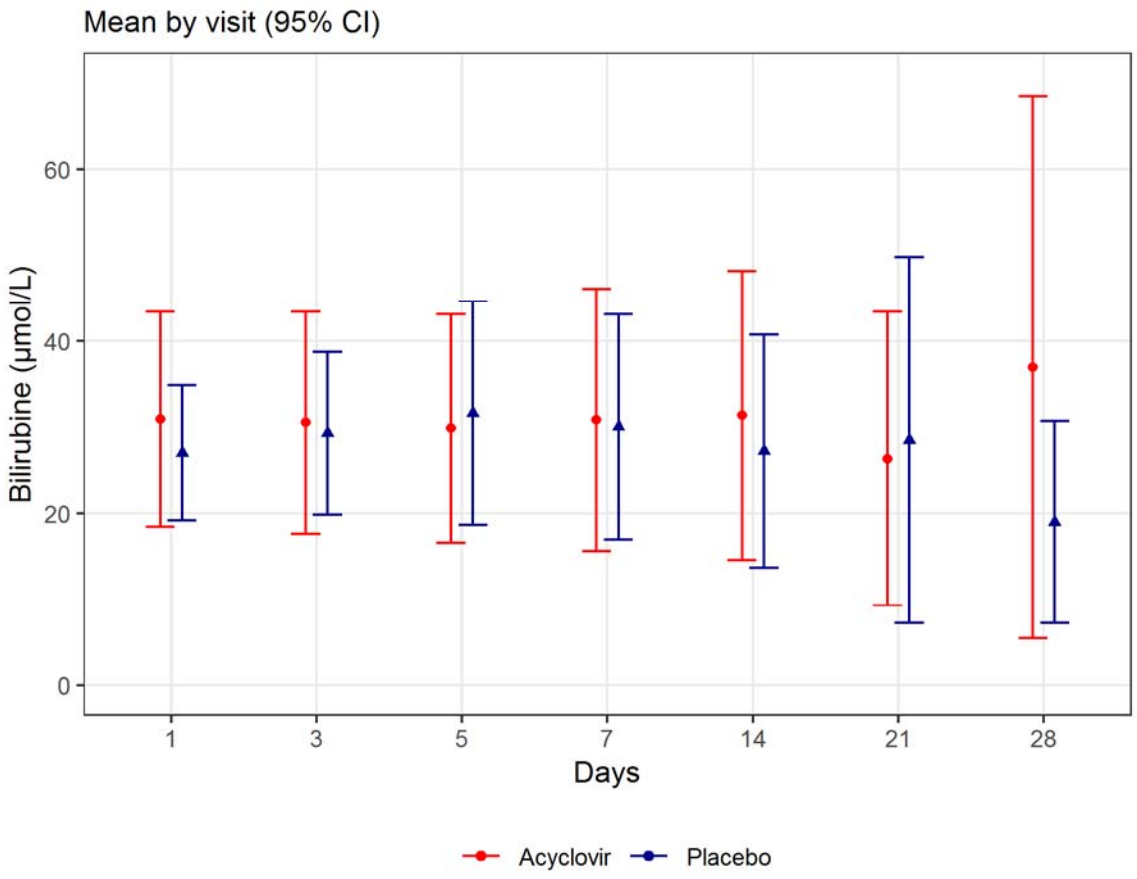
eFigure 11. Creatinine-Level Kinetics from Randomization to Day 28 According to Study Group.



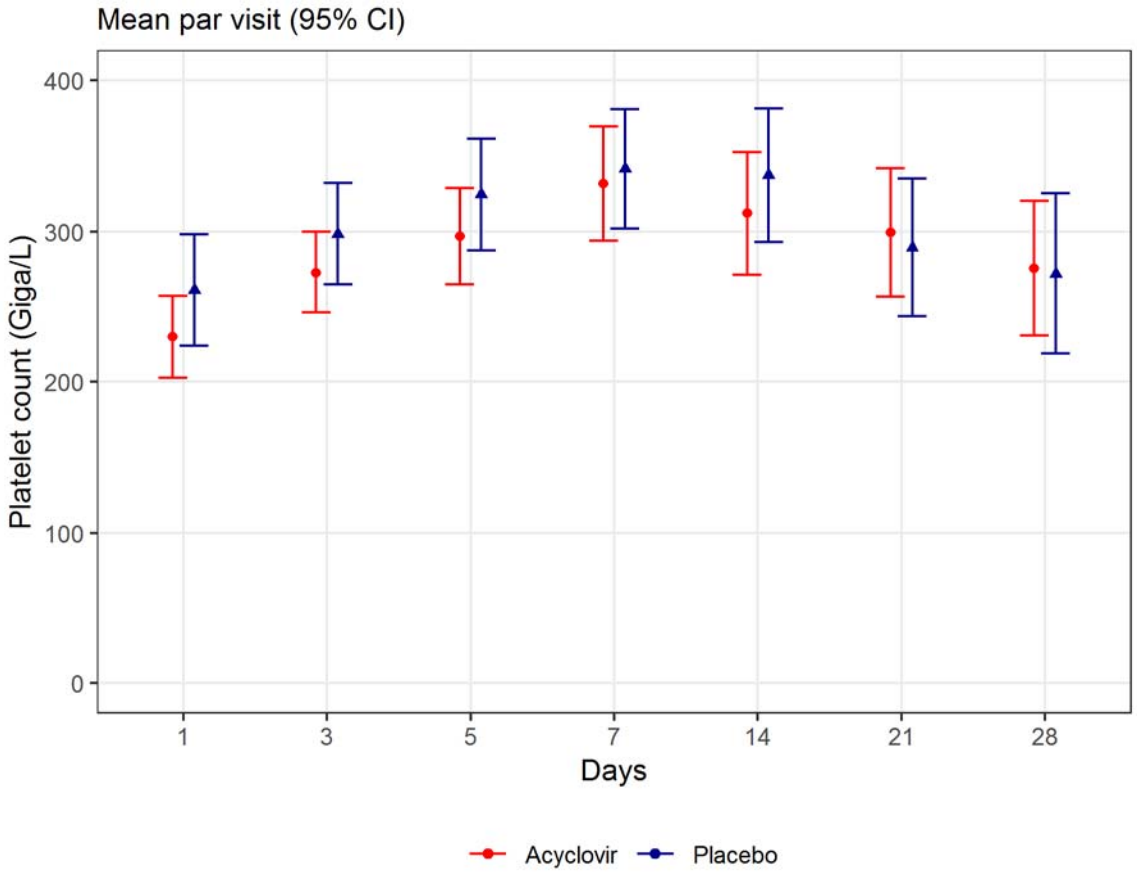
eFigure 12. Glasgow Coma Score Kinetics from Randomization to Day 14 According to Study Group.



eFigure 13. Bilirubin-Level Kinetics from Randomization to Day 28 According to Study Group.



eFigure 14. Platelet-Count Kinetics from Randomization to Day 28 According to Study Group.



eReferences

1. Weinberg PF, Matthay MA, Webster RO, Roskos KV, Goldstein IM, Murray JF. Biologically active products of complement and acute lung injury in patients with the sepsis syndrome. Am Rev Respir Dis 1984;130(5):791–796.

2. Luyt C-E, Chastre J, Fagon J-Y. Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. Intensive Care Med 2004;30(5):844–852.

3. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22(7):707–710.

