Informed Consent Form

IRB Approved: June 11, 2020

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

NCT04374149

CONSENT TO PARTICIPATE IN A RESEARCH STUDY

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)

Study to be Conducted at: **Prisma Health–Upstate**
Greenville Memorial Hospital Campus
North Greenville Hospital Campus
Greenville, SC

Sponsor Name: **Prisma Health–Upstate**

Principal Investigator: **W. Larry Gluck, MD**

KEY INFORMATION

You are being asked to participate in a research study. Participation in a research study is voluntary. The information in this consent form is meant to better inform you so you may decide whether or not to participate in this research study. Please ask the study doctor to explain anything you do not understand.

This study is being conducted in response to the COVID-19 public health emergency. Some patients with COVID-19 virus become very sick. Doctors and researchers have found that the cause may be the body's own immune system overreacting to the virus. When this happens, the person's immune system triggers a runaway response that causes more damage to its own cells than to the virus. This is known as a cytokine release syndrome (CRS). Cytokines are small proteins that act as messengers to help direct the body's immune response. However, high levels of cytokines may cause increased inflammation throughout the body. This can be harmful and interfere with how the body functions. In severe cases, CRS can cause organ failure that may affect heart, lung, kidney, liver and brain function and may result in death.

CRS is treated based on the patient's specific symptoms. Some patient may need IV fluids, oxygen support, medicines to regulate blood pressure and support how the heart and kidneys function. Sometimes medicines are used to decrease the immune response.

The treatment in this study involves using therapeutic plasma exchange (TPE) alone or in combination with a drug called ruxolitinib to decrease the immune response.

TPE is a treatment that removes plasma from your blood. The removed plasma is replaced with a substitute. Plasma is the liquid portion of the blood that helps carry blood cells and other substances throughout your body. With CRS, your plasma can contain high levels of cytokines. TPE may help remove these.

Ruxolitinib (referred to hereafter as the study drug) is an FDA approved medication often used to treat other conditions. It is a type of drug called a protein kinase inhibitor. The action of this drug may create significant reduction of inflammatory cytokines. Therefore, it is being studied as a possible treatment for CRS.

Although TPE and the study drug are approved therapies, they are currently investigational for the treatment of CRS.

In addition, the following are laboratory tests are considered study related assessments: cytokine panel, GM-CSF, blood for pharmacogenomics, blood and plasma for the biorepository, fibrinogen on the days of TPE, and the ferritin on days 3, 6, 9 and 14.

The Institutional Review Board of the Prisma Health–Upstate has reviewed this study for the protection of the rights of human participants in research studies, in accordance with federal and state regulations.

PURPOSE

You are being asked to participate in this study because you have COVID-19 viral infection and have developed cytokine release syndrome (CRS).

The purpose of this study is to find out what effects (good and bad) TPE with or without the study drug has on your CRS.

We expect to enroll 20 participants to this study. Your participation will last for 28 days. You may be in the hospital for the first two weeks of the study. However, if you are discharged from the hospital you will be asked to come into the office every day through day 14. After that, you will be asked to come back for a visit or have a telehealth visit on day 28 to see how you are doing.

HOW THE STUDY WORKS

You will be assigned to one of two study groups (cohorts). The first 10 participants will be in Cohort 1A and receive TPE alone. The second 10 participants will be in Cohort 1B and receive TPE in combination with the study drug.

Cohort 1A: TPE will be performed on days 1, 2, 4, 6 and 8.

Cohort 1B: TPE will be performed on days 1, 2, 4, 6 and 8.
Ruxolitinib 5mg tablet will be administered twice a day on days 0 through 13 (for a total of 14 days). If you are able to swallow, you will take this drug by mouth. If you are not able to swallow, the tablet will be crushed and given to you through a feeding or nasogastric tube (a tube that goes through your nose directly into your stomach).

How TPE is done

TPE uses a special machine to separate blood into its different parts. It then removes and replaces most of the plasma. Each plasma exchange takes about 2 hours.

- A special catheter is inserted into a large vein in your shoulder or groin. The doctor inserting the catheter will specifically discuss this procedure and possible risks with you.Your blood flows through tubing to the machine. Before the blood reaches the machine, medicines are added that prevent the blood from forming clots. These medicines are called anticoagulants.
- The machine separates blood into its various parts. It then removes the plasma.

- The machine adds a plasma substitute to the remaining blood. This may be a replacement fluid that contains saline and albumin, or it may be plasma from a human donor.
- The blood containing the new plasma returns to you through the tubing.

RESEARCH USE OF BIOSPECIMENS

This study involves the collection of biospecimens (bodily substances). The biospecimen that will be collected for this study is blood.

After use in this specific study, your identifiable private information will be removed from the biospecimens. These specimens and/or the information (other than identifiable information) may be used for future research or shared with another researcher without your consent. On the last page of this consent form, you can note whether you want your leftover specimen, if any, to be used for future research studies.

Your biospecimen may be used to develop new technologies, treatments or medications for different diseases. There may be financial gain by individuals or places using the information gathered from research on your biospecimen. You will not receive any financial compensation or share in any commercial profit that results from this research.

POSSIBLE RISKS

Any treatment has possible side effects. The treatments and procedures used in this study may cause all, some, or none of the side effects listed. There is always the risk of very uncommon or previously unknown side effects.

Possible Risks Associated with the Vascular Catheter placement for TPE

- Damage to the blood vessel
- Bruising or bleeding at the insertion site
- Infection
- Collapsed lung (pneumothorax)
- Pain at the insertion site

Possible Side Effects Associated with TPE

- Low blood pressure
- Shortness of breath
- Bleeding
- Increased risk for infection because your normal immune system proteins (antibodies) have been removed
- Too little calcium in the blood (hypocalcemia) which may cause nausea and tingling around the mouth
- Metabolic alkalosis (a condition which occurs when there is an acid and base imbalance) which can cause confusion, muscle twitching, nausea and vomiting
- When donor plasma is used: allergic reaction or disease transmission
- Removal of essential medications you are taking or are being given

Side Effects Associated with the Use of the study drug

Very Common (at least 10%)

- Anemia (low red blood cells)
- Thrombocytopenia (low platelets)
- Bruising
- Neutropenia (low white blood cells)
- Raised alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (blood proteins that may indicate mild liver damage)
- Hypercholesterolemia (increase in cholesterol)
- Hypertriglyceridemia (increase in triglycerides)
- Dizziness
- Headache
- Urinary tract infections
- Weight gain

Common (more than 1% but less than 10%)

- Flatulence (gas)
- Constipation
- Herpes zoster (shingles)
- Hypertension (high blood pressure)

The study drug may cause low blood cell counts (white blood cells, red blood cells, and platelets). If your white blood cell count becomes low while you take the study drug, this means you may have an increased chance of getting an infection, including urinary tract infections and viral infections. You also may become anemic (low red blood cell count) while you take the study drug, and that may cause you to feel tired all over or short of breath. If your platelet count becomes low while you take the the study drug, it may lead to bleeding and/or bruising. In some people taking the study drug, the decrease in blood cell counts have been serious. In most cases, low blood cell counts can be reversed by stopping the study drug temporarily or reducing the dose.

Uncommon: (occurring in fewer than 1% of patients)

These events were uncommon, but have occurred in patients with myelofibrosis (MF is a serious bone marrow disorder that disrupts your body's normal production of blood cells) during the study drug treatment and are potentially serious.

- Tuberculosis (TB) has occurred in a small number of patients (less than 1%) with MF who were treated with the study drug, but it is not known whether this was due to MF, the study drug, or other factors that are known to increase the risk of tuberculosis (such as diabetes, bronchitis, asthma, smoking, emphysema, or steroid use). Tell your doctor if you have been treated for TB in the past, or have ever had a positive skin test for TB. Additionally, you should tell your study Doctor immediately if you have any of the following symptoms while in the study: chronic cough with blood-tinged spit, fever, night sweats, weight loss.
- A rare disease called progressive multifocal leukoencephalopathy (PML) has been reported during long-term use of the study drug treatment for MF. PML comes from a viral infection that causes brain damage and can be fatal.

As with all medications, side effects may include allergic reactions. Allergic reactions may range from minor itching or rash to major reactions, which can lead to death.

Inserting a needle into a vein in the arm to receive fluids and study treatment and/or to collect blood samples may cause pain, redness, bleeding, bruising, fainting, a clot in the accessed vein and infection at the location where the needle is inserted.

REPRODUCTIVE RISKS

You should practice an adequate method of birth control while taking part in this study. If you think that you have become pregnant or caused a pregnancy during this study, you must tell the study doctor immediately. This study may involve unknown risks to an unborn or nursing child. Women who are pregnant or nursing a child may not be able to participate in this study. You should tell the study doctor if you intend to become pregnant during this study. If you are able to get pregnant, you will be required to take a pregnancy test before you participate or during the course of this study.

It is possible that receiving the study drug with your regular medications, supplements, or some food (for example, grapefruit juice) may change how the study drug, your regular medications, or your regular supplements work. It is very important that you tell the study doctor about all medications or supplements you are taking during the study. Tell the study doctor if you are taking any drugs, or non-prescription medications or supplements, including vitamins or herbs, other than those being used in this research study because of the risk of possible and/or serious drug interactions. Tell anyone who gives you medical care that you are participating in a research study.

POSSIBLE BENEFITS

It is not possible to know whether or not you may benefit from participating in this study. The treatment or procedures you receive may even be harmful. The information gained from this study may be useful and may help others.

It is possible that TPE alone or in combination with the study drug will improve your CRS.

ALTERNATIVE (OTHER) TREATMENTS

You can still receive evaluation and treatment for your condition if you do not participate in this study. Discuss any alternative treatments with your regular doctor and/or the study doctor before you decide to participate. The decision is entirely up to you. If you decide not to participate in the study, you will not be penalized or lose any benefits and your decision will not affect your relationship with your doctor or hospital.

- You may choose to have the standard of care treatment, which is IV fluids, oxygen support, medicines to regulate blood pressure and support how the heart and kidneys function
- You may choose to take part in a different research study, if one is available.
- You may choose not to be treated.
- You may choose to receive only comfort care to help relieve your symptoms, without receiving any treatment.

Please discuss these choices with your doctor.

NEW INFORMATION
Your doctor will tell you about new information that may affect your willingness to participate in this research study. Alternatives, or other choices, concerning your care will be discussed at that time.

There are no plans to share individual research results with you.

A Data Safety Monitoring Board will be reviewing the data from this research from time to time throughout the study. It will notify the study doctor of any new information that should be shared with you.

COST TO YOU FOR PARTICIPATING IN THIS STUDY
TPE, the catheter and placement of the catheter, and the study drug, ruxolitinib, will be supplied free of charge.

In addition, the following are considered study related assessments that will not be charged to you:

- Laboratory tests: cytokine panel, GM-CSF, blood for pharmacogenomics, blood and plasma for the biorepository, fibrinogen on the days of TPE, ferritin on days 3, 6, 9 and 14.

We will bill you or your health insurer for routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. You will be responsible for the cost of any care not covered by insurance or study funds.

If you have any questions or are unsure about costs from taking part in the research, please speak with the study doctor or staff.

PAYMENT FOR PARTICIPATION
To You:
If you are discharged from the hospital and need to come to the office for any remaining study visits, you will be paid a one time amount of $25.00 for gas expense.

To process your study payment, you will be asked to complete a W-9 form with your name, address, date of birth, and Social Security number. If you receive $600 or more for study participation in this research study, or a combination of studies at Prisma-Health Upstate in one tax year, Prisma-Health Upstate will send you an IRS Form 1099 for tax purposes.

You will be paid via ClinCard, a reloadable debit card. The ClinCard program is owned by a company called Greenphire. The study team will give Greenphire your name, address, date of birth and Social Security number as part of the payment system. Greenphire will only use this information to make sure you get paid. Greenphire will not use your information for any other purposes, and they will not give or sell your information to any other company. The study team will provide you more information about the ClinCard program following study enrollment.

To Institution:
The Prisma Health Upstate may receive funding from Incyte Corporation and Terumo BCT for administrative costs associated with conducting this study.

COMPENSATION FOR INJURY AS A RESULT OF STUDY PARTICIPATION

Prisma Health–Upstate will provide you the care needed to treat any injury, or illness, that directly results from taking part in this research study.

Injuries sometimes happen in research even when no one is at fault. Prisma Health–Upstate, or the investigators as part of this study have no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the 'Contact for Questions' section of this consent.

VOLUNTARY PARTICIPATION

Participation in this research study is voluntary. You may refuse to participate or withdraw from the study at any time. If you refuse to participate or withdraw from the study, you will not be penalized or lose any benefits and your decision will not affect your relationship with your doctor or hospital.

However, if you decide to stop study participation, you are encouraged to talk with your doctor regarding safe removal from the study. Further treatment would be discussed.

Your doctor may decide to take you off this research study if:

- you withdraw consent either from treatment or from the study
- you are lost to follow-up
- you experience a side effect that per the protocol requires your treatment to end
- your Study Doctor thinks it is in your best interest to stop
- you are found to not have been eligible to participate in the study and continued treatment in this study is not in your best interest
- you are found to be pregnant or intend to become pregnant
- you are noncompliant with the study requirements as determined by the Sponsor or the Study Doctor
- your disease worsens and continued treatment is not in your best interest
- the Sponsor stops the study

If your participation in this research study is stopped, your study doctor will discuss any tests or procedures that might be needed for your health and safety, but you may refuse any or all of these tests or procedures. Following this discussion with your study doctor, you still have the right to refuse any or all of these tests or procedures.

AUTHORIZATION TO USE AND DISCLOSE (RELEASE) MEDICAL INFORMATION

As part of this research study, the study doctor and his/her research team will keep records of your participation in this study. These study records may be kept on a computer and will include all information collected during the research study, and any health information in your medical records that is related to the research study. The study doctor and his/her research team will use and disclose (release) your health information to conduct this study. This study may result in scientific presentations and publications, but steps will be taken to make sure you are not identified.

Some of the organizations/entities that may receive your information are:

- The study sponsor and any company supporting the study (the sponsor's authorized representatives)
- The Institutional Review Board, which is a group of people who review research with the goal of protecting the people who take part in the study
- The Food and Drug Administration (FDA) and the groups it works with to review research.

Under federal privacy laws, your study records cannot be used or released for research purposes unless you agree. If you sign this consent form, you are agreeing to the use and release of your health information. If you do not agree to this use, you will not be able to participate in this study. Once your health information has been released, federal privacy laws may no longer protect it from further release and use.

The right to use your health information for research purposes does not expire unless you withdraw your agreement. You have the right to withdraw your agreement at any time. You can do this by giving written notice to the study doctor. If you withdraw your agreement, you will not be allowed to continue participation in this research study. However, the information that has already been collected will still be used and released as described above. You have the right to review your health information that is created during your participation in this study. After the study is completed, you may request this information.

If you have any questions about the privacy of your health information, please ask the study doctor.

CONFIDENTIALITY

Your study records are considered confidential (private), but absolute confidentiality cannot be guaranteed. Information may be kept on a computer. All records may be examined and copied by the Institutional Review Board of Prisma Health–Upstate, and other regulatory agencies. This study may result in presentations and publications, but steps will be taken to make sure you are not identified by name.

CONTACT FOR QUESTIONS

For more information concerning this study and research-related risks or injuries, or to give comments or express concerns or complaints, you may contact the principal investigator, whose information is included below.You may also contact a representative of the Office of Human Research Protection of Prisma Health–Upstate for information regarding your rights as a participant involved in a research study or to give comments or express concerns, complaints or offer input. You may obtain the name and number of this person by calling (864) 455-8997.

Principal Investigator Name:	W. Larry Gluck, MD
Telephone Number:	(864) 455-3600

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

CONSENT TO PARTICIPATE

The study doctor, _____, has explained the nature and purpose of this study to me. I have been given the time and place to read and review this consent form and I choose to participate in this study. I have been given the opportunity to ask questions about this study and my questions have been answered to my satisfaction. I have been given the opportunity to review my study doctor's Notice of Privacy Practices. I agree that my health information may be used and disclosed (released) as described in this consent form. After I sign this consent form, I will receive a copy of it for my own records. I do not give up any of my legal rights by signing this consent form.

_____
Printed Name of Participant

_____ _____ _____
Signature of Participant Date Time

CONSENT FOR ANY REMAINING SPECIMEN TO BE STORED FOR FUTURE RESEARCH

I understand that I will have a specimen collected as part of this study. If any of my specimen is left over after use in this study, I understand that my study doctors would like to remove my identifiable information from the specimen and store it for use a future research study.

☐ I DO agree to have any leftover specimen stored for future research, with the understanding that the specimen will not be labeled with any information that could be used to identify me.

or

☐ I DO NOT agree to have any leftover specimen stored for future research, with the understanding that the specimen will not be labeled with any information that could be used to identify me.

_____ _____
Initials Date

_____
Participant's Initials

INVESTIGATOR STATEMENT

I have carefully explained to the participant the nature and purpose of the above study. The participant signing this consent form has (1) been given the time and place to read and review this consent form; (2) been given an opportunity to ask questions regarding the nature, risks and benefits of participation in this research study; and (3) appears to understand the nature and purpose of the study and the demands required of participation. The participant has signed this consent form prior to having any study-related procedures performed.

_____ _____ _____

Signature of Investigator | Date | Time

Principal Investigator	**Phone**
W. Larry Gluck, MD	(864) 455-3600

Co-Investigators	**Phone**
Rob Brevetta, MD	(864) 455-3600
Sean Callahan, MD	(864) 455-3600
Antine Stenbit, MD	(864) 455-3600
W. Jeffery Edenfield, MD	(864) 455-3600
Julie Martin, DNP	(864) 455-3600

_____
Participant's Initials

Legally Authorized Representative (LAR)

You are being asked to enroll an individual in a research study because you are their Legally Authorized Representative (LAR). Research studies include only people who choose to take part. This document is called an informed consent form. Please read this information carefully and take your time making your decision. Ask the researcher or study staff to discuss this consent form with you. Please ask him/her to explain any words or information you do not clearly understand. We encourage you to talk with your family and friends before you decide to enroll your loved one in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are contained in this document. Please tell the study doctor or study staff if your loved one is taking part in another research study

Consent of Legally Authorized Representative (LAR) and Authorization for the Collection, Use and Disclosure of Health Information

I give consent to have _____ take part in this study and authorize that his/her health information be disclosed/collected as outlined above. I have received a signed copy of this form to take with me.

I understand that I am being asked to serve as the LAR and give permission for the individual outlined above to participate in this IRB reviewed and approved research study. My decision is based on what I believe this individual would choose for him/herself and what I believe is now best for him/her, based on the information I have been provided. I do not have any financial conflict of interest nor am I receiving payment for this individual's participation in the research study.

_____ _____ _____

Signature of Legally Authorized Representative | Date | Time

_____

Printed Name Legally Authorized Representative

If this consent is obtained via telephone communication:

- **2 witnesses are required**
- **and a copy of the consent form must be provided to the LAR**

_____ _____

#1 Witness Signature | Date | Time

_____

#2Witness Signature | Date | Time

Prisma Health-Upstate
IRB Number: Pro00100939
Date Approved 6/11/2020
Version Valid Until: 6/10/2021

_____
Participant's Initials

Statement of Person Obtaining Informed Consent / Research Authorization

I have carefully explained to the LAR of the person taking part in the study what he or she can expect from participation, the nature of the study, and the purpose of the study. I confirm that this research subject speaks the language that was used to explain this research and is receiving an informed consent form in their primary language. The participant signing this consent form has (1) been given the time and place to read and review this consent form; (2) been given an opportunity to ask questions regarding the nature, risks and benefits of participation in this research study; and (3) appears to understand the nature and purpose of the study and the demands required of participation. This research subject has provided legally effective informed consent.

Signature of Investigator	Date	Time

Principal Investigator	**Phone**
W. Larry Gluck, MD	(864) 455-3600

Co-Investigators	**Phone**
Rob Brevetta, MD	(864) 455-3600
Sean Callahan, MD	(864) 455-3600
Antine Stenbit, MD	(864) 455-3600
W. Jeffery Edenfield, MD	(864) 455-3600
Julie Martin, DNP	(864) 455-3600

Participant's Initials