Study Protocol and Statistical Analysis Plan

Dated: June 04, 2020

Therapeutic Plasma Exchange Alone or in Combination With Ruxolitinib in COVID-19 Associated CRS

NCT04374149

Study Title: PHU COVID-19-002 Interventional Study to Evaluate the Efficacy of Therapeutic Plasma Exchange (TPE) Alone or in Combination with Ruxolitinib in COVID-19 Positive Patients with PENN Grade 2, 3, 4 Cytokine Released Syndrome (CRS)

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Study Location: Prisma Health, South Carolina

- Greenville Memorial Campus
- North Greenville Campus

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Background and Rationale

A virally mediated pandemic of 2020 is linked to a novel Beta Coronavirus (COVID-19) sharing subgenus classification with the SARS virus. The predominant modes of transmission are respiratory aerosolization and contaminated surface contact.[1,2] COVID-19 infection is characterized by a wide range of severity and disease manifestations from asymptomatic to respiratory and multi organ failure. Definitive treatment is lacking, but there is an increasing awareness of its associated systemic cascade of inflammatory molecules that offers avenues to explore therapeutically.

P. Conti[3] and colleagues have recently outlined the binding of COVID-19 to the Toll-like receptor (TLR) with subsequent multi step generation of mature IL-1 β to trigger fever and pneumonitis. Many investigators draw similarity to the evolving understanding of cytokine storm or the cytokine release syndrome. Mehta et al[4] note the resemblance of severe COVID-19 expression to secondary hemaphagocytic lymphohistiocytosis (sHLH) long regarded as a fatal hypercytokinemic state with excessive elaboration of IL2, IL-7 TNF and macrophage inflammatory protein 1-alpha among others.

Therapeutic plasma exchange (TPE) offers an immediate and scientifically grounded intervention for the removal of a host of pathogenic antibodies and toxic molecules by centrifugal separation of plasma or plasma membrane filtration. Xiao[5] and colleagues successfully incorporated TPE in the management of a patient with severe CRS following CAR-T treatment in conjunction with Tocilizumab and steroids with daily documentation of cytokine levels.

Precedence for consideration of TPE in a variety of inflammatory dominant disease states is well known. Interest in adjuvant treatment for management of sepsis and multi organ dysfunction is reflected in Busund[6] and Rimmer[7] manuscripts. Patel et al[8] successfully used TPE in three pediatric patients with pH1N1 influenza A acute respiratory failure and hemodynamic shock despite failure of best supportive care. All three survived with "good functional recovery."

Ruxolitinib is a JAK/STAT pathway inhibitor which is FDA approved for polycythemia rubra vera, myelofibrosis and graft versus host disease. Kenderion et al[9] reported a murine model of CRS following CAR-T cellular therapy with marked elevation of IL-6, interferon-gamma, TNF alpha mimicking human CAR-T therapy induced CRS. Ruxolitinib treated mice demonstrated clinical amelioration and decrement in inflammatory cytokines. Incyte Corporation has announced plans to launch a Phase III trial of single agent ruxolitinib for COVID-19 associated cytokine storm.

This protocol will evaluate the efficacy of TPE alone or in combination with ruxolitinib in COVID positive patients with PENN grade 2, 3, 4 CRS. It is hypothesized that dual intervention of acute aphaeretic depletion of cytokines and concomitant suppression of production will produce superior amelioration of the cytokine load and to help to prevent cytokine load rebound. This protocol is envisioned as a pilot study (n=20) for hypothesis generation for future investigation.

Primary Endpoints

1. To document the efficacy of TPE alone or in conjunction with ruxolitinib in decreasing the cytokine load over a 14-day intervention study
2. Analysis of all therapy related adverse events (AEs)

Secondary Endpoints

1. To correlate the clinical course of participants with the degree of specific cytokine reductions
3. To calculate time to independence from mechanical ventilation
4. To calculate time to independence from supplemental oxygen therapy
5. To measure CRP, ferritin and cytokine levels (IL-6, IL-8, IL-10, TNFα, IFNγ, GM-CSF) to map the cytokine landscape over the course of the study
6. To explore correlative biomarker studies
7. To bank plasma and other blood derivatives in the Prisma Health ITOR Biorepository for future investigation

Study Design

Study type:	Interventional Pilot Clinical Trial
Estimated Enrollment	20 patients
Allocation	Two sequential cohorts, 10 patients per cohort First 10 patients will receive TPE alone (Cohort 1A) Second 10 patients will receive TPE in combination with ruxolitinib
Masking	None (open label)
Primary purpose	Treatment efficacy
Official title:	Interventional Study to Evaluate the Efficacy of Therapeutic Plasma Exchange (TPE) Alone or in Combination with Ruxolitinib in COVID-19 Positive Patients with PENN Grade 2, 3, 4 Cytokine Released Syndrome (CRS)

Study Population

COVID-19 positive patients with PENN grade 2, 3, 4 CRS and respiratory failure.

Eligibility

Inclusion:

1. Patients positive for COVID-19 by PCR or alternative accepted methodology
2. PENN class 2,3,4 CRS[10]
3. Respiratory insufficiency with supplemental oxygen to maintain O2 sat greater than 89%
4. Clinically positive imaging by CXR or CT scan with evidence of bilateral pulmonary infiltrates, ground glass opacification or other pattern of consolidation felt likely to be linked to COVID infection or complication thereof
5. Adults 22 years of age or older

Exclusion:

1. Pregnancy
2. Breast feeding
3. Class 3-4 NYHA heart failure
4. Current use of synthetic disease modifying anti-rheumatic drugs (DMARDS), with the exception of hydroxychloroquine, or IL-6 inhibitors or other immunosuppressive therapies outside of number five below
5. Current use of chronic corticosteroids if in excess of prednisone 10mg per day or equivalent
6. Suspected or confirmed clinically significant bacterial infection
7. History of TB
8. History of HIV
9. History of IBD
10. JAK inhibitor use within last 30 days
11. Creatinine clearance less than 15 ml / min
12. Absolute neutrophil count < 1000
13. Platelet count < 50,000
14. AST or ALT > 5 times the upper limit of normal
15. Clinical assessment that TPE or ruxolitinib could pose unacceptable risk by study participation or the treatment is deemed inappropriate by a study investigator
16. Current enrollment on another investigational protocol for COVID-19 induced CRS
17. Stage 4 obstructive lung disease with chronic hypoxic respiratory failure requiring supplemental O2 at baseline, or ILD with chronic hypoxic respiratory failure requiring supplemental O2 at baseline

Treatment Plan

Device: Spectra Optia Apheresis System

Intended Use of Device: Therapeutic Plasma Exchange performed per marketed labeling

Drug: Ruxolitinib (generic) marketed as brand name, Jakafi ,manufactured by Incyte Corporation, will be used per the marketed package insert.

Cohort 1A: TPE, five single plasma volume exchanges over 7 days (every day x 2 then every other day x 3) with albumin or FFP replacement if underlying coagulopathy per institutional protocol (Appendix A).

Other – standard medical care

Cohort 1B: TPE as in cohort 1A combined with ruxolitinib 5mg po BID beginning day prior to first TPE and continuing BID for total of 14 days. On days of TPE, ruxolitinib dosing will be immediately post procedure and a second dose approximately 8 hours later.

Other – standard medical care

Schedule of Assessments

Pre Treatment

Standard of Care Assessments

- Complete Blood Count (CBC)
- Comprehensive Metabolic Panel (CMP)
- C-Reactive Protein (CRP)
- Ferritin
- lipid panel
- Hepatitis B Surface Antigen, Hepatitis B Surface Antibody, Hepatitis B Core Antibody and Hepatitis C Antibody
- PT/INR
- Partial Thromboplastin Time (PTT)
- Fibrinogen
- type and screen
- serum pregnancy test
- physical examination

Study Related Assessments

- cytokine panel
- peripheral blood for biorepository
- peripheral blood for pharmacogenomics

During Treatment (On Study)

Standard of Care Assessments

- daily CBC
- daily Basic Metabolic Panel BMP)
- daily CRP
- physical examination
- PaO2/FiO2 ratios days (with ABGs) per Appendix B
- amount of supplemental O2, SPO2%, respiratory rate, imaging per MD discretion ***(for non-intubated patients)***
- measure daily SPO2% , FiO2; PEEP; and lung compliance (inspiratory pause – Vt/Pplat – PEEP) or plateau pressures ***(mechanically vented patients)***

Study Related Assessments

- daily collection of study related adverse events and/or serious adverse events
- Fibrinogen (on days of TPE only)
- daily cytokine panel and GM-CSF
- repeat cytokine panel and GM-CSF within 60 minutes post TPE (on days of procedure only)
- serum ferritin per Appendix B
- perhipheral blood and plasma waste for biorepository per Appendix B
- day 28 office visit or virtual health visit to assess clinical status of the patient

Risk Analysis

The proposed patient population is not anticipated to be at an increased risk compared to a clinically similar population without COVID-19 infection. The device and drug will be used as marketed. Standard risks for the device and drug are outlined in the patient informed consent document. Risks will be minimized by conducting the trial in the inpatient setting of an acute care hospital with dedicated and trained therapeutic apheresis staff, licensed medical personnel and experienced research team members under the direction and oversight of the principal investigator. In the event of patient status improvement, discharge will be acceptable after completion of therapeutic plasma exchange. Daily outpatient follow-up through patient completion of study required assessments will occur in a dedicated phase I research unit.

Removal of medications with TPE is a risk. However, consultation with a hospital pharmacist will occur as needed to determine if a change in timing of medication administration is needed or if medication reloading should occur post TPE.

Dose Modifications

The starting dose of ruxolitinib is 5mg po bid. The need for dose adjustments will be assessed on a daily basis by the research team and pharmacist.

- AST/ALT > 5x ULN, reduce dose of ruxolitinib to 5mg po once daily[11]
- Platelet count between 25,000 and 35,000, reduce dose of ruxolitinib to 5mg po once daily. Platelet count < 25,000, hold ruxolitinib. May resume once platelet count >25,000 with dosing based on actual platelet count.
- Absolute neutrophil count < 500, hold ruxolitinib until > 500 then resume at full dose
- Creatinine Clearance <15ml/min, discontinue ruxolitinib

Duration of Investigations

A six month patient recruitment period is anticipated. Patient participation is 15 days in duration. An additional six month period of data analysis is anticipated for an overall period of investigation equaling 12 months

Treatment Discontinuation

Treatment discontinuation will occur under the following conditions:

- The patient withdraws consent either from treatment or from the study
- The patient is lost to follow-up
- The patient experiences a side effect that per the protocol requires treatment to end
- The physician deems treatment discontinuation is in the best interest of the patient
- The patient is found to be eligible to participate in the study after being enrolled and continued treatment in this study is not in the best interest of the patient
- The patient is found to be pregnant or intends to become pregnant
- The patient is noncompliant with the study requirements your disease worsens

Data Handling and Recordkeeping

The principal investigator will carefully monitor study procedures to protect the safety of research subjects, the quality of data, and the integrity of the study. All study subject material will be assigned a unique identifying code or number. The key to the code will be kept in a locked file in the Research Division of the Prisma Health Cancer Institute.

Data Collection, Analysis and Outcomes

REDCap EDC software will be used for data management and future statistical analysis. Designated Cancer Institute research staff will perform extraction of patient records.

Overall Response Rate (ORR) will be defined as $\geq$ 33% decrease in the cytokine load from peak value through study day 14 in one-third or more participants.

Ethical Considerations

This study will be conducted in accordance will all applicable government regulations and Prisma Health research policies and procedures. This protocol and any amendments will be

submitted and approved by the Prisma Health Institutional Review Board (IRB) prior to any study activity.

All study participants will provide informed consent allowing for their tissue and de-identified clinical information to be used for research purposes.

Safety Monitoring and Reporting

A Drug Safety Monitoring Board (DSMB) will be established consisting of a hematologist, pulmonologist and infectious disease specialist not associated with the research team for this investigation. The committee will review all serious adverse events within 48 hours and will review all patient outcomes for cohort 1a before proceeding to enrollment of cohort 1b.

Adverse Events

Adverse events (AEs) are defined as an unexpected medical problem that happens during treatment with a drug or other therapy. The NCI Common terminology criteria for adverse events (CTCAE Version 5.0) will be used as the standardized severity grading system. AEs will also be reported by degree of relatedness as not related, possibly related, likely related or related to the study drug or study therapy.

SAE Reporting to Incyte

The Principal Investigator (PI) must report all Serious Adverse Events (SAEs) to Incyte within 24 hours of learning of an event, regardless of the PI's causality assessment. This notification will be provided on a completed Serious Adverse Event (SAE) form. SAE reporting for each subject begins the day the informed consent is signed by the patient and within 30 days after subject has completed or discontinued from the study or has taken last dose of the study drug, or as described in the protocol.

SAEs, occurring using Incyte study drug, are reported in accordance with the effective protocol. SAEs occurring with any other commercial drug are reported to the manufacturer of that drug in accordance with regulations and protocol.

Initial SAEs and/or subsequent follow-up reports will be reported via email to SafetyReporting@Incyte.com or fax (+) 1-866-981-2057. SAE reports should be for a single subject. SAE forms should be sent with a cover sheet and any additional attachments.

All adverse event information is reported to Incyte on MedWatch Form FDA 3500A. The Principal Investigator does not provide medical records (e.g., discharge summary) to Incyte, unless specifically requested.

In addition, all SAEs will be reported to the Prisma Health IRB per the institutional policy for reporting.

Reporting of Pregnancy to Incyte

An "Initial Pregnancy Report" or equivalent must be completed in full and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 24 hours of discovery of a pregnancy of a subject who has taken the Incyte product or the pregnancy of a partner

for a subject who has taken the Incyte product. The "Follow-up Pregnancy Report Form" or equivalent must be completed and emailed to SafetyReporting@Incyte.com or faxed to (+) 1-866-981-2057 within 30 days after delivery, so that Incyte is provided with information regarding the outcome of the pregnancy. If the pregnancy results in any events which meet the serious criteria (i.e., miscarriage or termination), the SAE reporting process needs to be followed and the timelines associated with a SAE should be followed.

Statistical Analyses

General Statistical Considerations

Standard statistical methods will be employed to analyze all data. It is anticipated that the following techniques may be used: descriptive statistics, t-test, Chi-square, Fisher's exact test, Kaplan-Meier analysis, and graphical displays. This protocol may not reflect all analyses planned for the study; additional analyses may be conducted for observational purposes only.

Summary statistics will consist of numbers and percents of responses in each category for discrete measures, and of mean, n, standard deviation, median, minimum, maximum and 95% confidence intervals for continuous measures.

Sample Size Determination

The initial sample size is 20. Each cohort will enroll 10 patients. This number is considered sufficient for an exploratory pilot study to provide information for planning further investigations.

Analysis of Safety

The safety evaluation will compare the proportion of Subjects in each treatment group who exhibit treatment-related adverse effects. These adverse events will be presented for individual patients as a listing of events.

Dissemination of Results

Results of this study may be used for presentations, posters, publications, or extramural grant applications. The publication will not contain any identifiable information that could be linked to a study patient.

References

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APPENDIX A:

TPE-Plasma Therapy Plan

Apheresis Orders	**Frequency**
• Therapeutic Plasma Apheresis with Plasma Replacement	As Ordered
IV Access	
• Initiate peripheral IV Protocol	Daily
• Access Central Venous Catheter	Daily
• Access A/V Fistula for Procedure	Daily
Pre-Procedure Labs (Baseline)	
• CBC with Differential	Once
• CMP	Once
• LDH	Once
• Haptoglobin	Once
• PT/INR	Once
• PTT	Once
• Reticulocyte Count	Once
• ADAM TS 13 Activity	Once
• Type and Screen	Once
• Bilirubin Total and Direct	Once
• Prepare Plasma	Once
Labs	
• CBC with Differential	Daily
• CMP	Daily
• LDH	Daily
• Haptoglobin	Daily
Anticoagulant Prime	
• Anticoagulant citrate dextrose injection 500 ml	PRN
Medications	
• diphenhydramine (Benadryl) 25 mg IV	Once
• calcium gluconate 3g in NS 250ml IV	Once
• calcium gluconate 3g in NS 250ml IV	PRN
• calcium carbonate tablet 1500 mg PO	PRN
• alteplase 2mg in 10ml syringe	PRN clot clearance
Hypersensitivity Regimen	
• at any sign of anaphylaxis, stop infusion, notify MD and administered prescribed medications	PRN
• diphenhydramine (Benadryl) 50 mg IV	PRN
• methyleprednisolone (Solu-Medrol) 40 mg IV	PRN
• famotidine (Pepcid) 20 mg IV	PRN
Nursing Orders	
• Transfuse Plasma	Once

TPE-Albumin Therapy Plan

Apheresis Orders	**Frequency**
• Therapeutic Plasma Apheresis with Albumin Replacement	As Ordered
IV Access	
• Initiate peripheral IV Protocol	Daily
• Access Central Venous Catheter	Daily
• Access A/V Fistula for Procedure	Daily
Pre-Procedure Labs (Baseline)	
• CBC with Differential	Once
• CMP	Once
• Fibrinogen	Once
Anticoagulant Prime	
• Anticoagulant citrate dextrose injection 500 ml	PRN
Medications	
• calcium carbonate tablet 1000 mg PO	PRN
• calcium gluconate 2.5g in NS 250ml IV	PRN
• alteplase 2mg in 10ml syringe	PRN clot clearance
Hypersensitivity Regimen	
• at any sign of anaphylaxis, stop infusion, notify MD and administered prescribed medications	PRN
• diphenhydramine (Benadryl) 50 mg IV	PRN
• methylprednisolone (Solu-Medrol) 40 mg IV	PRN
• famotidine (Pepcid) 20 mg IV	PRN
Nursing Orders	
• Infuse Albumin	Once

Appendix B:	**COHORT 1A Schedule of Assessments: Therapeutic Plasma Exchange alone**																
Assessment	**Screening (24 hours)**	**Study Day**															
		1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**28**
Informed Consent and Medical History	X																
Physical Examination[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Complete Blood Count (CBC)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Metabolic Panel (CMP)	X																
Basic Metabolic Panel (BMP)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
C-Reactive Protein (CRP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Ferritin	X			X			X			X					X		
Hepatitis Serology[b]	X																
Lipid Panel[b]	X																
PT/INR	X																
PTT	X																
Fibrinogen	X	X	X		X		X		X								
Type and Screen[b]	X																
Serum Pregnancy Test[b]	X																
Cytokine Panel (IL-6, IL-8, IL-10, TNFα, IFNγ)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
GM-CSF[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Peripheral Blood for biorepository	X					X			X							X	
Peripheral Blood for pharmacogenomics	X																
PaO2/FiO2 ratios (with ABGs) - (mechanically vented patients only)		X		X		X											
Supplemental O2, SPO2%, Respiratory Rate, Imaging at MD discretion (for NON-intubated patients)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
SPO2%, FiO2, PEEP, Lung compliance (inspiratory pause - Vt/Pplat-PEEP) or plateua pressures (mechanically vented patients only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Therapeutic Plasma Exchange (TPE) (plus waste for biorepository)		X	X		X		X		X								

[a] If patient is discharged from the hospital, daily physical examination will not be required. Perform one physical exam prior to the patient's last study visit. Day 28 may be a virtual visit if needed.

[b] Hepatitis serology, Lipid panel, Type and Screen, Serum Pregnancy Test acceptable within 7 days prior to enrollment.

[c] Cytokine Panel and GM-CSF are to be repeated within 60 minutes post TPE on days of plasma exchange procedure only.

Appendix B:	**COHORT 1B Schedule of Assessments: Therapeutic Plasma Exchange Plus Ruxolitinib**																
Assessment	**Screening (24 hours)**	**Study Day**															
		0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**28**
Informed Consent and Medical History	X																
Physical Examination[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Complete Blood Count (CBC)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Comprehensive Metabolic Panel (CMP)	X																
Basic Metabolic Panel (BMP)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
C-Reactive Protein (CRP)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Ferritin	X			X			X			X					X		
Hepatitis Serology[b]	X																
Lipid Panel[b]	X																
PT/INR	X																
PTT	X																
Fibrinogen	X		X	X		X		X		X							
Type and Screen[b]	X																
Serum Pregnancy Test[b]	X																
Cytokine Panel (IL-6, IL-8, IL-10, TNFα, IFNγ)[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
GM-CSF[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Peripheral Blood for biorepository	X					X			X							X	
Peripheral Blood for pharmacogenomics	X																
PaO2/FiO2 ratios (with ABGs) - (mechanically vented patients only)		X		X		X											
Supplemental O2, SPO2%, Respiratory Rate, Imaging at MD discretion (for NON-intubated patients)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
SPO2%, FiO2, PEEP, Lung compliance (inspiratory pause - Vt/Pplat-PEEP) or plateua pressures (mechanically vented patients only)		X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Therapeutic Plasma Exchange (TPE) (plus waste for biorepository)			X	X		X		X		X							
Ruxolitinib Dosing		X	X	X	X	X	X	X	X	X	X	X	X	X	X		

[a] If patient is discharged from the hospital, daily physical examination will not be required. Perform one physical exam prior to the patient's last study visit. Day 28 may be a virtual visit if needed.

[b] Hepatitis serology, Lipid panel, Type and Screen, Serum Pregnancy Test acceptable within 7 days prior to enrollment.

[c] Cytokine Panel and GM-CSF are to be repeated within 60 minutes post TPE on days of plasma exchange procedure only.