

Appendix

Supplementary Appendix

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

Supplement to: Sullivan, Gebo Shoham et al

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The CSSC leadership

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The Bliss Group and The Next Practice - Clinical Trial Recruitment Acceleration and Diversity

Specialists The Bliss Group - Michael Roth, Quintin Maidment, Meg Wildrick

The Next Practice - Colin Foster, Desiree Huitt, David Pierpont

Summary of protocol changes

Inclusion/Exclusion

1. Removed receipt of previous blood products as holdover from merged donor and recipient protocols
2. Any positive molecular test including saliva will qualify for study. PCR test is no longer sole means of qualified test.
3. Excluded participants with prior to enrollment drug receipt with established viral activity against virus.
4. Steroid treatment does not influence eligibility.
5. Receipt of vaccine prior to enrollment also does not exclude participation
6. Prior monoclonal receipt before study plasma excludes participation. However, study participants who choose may receive monoclonals after study plasma based upon availability.

Study plasma product

1. Qualified plasma at greater than 1:320 titer only without FDA current standard which did not exist in 2020.
2. Control plasma collected after Dec 31, 2019 will be tested seronegative for SARS-CoV-2 antibody.
3. Added minimum infusion volume of 175 mL with no maximum for both convalescent and control plasma.
4. After July 2021, convalescent plasma used in trial must also meet FDA criteria for high titer plasma in addition to greater than 1:320 titer.

Statistical analytic plan

1. Modified to one sided Type 1 error for superiority
2. Added futility evaluation by DSMB at 40% enrollment after 28 day visit.
3. Added TMLE to statistical analysis plan
4. Target of older age group recruitment was made “not binding” because of vaccines and monoclonals restricting older ages in study.
5. Detailed severity score of COVID-19

Protocol implementation

1. Added visit study windows to define time frame for assessment.
2. Clarified that full range of medical rescue therapy after reaching hospital endpoint with full participation in rest of protocol. Participants remain blinded during hospitalization and for remaining study visits.
3. Because of surge in occupancy of hospital beds an extended stay in ER for COVID-19 treatment or home oxygen will qualify for hospital equivalents.

Medical monitoring

1. Added independent medical monitor for safety review.
2. Added independent three physician panel to adjudicate COVID-19 related hospitalizations and severity levels of site principal investigators with majority rule decisions.

Supplement Table 1 Cumulative incidence of grade 3 or 4 adverse events by treatment status

	Control		P-Value¹
	(N=589)	CCP (N=592)	
Number of Grade 3 or 4 events	53	34	
Total person-years	127.89	133.39	
Rate per person-years	0.41	0.25	
Median [IQR] observation time, days	90 [83,92]	90 [84,93]	
Rate difference (95% CI)		0.16 (0.02, 0.30)	0.03

	Control		P-value²
	(N=589)	CCP (N=592)	
Number randomized, n	615	610	
Number transfused, n	589	592	

Details of grade 3 or 4 adverse events,

n

Pneumonia	30 (56.6%)	14 (41.2%)
Bronchial infection	1 (1.9%)	0 (0%)
Dyspnea	1 (1.9%)	0 (0%)
Hypoxia	3 (5.7%)	0 (0%)
Pneumonitis	2 (3.8%)	0 (0%)

¹ P-value for risk difference between Control and Convalescent

² P-values calculated using Fisher's exact test for count data

Chest pain - cardiac	1 (1.9%)	0 (0%)
Hypertension	1 (1.9%)	2 (5.9%)
Hypotension	1 (1.9%)	0 (0%)
Non-cardiac chest pain	1 (1.9%)	1 (2.9%)
Headache	1 (1.9%)	0 (0%)
Sinus pain	1 (1.9%)	0 (0%)
Vasovagal reaction	2 (3.8%)	4 (11.8%)
Infusion related reaction	1 (1.9%)	1 (2.9%)
Vomiting	1 (1.9%)	1 (2.9%)
Pancreatitis	1 (1.9%)	1 (2.9%)
Renal calculi	1 (1.9%)	0 (0%)
Urinary tract obstruction	1 (1.9%)	0 (0%)
Leukocytosis	1 (1.9%)	0 (0%)
Neutrophil count decreased	1 (1.9%)	0 (0%)
White blood cell decreased	1 (1.9%)	0 (0%)

Supplement Table 2 Cumulative incidence of severe transfusion reactions by treatment status

	Control (N=589)	CCP (N=592)	P-Value ³
Total severe transfusion reactions	0	2	
Total person-years⁴	42.03	43.32	
Rate per person-years	0.00 cases/py	0.05 cases/py	
Median [IQR] observation time, days	28.0 [28.0, 28.0]	28.0 [28.0, 28.0]	
Rate difference (95% CI)		-0.05 (-0.11, 0.02)	0.16

	Control (N=589)	CCP (N=592)	P-value ⁵
Number randomized, n	615	610	
Number transfused, n	589	592	
Number of severe transfusion reactions,			
n	0	2	0.50
Details of severe transfusion reactions,			
n			
Pneumonia	0 (0.0%)	1 (50.0%)	
Infusion related reaction, unspecified	0 (0.0%)	1 (50.0%)	

³ P-value for risk difference between Control and Convalescent

⁴ Participants administratively censored at Day 28

⁵ P-values calculated using one-sided Fisher's exact test for count data

Supplement Table 3 Cumulative incidence of ARDS by treatment status

	Control (N=589)	CCP (N=592)	P-Value⁶
Number of ARDS cases	1	0	
Total person-years⁷	127.89	133.39	
Rate per person-years	0.01 cases/py	0.00 cases/py	
Median [IQR] observation time, days	90 [83,92]	90 [84,93]	
Rate difference (95% CI)		0.01 (-0.01, 0.02)	0.32

⁶ P-value for risk difference between Control and CCP

⁷ Participants censored at study closeout