Supplemental Materials

Table S1. Baseline characteristics stratified by treatment arm and 28-day survival status

Baseline characteristic		Control Arm, N =39		Plasma Arm, N = 40	
		Survival N = 29	Death N = 10	Survival N = 38	Death N = 2
Enrollment	May-Jun 2020	8	2	9	0
	Jul-Aug 2020	8	1	10	0
	Sep-Oct 2020	3	2	5	0
	Nov-Jan 2021	10	5	14	2
Sex	Female	19	5	18	1
	Male	10	5	20	1
Age	<45	2	0	10	0
	45-60	12	3	6	0
	61-74	10	2	13	1
	75+	5	5	9	1
Race	African American	18	3	21	0
	Caucasian	10	6	12	2
	Other/Unknown	1	1	5	0
SARS-CoV-2 Serostatus	Negative	16	8	21	2
	Positive	13	2	17	0
Blood type	A, B, AB	16	5	14	1
	O	13	5	24	1
Obesity	No	12	7	22	2
	Yes	17	3	16	0
Hypertension	No	7	2	15	2
	Yes	22	8	23	0
Diabetes	No	16	4	25	2
	Yes	13	6	13	0
Congestive Heart Failure	No	27	9	30	1
	Yes	2	1	8	1
Chronic Kidney Disease	No	18	6	27	2
	Yes	11	4	11	0
Cancer	No	22	6	29	1
	Yes	7	4	9	1
Immune Deficiency	No	24	9	33	2
	Yes	5	1	5	0

Number of comorbidities	0 or 1	2	0	12	2
	2 or more	27	10	26	0
Steroid use	No	4	0	9	0
	Yes	25	10	29	2
Anti-thrombotic use	No	10	3	26	1
	Yes	19	7	12	1

Table S2. Comparison of the treatment effect in Cox regression model for mortality censored at 28 days, adjusted versus unadjusted – where each baseline factor was added one at a time.

	Treatment Effect	
	HR (95% CI)	**P-value**
Unadjusted Model	0.19 (0.04, 0.84)	0.029
Adjusted for Enrollment	0.18 (0.04, 0.81)	0.026
Adjusted for Male Sex	0.17 (0.04, 0.80)	0.024
Adjusted for Age	0.18 (0.04, 0.80)	0.025
Adjusted for Race	0.18 (0.04, 0.86)	0.031
Adjusted for SARS-CoV-2 Seronegativity	0.19 (0.04, 0.86)	0.031
Adjusted for O Blood type	0.18 (0.04, 0.85)	0.030
Adjusted for Obesity	0.16 (0.04, 0.75)	0.020
Adjusted for Hypertension	0.18 (0.04, 0.81)	0.026
Adjusted for Diabetes	0.19 (0.04, 0.87)	0.033
Adjusted for Congestive Heart Failure	0.16 (0.03, 0.76)	0.021
Adjusted for Chronic Kidney Disease	0.18 (0.04, 0.84)	0.029
Adjusted for Cancer	0.19 (0.04, 0.86)	0.032
Adjusted for Immune Deficiency	0.18 (0.04, 0.83)	0.028
Adjusted for 2 or more comorbidities	0.15 (0.03, 0.77)	0.023
Adjusted for Steroid use	0.22 (0.05, 0.98)	0.047
Adjusted for Anti-thrombotic use	0.21 (0.04, 0.99)	0.048

*Steroid use model was degenerate. All deaths were in those with steroid use in both plasma and control
* Age used 3 categories (<=60 61-74 75+), due to no deaths in the <45 category; race used 3 categories (African American, Caucasian, Other/Unknown)

Table S3. Comparison of the treatment effect in a linear regression model for the ranks of the severity score adjusted versus unadjusted – where each baseline factor was added one at a time.

	Treatment Effect	
	β (95% CI)	**P-value**
Unadjusted Model	-10.79 (-20.68, -0.89)	0.036
Adjusted Models		
Adjusted for Enrollment	-10.65 (-20.56, -0.75)	0.038
Adjusted for Male Sex	-10.55 (-20.60, -0.50)	0.043
Adjusted for Age	-10.94 (-20.47, -1.42)	0.027
Adjusted for Race	-11.58 (-21.61, -1.56)	0.026
Adjusted for SARS-CoV-2 Seronegativity	-10.26 (-19.81, -0.71)	0.038
Adjusted for O Blood type	-10.62 (-20.71, -0.52)	0.043
Adjusted for Obesity	-11.72 (-21.57, -1.86)	0.022
Adjusted for Hypertension	-9.76 (-19.88, 0.36)	0.062
Adjusted for Diabetes	-10.38 (-20.46, -0.30)	0.047
Adjusted for Congestive Heart Failure	-11.55 (-21.69, -1.40)	0.029
Adjusted for Chronic Kidney Disease	-10.36 (-20.36, -0.37)	0.046
Adjusted for Cancer	-10.78 (-20.74, -0.81)	0.037
Adjusted for Immune Deficiency	-10.60 (-20.52, -0.68)	0.040
Adjusted for 2 or more comorbidities	-10.42 (-21.15, 0.30)	0.061
Adjusted for Steroid use	-11.41 (-21.48, -1.35)	0.029
Adjusted for Anti-thrombotic use	-11.12 (-21.72, -0.53)	0.043

Figure S1. Kaplan-Meier survival curves censored at Day 28 by treatment arm (top panel; log-rank test p value= 0.013). Cumulative incidence curves for discharge (bottom panel; p value = 0.006).

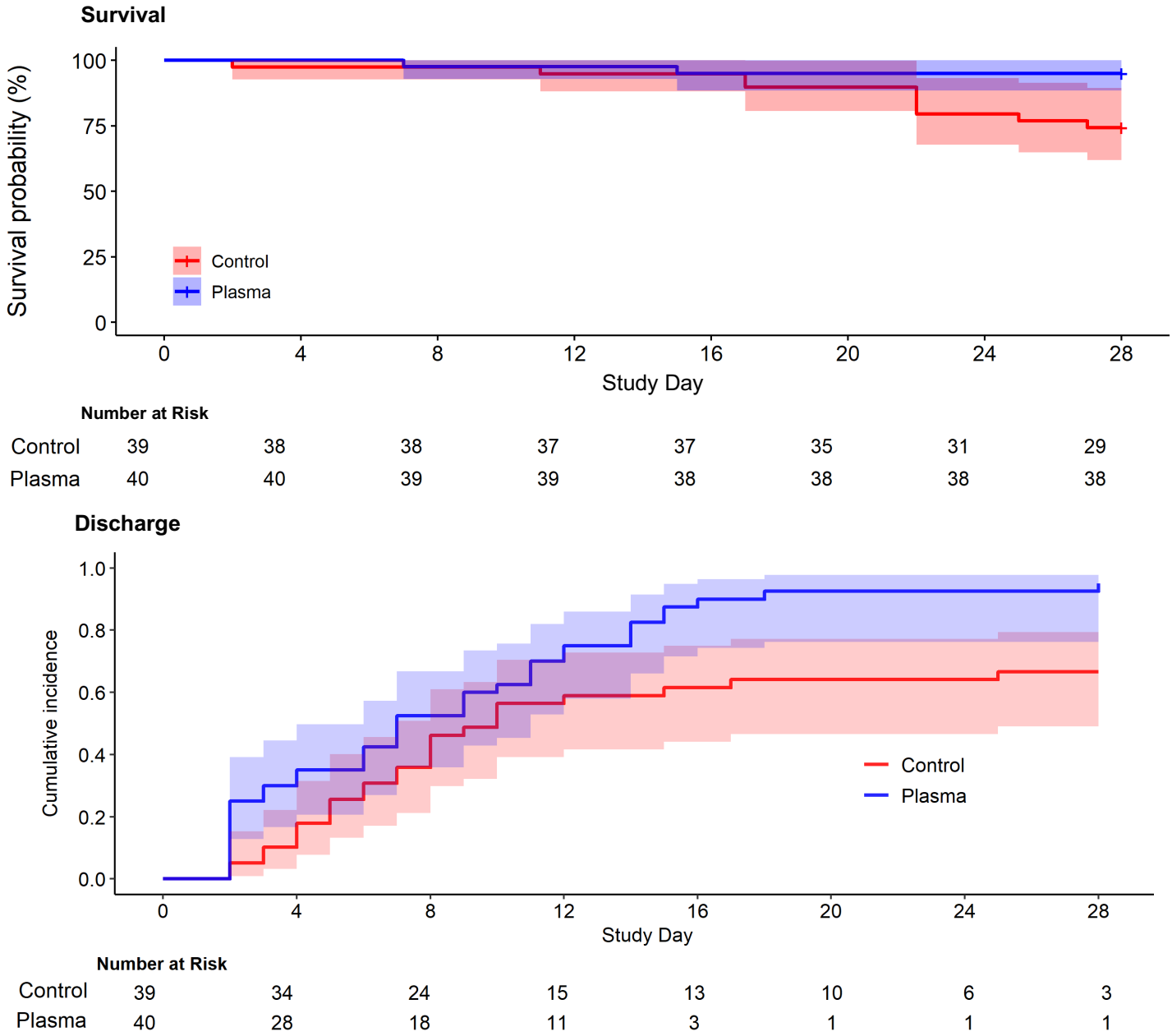
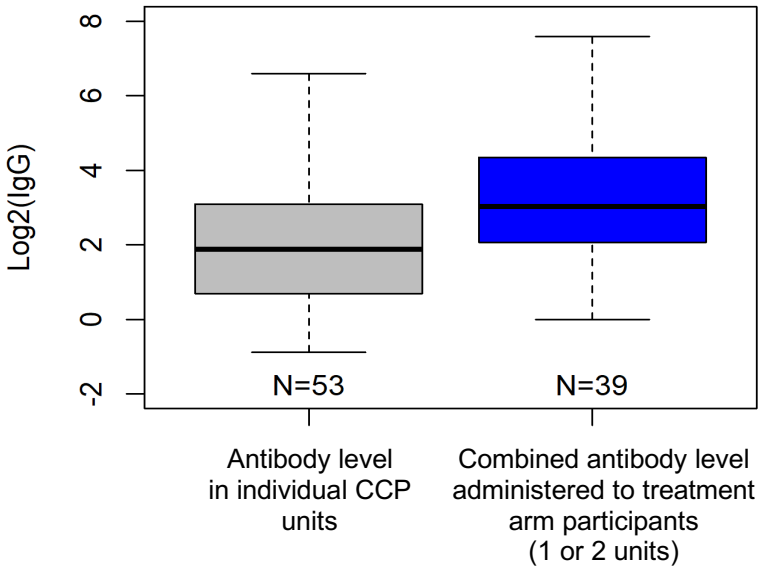
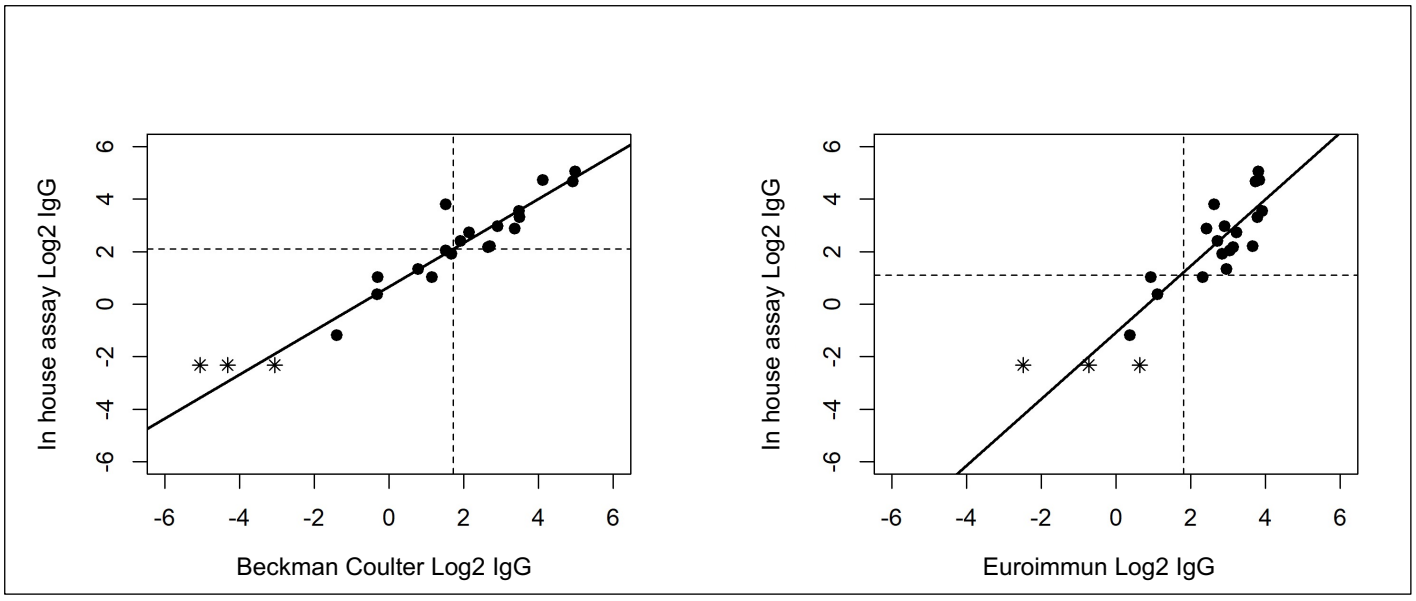


Figure S2. Donor plasma anti-SARS-CoV-2 RBD IgG levels.



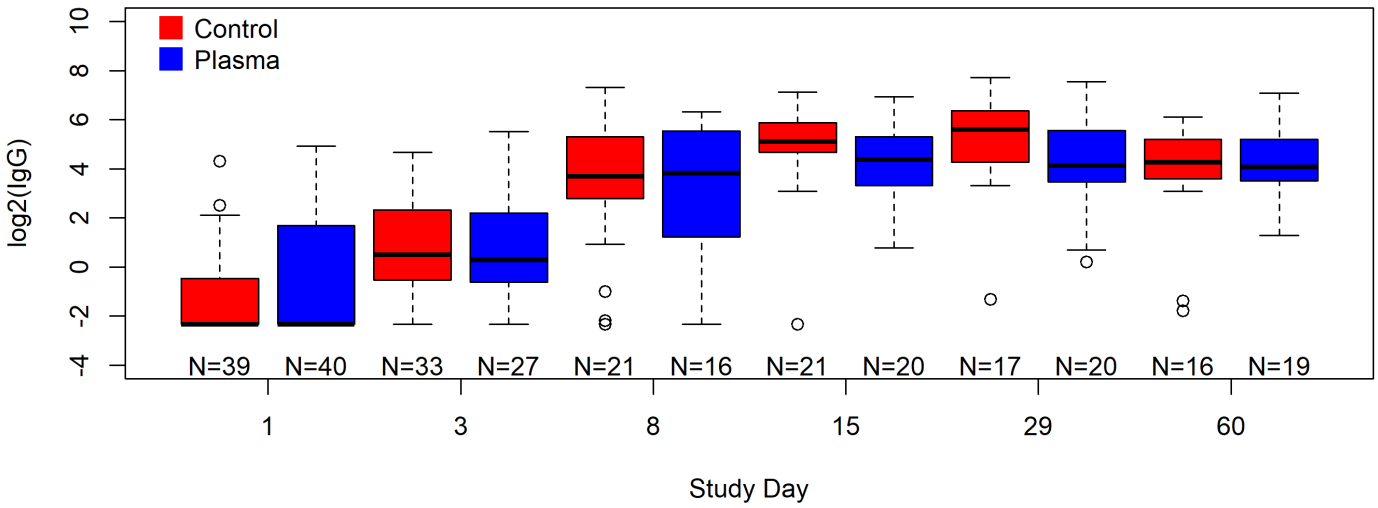
Median (IQR) of anti-SARS-CoV-2 RBD antibody levels measured in plasma from each of the CCP units used in the study (at left) and the median (IQR) of the combined antibody levels received by each of the 39 plasma recipients (in the one or two donor units administered) in the treatment arm (at right).

Figure S3. Correlation between in house and commercial (Beckman and Euroimmun) anti-SARS-CoV-2 RBD IgG assays.



Comparisons of the anti-RBD SARS-CoV-2 antibody titers as measured by in-house anti-RBD assay[19] (Y-axis) and two FDA-approved commercial assays, Beckman Coulter (left) and Euroimmun (right). Vertical dashed lines are at defined commercial assay cutoffs for “high-titer” plasma of log2(3.3) = 1.722 and log2(3.5) = 1.807 for Beckman Coulter and Euroimmun, respectively. Solid line is the linear model predicting the in-house assay levels, displayed as log2 IgG, excluding the three * points that are plasmas with undetectable values by this platform, log2(0.20)= -2.322. The horizontal dashed lines are the estimated high-titer cutoff value for the in-house assay level equivalents of log2 (4.296)= 2.103 and log2 (2.153)=1.106 by Beckman Coulter and Euroimmun, respectively.

Figure S4. Anti-SARS-CoV-2 levels



The median and IQR of anti-SARS-CoV-2 antibody levels were measured in available plasmas at baseline and study days 3, 8, 15, 29 and 60, segregated by control arm participants (red) and treatment arm participants (blue).

Statistical Analysis Plan for CCP2

Section 1. Clinical Endpoints

Primary Endpoint
Clinical severity score based on death and recovery endpoints (see Section 2)

Secondary Endpoints

- 14-Day Mortality (binary endpoint)
- Day 14 WHO8 score
- 28-Day Mortality (binary endpoint)
- Day 28 WHO8 score
- Receipt of mechanical ventilation in-hospital through day of discharge/Day 28
- Number of days on Mechanical ventilation in-hospital through discharge/Day 28
- Number of days of oxygen support in-hospital up to discharge/Day 28
- Maximum grade AE through Day 28
- Numbers of AE through Day 28
- Time to death, censored at Day 28
- Time to discharge, censored at Day 28

Section 2. Calculation of primary endpoint statistical severity score.

This calculation follows Shaw and Fay (Statistics and Medicine, 2016). Let

Delta_death28 = binary indicator if died before day 28
Delta_disch28 = binary indicator if recovered (discharge or WHO8=3 or less) by day 28
ttdeath = day of death
ttdischarge = day of recovery (discharge or first day WHO8=3 or less)

If there are no ties for day of death or day of discharge this is what it will be:

Severity_score = delta_discharge28 * (ttdischarge) + (1-delta_discharge28)*(1-delta_death28)*29 +
(1-delta_discarge28)* delta_death28* (29+ (29-ttdeath)) (Eq 1)

Thus, if recovered on or before day 28, and surviving through Day 28, gets a score of 1-28; the best score (least severe) is a 1 and goes to the person who recovered on Day 1.
For someone who is alive but still in hospital at day 28 with WHO8 score >3, the clinical severity score is 29.
Next worse score is 30, which is if you died on day 28
Absolute worst severity score is 57 (29+28), which is if died on day 1.

Examples: Here are 7 people, using formula

Patient 1, died day 1, score= 57
Patient 2 died day 12, score = 29+(29-12)= 46
Patient 3 died day 28, score = 29+ (29-28)= 30
Patient 4 in hospital alive day 28, score= 29
Patient 5 recovered day 28, score= 28
Patient 6 recovered day 12, score= 12
Patient 7 recovered day 1, score= 1

According to this formula (Eq 1), all deaths have a higher severity score compared to those who survive; quicker deaths have a worse score (larger rank); quicker recovery/discharges have a better score (lower rank).

Severity score in case of ties amongst survivors (clinical severity score <30):

For patients who die on same day or recover on the same day, their severity with no further modification would be tied. For purposes of ranking patients, the clinical severity score, in cases of ties amongst survivors, will be further refined by considering other endpoints in a prioritized fashion, according to this order, stopping once the time has been broken.

1. Max WHO8 score while in-hospital between Day 1 and first of (day of discharge, day 28)
2. Number of days on any O2 support while in-hospital between Day 1 and first of (day of discharge, day 28)
3. Numbers of days on mechanical ventilation between Day 1 and first of (day of discharge, day 28)
4. Highest grade AE between Day 1 and first of (day of discharge, day 28)
5. Total number of AE reported and first of (day of discharge, day 28)

Example
Suppose there are exactly two patients, Patients 1 and 2, who both recover on Day 26. This means that according to Eq 1, two patients have a clinical severity score of 26. Suppose the worst WHO8 score is a 7 for both of these patients. Thus, we move onto endpoint #2, Days of oxygen support, in order to break the tie in clinical severity. If Patient 1 had 18 days of oxygen support and Patient 2 had 23 days of oxygen support, then Patient 1 would get a score of 26 and Patient 2 would get a score of 26.5. In this manner, Patient 1 has a better (lower) clinical severity score than Patient 2. Because we will analyze these scores using a non-parametric Wilcoxon rank sum test, the size of the difference between the scores is not important, only that the scores will result in a clear ranking of better or worse (i.e., $26 < 26.5$), while preserving the overall order with respect to the other patients who survived longer or shorter amount of time.

Missing Data in Survival status

In the MITT cohort (N=79), all but 2 subjects had complete information for their Day 29 Study visit. Subject 21 did not receive study treatment and withdrew on Study Day 9, the day of discharge. Subject 21 is assumed to have survived through Day 28. A second subject (Subject 71) had a WHO8 score of 1 on Day 15 and a WHO8 score of 1 on Day 60.

Section 3. Statistical tests for unadjusted treatment comparisons

Note one randomized person (subject 43) dropped out on Day 1 (day of randomization) without any treatment. This person is excluded from the modified intent to treat analysis (MITT, N=79). Some imputation is needed. Subject 21 discharged and withdrew on Day 9, they will be assumed to live through day 28 for the primary analysis. Sensitivity analyses will also be considered.

Table 1 Unadjusted statistics.

Endpoint	Statistical test	Missing data Comments
Primary		
Clinical severity score	Wilcoxon rank sum, asymptotic p-value	Assume early withdraw survives 28 days. Pt 21
Secondary		
14-day mortality	Fisher's exact; Clopper-Pearson 95% confidence intervals	Assume early withdraw survives 28 days. Pt 21
Day 14 WHO8 score	Proportional odds model	Assume early withdraw survives 28 days. Pt 21 withdrew on day 9 Impute day of discharge (DOD) score as Day 14 WHO8 score if missing this score. Pt 21, missing day 14 WHO8, impute DOD WHO8

28-day mortality	Fisher's exact; Clopper-Pearson 95% confidence intervals	Assume early withdraw survives 28 days. Pt 21
Day 28 Who 8 score.	Proportional odds model	Assume early withdraw survives 28 days. Impute closest of Day of discharge (DOD) score or Day 14 as Day 28 WHO8 score if missing this score. Pt 21: use DOD WHO8
% receiving Mechanical ventilation in-hospital: at any time between Day 1 and first of day 28/discharge	Fisher's exact; Clopper-Pearson 95% confidence intervals	No missing data
Days of mechanical ventilation (MV)	Lachenbruch test (SMMR 2002)	Days censored at Day 28, For Lachenbruch, add together chi-squared test for proportion who had any MV + Wilcoxon for number of MV days, and compare to a chi-squared 2 (5.99 is critical value for 0.05) If the two tests (proportion & Wilcoxon, are in different directions for the two groups then use the vaccine two-part randomization test of Proschan and Hu.
Days of any Oxygen support in hospital: up to first of day of discharge or Day 28	Wilcoxon	No missing data
Maximum grade AE per subj	Proportional odds model	Count max AE grade observed through Day 28.
Numbers of AE per subj through Day 28	Lachenbruch test	Count AE through Day 28, For Lachenbruch, Add together chi-squared test for proportion who had any AE + Wilcoxon for number of AE. and compare to a chisquared 2 (5.99 is critical value for 0.05) If the two tests (proportion & Wilcoxon, are in different directions for the two groups then use the vaccine two-part randomization test of Proschan and Hu.
Time to death, censored at Day 28	Log rank; HR and pvalue can be from log-rank test.	Note: 1 person imputed to survival to Day 28 (Pt 21 withdrew on DOD, Day 9). Then no missing data for survival data in analysis of time to death censored at Day 28, can use traditional Kaplan-Meier curve and Peto-Peto logrank test (rho=1 in survdiff).
Time to discharge, censored at Day 28	Wald test for the HR from the cause specific Cox proportional hazards model, treating death as a competing risk	Need to plot cumulative incidence curves for time to discharge, but interested in the cause-specific HR and p-value, and not the Gray's test.
Exploratory/supportive		
Oxygen support as a 3-level ordinal variable: None, non-invasive, invasive	Proportional odds model, with linear treatment effect	Optional model to gain insight if want more complete description on tx effect on oxygen support. Does treatment increase the odds of higher level of support.