Document:
Informed Consent Form

Official Study Title:
CONNECTS Master Protocol for Clinical Trials targeting macro-, micro-immuno-thrombosis, vascular hyperinflammation, and hypercoagulability and renin-angiotensin-aldosterone system (RAAS) in hospitalized patients with COVID-19 (ACTIV-4 Host Tissue)

Document Date: July 17, 2023

NCT: 04924660

Institutional Review Board
Informed Consent Document for Research
MASTER CONSENT

Study Title: **CONNECTS Master Protocol for Clinical Trials targeting macro-, micro-immuno-thrombosis, vascular hyperinflammation, and hypercoagulability and renin-angiotensin-aldosterone system (RAAS) in hospitalized patients with COVID-19 (ACTIV-4 Host Tissue)**

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Part 1 of 2: MASTER CONSENT

Name of participant: _____ Age: _____

You are being invited to take part in a research study. This is a multi-site study, meaning it will take place at several different locations. Because this is a multi-site study this consent form includes two parts. Part 1 of the consent form is the Master Consent and includes information that applies to all study sites. Part 2 of the consent form is the Study Site Information and includes information specific to the site where you are being asked to enroll. Both parts together are the legal consent document and must be provided to you.

Key Information:
The first section of this document contains some key points that the research team thought you would find important. The study is described in more detail after this section. If you do not understand something, please ask the person who is talking to you about the study.

Key information about this study

The purpose of this study is to understand if new drugs help patients in the hospital with COVID-19 get better faster. Getting better faster includes getting off oxygen and going home from the hospital. This study will enroll up to 2000 people at up to 100 sites.

COVID-19 can cause serious health problems, including difficulty with breathing, failure of the lungs, and death. In this study, researchers are testing drugs that might help people recover from COVID-19 and prevent serious complications, such as long-term use of oxygen, lung failure and death. No one knows for sure if these drugs help will people get better from COVID-19. The purpose of this study is to figure out if the drugs being studied are helpful for people like you who are in the hospital with COVID-19.

If you join this study, you will receive standard medical treatments for COVID-19. In addition, you will receive study drug or placebo.

You will be in the study for about 90 days. We will draw blood and record your blood tests. The study team will check on you while you are in the hospital and contact you after you leave the hospital.

Detailed Information:
The rest of this document includes detailed information about this study.

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You are being asked to take part in this research study because you have Coronavirus Disease 2019 (COVID-19) and are being treated for it in the hospital.

Doctors and researchers think that the drugs being studied in this research study might help patients with COVID-19 get better faster, but no one knows for sure. The goal of the drugs being studied is to try to prevent or reverse some of the damage from COVID-19.

Some patients may need to have one of their home drugs changed or stopped because it may interact with the study drug. You will be told if any of your home drugs need to be changed or stopped for you to take part in this study.

This study is a randomized, blinded and placebo-controlled platform trial. Randomized means that no one can choose who receives study drug and who receives placebo. It is up to chance. Blinded means that you, your doctors, nurses, and the study team will not know if you get the study drug or placebo. A placebo is made to look like a study drug but does not have any drug in it. Researchers use a placebo to see if the study drug works better or is safer than not taking study drug. Platform means that there are many study drugs, and you could get one of several study drugs or placebos.

We do not know if the study drug(s) will make you better or worse or have no effect. The study drugs are not approved to treat COVID-19 by the Food and Drug Administration (FDA). The researchers have permission from the FDA to study these drugs to figure out if they work for COVID-19.

Chance of getting a study drug or placebo.
Your chance of getting one of the study drugs or a placebo depends on the number of study drugs available at the time you start the study. You will also get information about each drug that you might get. Each patient will get only one study drug or one placebo.

Here are your chances of getting a study drug or placebo:

Number of study drugs	**Chance of getting a study drug**	**Chance of getting a placebo**
1 study drug	1 out of 2	1 out of 2
2 study drugs	2 out of 3	1 out of 3
3 study drugs	3 out of 4	1 out of 4
4 study drugs	4 out of 5	1 out of 5
5 study drugs	5 out of 6	1 out of 6

You do not have to be in this research study. You may choose not to be in this study, and to get other treatments, without changing your healthcare, services, or other rights. You can stop being

in this study at any time. If we learn something new that may affect the risks or benefits of this study, you will be told so that you can decide whether or not you still want to be in this study.

Side effects and risks that you can expect if you take part in this study:
Are there any risks to me?
A risk of taking part in this study is the possibility of a loss of confidentiality or privacy. Loss of privacy means having your personal information shared with someone who is not on the study team and was not supposed to see or know about your information. The study team plans to protect your privacy.

Blood Draw
Pain, redness, soreness, bruising, or infection may occur at the needle stick site. Rarely some people faint.

Risks that are not known
Because this treatment is investigational, meaning non-FDA approved for COVID-19, there may be risks that we do not know about at this time.

Good effects that might result from this study:
The benefits to science and humankind that might result from this study. Researchers will learn more about which drugs help patients recover from COVID-19 and will also learn more about how COVID-19 makes people sick.

Procedures to be followed:
Baseline and Randomization (Day 0)
Before you start the study drug, we will review your medical record and collect information about you, including your COVID-19 symptoms (such as, fever, cough, and shortness of breath) and other health conditions. We will confirm that you have a positive COVID-19 test. We will draw about 36 ml (about 7 teaspoons) of blood to check your health and for research purposes (if you are enrolled at a site taking part in research blood collection).

Study Drug or Placebo
You will start taking a study drug or placebo while you are in the hospital. The details of each drug are shown on the drug information sheets.

Day 1 thru Day 28
We may draw 5 mL (about 1 teaspoon) of blood each day you are receiving study medication to look at your health.

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On Days 1, 3, and after study drug has stopped, we may draw an additional 36 mL (about 7 teaspoons) of blood for research purposes (if you are enrolled at a site taking part in research blood collection). Some of this blood will be stored for future research.

Between Day 1 and Day 28, we will check on you on Days 1, 3, 7, 14, 21, and 28. If you are out of the hospital, we will contact you by phone or email, text, or survey.

Day 60
Around day 60, we will contact you to check on how you are doing. If you are out of the hospital, we will check on you by phone or email, text, or survey.

Day 90
Around day 90, we will contact you to check on how you are doing. If you are out of the hospital, we will check on you by phone or email, text, or survey.

Will I ever know if I received an active study drug or a placebo?
The study team does not plan to tell you if you received study drug or placebo. You may request to receive this information (whether you received study drug or placebo) after all people who were treated have completed the 90-day follow-up. Please contact the site investigator (study doctor) where you were enrolled in the study to receive this information.

Reasons why the study doctor may take you out of this study:
The study doctor may stop you from taking part in this study at any time:
1. if it is in your best interest,
2. if you do not follow the study procedures, or
3. if the study is stopped.

Payments for your time spent taking part in this study:
If you complete the first visit for the study, which occurs in the hospital, you will receive $50. You will receive an additional $50 for completing all study activities through day 28, and an additional $50 for completing 90-day follow-up. Thus, if you complete all study procedures you will receive a total of $150.

What will happen if you decide to stop being in this study?
If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

If your study drug is stopped for any reason, we will still want to keep in contact with you for 90 days to be sure you have not had any problems related to the study and see how you are doing. If you leave this study early, or are withdrawn from the study, no additional information about

you will be collected; however, information already collected about you in the study may continue to be used.

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

Privacy
Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your research samples. These tests may help us, or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Researchers at other institutions outside of Vanderbilt University Medical Center (VUMC), which serves as the Coordinating Center for this study, who are working with VUMC may contact you to ask you to take part in future studies about how COVID-19 has affected you. These researchers will be provided with your contact information and may also request information from VUMC that was collected from you in this study.

National Institutes of Health (NIH) Data Sharing
De-identified data from this study will be shared with other researchers. De-identified means that your name will not be included in the shared data and no one outside the team doing this study will be able to figure out the data belongs to you. The National Institutes of Health (NIH), which is part of the United States government, is paying for this study. Data will be shared per the NIH Data Sharing Policy. Data and specimens will be shared using the two services listed below.

1. BioLINCC. Information is available at: https://biolincc.nhlbi.nih.gov/home
2. BioData Catalyst. Information is available at: https://biodatacatalyst.nhlbi.nih.gov

Study Results
The results of this study will be published but you will not be individually identified.

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Master Consent Drug Information Sheet

Study Drug: Fostamatinib

Introduction
The purpose of this addendum to the informed consent document is to tell you about one of the study drugs called **Fostamatinib**. You are being given this drug information sheet about **Fostamatinib** because you might get this drug if you join the study. This addendum is intended to be used with Part 1 (Master Consent) and Part 2 (Study Site Information) of the informed consent document.

About the study drug Fostamatinib
The study drug Fostamatinib is marketed in the United States (US) and the European Union under the brand names of Tavalisse and Tavlisse for the treatment of chronic immune thrombocytopenia but is not currently approved by the FDA to be used in the treatment of COVID-19 and is therefore considered investigational in this study. Due to previous studies, researchers believe fostamatinib could also help patients with COVID-19. The purpose of this study is to find out if fostamatinib helps COVID-19 patients. Fostamatinib is a kinase inhibitor indicated for the treatment of thrombocytopenia (low platelets). Researchers believe that using Fostamatinib could reduce the risk of bleeding and lung tissue injury and thereby allow people to come off oxygen faster and go home sooner. Fostamatinib has been used in over 4630 patients in other studies. Most of these studies were evaluating Fostamatinib in patients with other health problems besides COVID-19. Overall, Fostamatinib has been well tolerated by these patients in other studies, meaning that there were not many serious side effects seen. Possible side effects from Fostamatinib are listed in detail below in this document.

Will you definitely get Fostamatinib?
Each person in the study will be randomly assigned to receive either study drug or study placebo. This means that you have a 50/50 chance to get Fostamatinib or a placebo (a tablet that is made to look like Fostamatinib).

How is Fostamatinib given?
Fostamatinib is a tablet that will be taken two times a day for up to 14 days.

Fostamatinib placebo
In this study, you might get a placebo that looks like Fostamatinib. This placebo is a tablet that looks like Fostamatinib but contains no Fostamatinib. The Fostamatinib placebo is not expected to have any effect on your health. The Fostamatinib placebo tablet will be taken two times a day for up to 14 days.

If you are unable to take study treatment by mouth
If you are unable to take study treatment by mouth, for example if you are on a ventilator, the study treatment tablets can be crushed and added to approximately 10 mL of water. In this case, the study team will administer study treatment to you through a feeding tube, usually inserted through the nose.

If you are discharged from hospital before completing 14 days of study treatment
You will be asked to take the tablets yourself, twice daily by mouth, once in the morning and once in the evening (at least 8 hours apart). If you miss taking a tablet, please take the next dose at the normal time

and do not take 2 doses to make up for the missed dose. The tablets can be taken with or without food. If you experience an upset stomach, it may be best to take the tablets with food.

Possible benefits of Fostamatinib in COVID-19
We think Fostamatinib might prevent some of the lung damage caused by SARS-CoV-2, which is the virus that causes COVID-19. Fostamatinib might decrease the amount of swelling (inflammation) in the lungs and prevent the body from making small blood clots. Possible benefits include being able to breathe better, getting off oxygen faster, leaving the hospital sooner and preventing damage from SARS-CoV-2 to the heart and kidneys. We do not know if you will have these benefits or not.

Possible Side Effects and Risks of Fostamatinib
Like all drugs, Fostamatinib can have side effects, which are problems caused by the drug. We do not expect everyone who takes Fostamatinib to have side effects. People in the study will be carefully monitored to see if side effects are happening. Most of the information on possible side effects from Fostamatinib comes from studies in patients who did not have COVID-19. The list below shows the side effects that people have had in other studies. Side effects could be different in patients with COVID-19. During the study, we will carefully monitor for the side effects listed below and other ones.

<u>Common side effects (≥10% of patients):</u>
- Diarrhea (loose stool)
- Hypertension (new or worsening high blood pressure)
- Nausea (feeling sick to the stomach)
- Dizziness (tiredness)
- High levels of certain liver blood tests (increased liver enzymes, increased alanine aminotransferase, or increased aspartate aminotransferase)
- Upper and lower respiratory tract infection

<u>Uncommon side effects (1-10% of patients):</u>
- Rash (change in the color and texture of skin that usually causes an outbreak of red patches or bumps on the skin)
- Chest pain not caused by heart disease
- Fatigue (tiredness)
- Decreased number of white blood cells that fight infection (neutropenia)
- Abdominal pain (pain in the stomach)
- Abnormal taste
- An inflammation of lining in the tubes carrying air to your lungs (bronchitis)
- Infection of the urinary system (the kidneys, bladder, or urethra)

<u>Rare side effects (<1% of patients)</u>
- Serious diarrhea (lots of loose stool)
- Sepsis (the body's overwhelming and life-threatening response to infection that can lead to tissue damage, organ failure, and death)
- Increased blood lactate dehydrogenase (LDH) (increased enzyme level related to tissue damage)
- Peripheral edema (swelling in the lower legs and/or hands

You should talk to your study doctor about any side effects that you have while taking part in the study. You should tell the study doctor if you have any problems with your health or the way you feel while taking part in the study, whether or not you think it is related to the study.

In addition to the risks or discomforts listed here, there may be other risks that are currently not known. Also, the risks or discomforts described may occur more often or be more severe than have been seen before.

Allergic Reaction Risks
Sometimes people have allergic reactions to drugs. Some signs that you may be having an allergic reaction are:
- Rash or hives
- Having a hard time breathing
- Wheezing when you breathe
- Sudden change in blood pressure (making you feel dizzy or lightheaded)
- Swelling around the mouth, throat, or eyes
- Fast pulse
- Sweating

Some allergic reactions can be serious and life-threatening, and very infrequently may result in death. You should get medical help and contact the study doctor or staff if you have any of these or any other side effects during the study.

The study drug must be taken only by you. It must be kept out of the reach of children and others.

Pregnancy and Breast Feeding with Fostamatinib
Pregnancy related instructions for women
The use of Fostamatinib in pregnancy presents a significant risk of birth defects based on studies in pregnant animals. As such, women who are pregnant will not be included in this study. Women who have childbearing potential will be able to participate in the study if they have a negative pregnancy test. Women are considered to have childbearing potential unless they have one or more of the following:
1) no menstrual periods for more than one year after menopause (change of life)
2) a prior sterilization surgery (tubes tied)
3) a prior hysterectomy (removal of uterus or womb)

If you are a woman of childbearing potential, you must agree to take medically acceptable steps to not get pregnant between the first dose of study drug and 24 hours after your last dose of study drug. Medically acceptable steps to not get pregnant include any of the following:
1) not having sex with a male partner
2) using an approved hormonal contraceptive medication (such as birth control pills, Depo-Provera, or Lupron Depot)
3) using a barrier method (such as a condom or diaphragm) along with spermicide during sex
4) having an intrauterine device (IUD) in place

It is important for you to tell the study doctor immediately if you become pregnant between the first dose of study drug and 30 days after the last dose of study drug. If this happens, the study doctor will discuss

with you what to do. If you become pregnant during the study, no additional study drug doses will be given. Additional information will be collected about the pregnancy and the baby.

Breast-feeding related instructions
The effects of Fostamatinib on breastmilk and children who ingest breastmilk with Fostamatinib are unknown. If you are breastfeeding, you will be excluded from this study.

Pregnancy-related instructions for men
The effects of Fostamatinib on sperm are unknown. If you are a man and could impregnant a woman, you must agree to take medically acceptable steps to prevent pregnancy between your first dose of study drug until 7 days after your last dose of study drug. Men who have had either of the following procedures are considered not to have the potential to impregnant a woman:

1) vasectomy (cutting of the vas deferens)
2) bilateral orchiectomy (removal of both testicles; castration)

Medically acceptable steps to prevent pregnancy for men who have the potential to impregnant a woman include:

1) not having sex with a female partner
2) female partner using an approved hormonal contraceptive medication (such as birth control pills, Depo-Provera, or Lupron Depot)
3) using a barrier method (such as a condom or diaphragm) along with spermicide during sex
4) female partner having an intrauterine device (IUD) in place

It is important for you to tell the study doctor immediately if sexual activity between the first dose of study drug and 30 days after the last dose of study drug resulted in pregnancy. If this happens, the study doctor will discuss with you what to do.

What are the risks of using Fostamatinib in combination with other drugs?
Tell the study doctor or his/her study staff about any drugs you are taking, have taken recently, or are planning to take, including herbal medicines, supplements, and drugs you take without a prescription. There are certain medications that you should not take during the study. Your study doctor will discuss these with you. Please discuss any concerns you may have with the study doctor. You should refrain from drinking alcohol while taking study drug.

Additional monitoring while taking Fostamatinib:
Your blood pressure, blood counts, and your liver function will be checked daily during hospitalization while on study drug. If there is a change in status, you will have these tests repeated after hospital discharge. After discharge from the hospital, you may need to have your blood pressure checked and have 10 ml of blood drawn to check your liver function or blood counts at more than one time point. If this needs to be done somebody could come to your house or you could come to the hospital or go to a local lab after discussion with the study team. If you only need to have your blood pressure checked, we may send you home with a blood pressure device and instructions to check your blood pressure at home. You will need to check your blood pressure 7 days after discharge and if needed one more time. You will not need to return the blood pressure device.

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Version Date: October 19, 2021

Master Consent Drug Information Sheet
Study Drug: TRV027

Introduction
The purpose of this addendum to the informed consent document is to tell you about one of the study drugs called **TRV027**. You are being given this drug information sheet about **TRV027** because you might get this drug if you join the study. This addendum is intended to be used with Part 1 (Master Consent) and Part 2 (Study Site Information) of the informed consent document.

About the study drug TRV027
The study drug TRV027 works in the body in what is called the Renin Angiotensin Aldosterone System (RAAS). The RAAS normally helps control blood pressure and the amount of water and salt in the body. The virus that causes COVID-19 (which is called SARS-CoV-2) attacks the RAAS, which likely causes some of the symptoms and lung problems of COVID-19. TRV027 attaches to one of the receptors in the RAAS. We think that by attaching to this receptor, TRV027 might prevent lung problems from COVID-19 and allow people to come off oxygen faster and go home faster. TRV027 is an investigational drug, meaning that it is not available outside of research studies and has not been approved by the US Food and Drug Administration (FDA). TRV027 has been used in over 300 patients in other studies. Most of these studies were evaluating TRV027 as a treatment for heart failure. More recently, TRV027 has been studied in patients with COVID-19. Overall, TRV027 was well tolerated by these patients in other studies, meaning that there were not many serious side effects seen. Possible side effects from TRV027 are listed in detail below in this document.

Will you definitely get TRV027?
No, all patients in the study will not get TRV027. Several drugs are being studied. You will be shown information on all the study drugs that you might get during the study. Each person in the study will be randomly assigned to receive one study drug or to receive one study placebo. This means that you have a chance to get TRV027 or a placebo (salt water that is made to look like TRV027) but are not guaranteed to get either TRV027 or the placebo that looks like TRV027.

How is TRV027 given?
TRV027 is given through your IV line (a small plastic hose in your vein). It will be given for 24 hours per day for 5 days or until you are ready to leave the hospital, whichever happens first.

TRV027 placebo
In this study, you might get a placebo that looks like TRV027. This placebo is sterile saline (salt water) and is not expected to have any effect on your health. The TRV027 placebo is given through your IV line (a small plastic hose in your vein) for 24 hours per day for 5 days or until you are ready to leave the hospital,

whichever happens first. You, your doctors and nurses, and the study team will not know if you are getting TRV027 or the placebo.

Possible benefits of TRV027 in COVID-19
TRV027 attaches to a receptor in the RAAS system. We think this might prevent some problems caused by SARS-CoV-2, which is the virus that causes COVID-19. TRV027 might decrease the amount of swelling (inflammation) in the lungs and prevent the body from making small blood clots. Possible benefits include being able to breathe better, getting off oxygen faster, leaving the hospital sooner and preventing damage from SARS-CoV-2 to the heart and kidneys. We do not know if you will have these benefits or not.

Possible Side Effects and Risks of TRV027
Like all drugs, TRV027 can have side effects, which are problems caused by the drug. We do not expect everyone who takes TRV027 to have side effects. People in the study will be carefully monitored to see if side effects are happening. Most of the information on possible side effects from TRV027 comes from studies in patients who did not have COVID-19. The list below shows the side effects that people have had in other studies. Side effects could be different in patients with COVID-19. During the study, we will carefully monitor for the side effects listed below and other ones.

Common side effects (≥10% of patients):
- none

Uncommon side effects (1%-10% of patients):
- Feeling of fullness or tightness in the abdomen (abdominal distension)
- Tiredness (fatigue)
- Passing of gas (flatulence)
- Muscle twitching (myoclonus)
- Pain in the joints (arthralgia)
- Pain in the head (headache)
- Shaking (tremors)
- Dizziness
- Tingling (paresthesia)
- Feelings of dryness, itchiness, pain, or grittiness in the eye (eye irritation)
- Fast heart rate (tachycardia)

Rare (<1% of patients)
- Drop in blood pressure (hypotension)

Pregnancy and Breast Feeding with TRV027
Pregnancy related instructions for women

There have been no studies in pregnant women using this drug. Therefore, the risks of TRV027 in pregnancy are unknown. Women who are pregnant will not be included in this study. Women who have childbearing potential will be able to participate in the study if they have a negative pregnancy test. Women are considered to have childbearing potential unless they have one or more of the following:

1) no menstrual periods for more than one year after menopause (change of life)
2) a prior sterilization surgery ("tubes tied;" tubal ligation)
3) a prior hysterectomy (removal of womb or uterus)

If you are a woman of childbearing potential, you must agree to take medically acceptable steps to not get pregnant between the first dose of study drug and 24 hours after your last dose of study drug. Medically acceptable steps to not get pregnant include any of the following:

1) not having sex with a male partner
2) using an approved hormonal contraceptive medication (such as birth control pills, Depo-Provera, or Lupron Depot)
3) using a barrier method (such as a condom or diaphragm) along with spermicide during sex
4) having an intrauterine device (IUD) in place

It is important for you to tell the study doctor immediately if you become pregnant between the first dose of study drug and 24 hours after the last dose of study drug. If this happens, the study doctor will discuss with you what to do. If you become pregnant during the study, no additional study drug doses will be given. Additional information will be collected about the pregnancy and the baby.

Breast-feeding related instructions

The effects of TRV027 on breastmilk and children who ingest breastmilk with TRV027 are unknown. If you are breastfeeding, you will be excluded from this study.

Pregnancy-related instructions for men

The effects of TRV027 on sperm are unknown. If you are a man and could impregnant a woman, you must agree to take medically acceptable steps to prevent pregnancy between the first dose of study drug until 24 hours after your last dose of study drug. Men who have had either of the following procedures are considered not to have the potential to impregnant a woman:

1) vasectomy (cutting of the vas deferens)
2) bilateral orchiectomy (removal of both testicles; castration)

Medically acceptable steps to prevent pregnancy for men who have the potential to impregnant a woman include:

1) not having sex with a female partner
2) female partner using an approved hormonal contraceptive medication (such as birth control pills, Depo-Provera, or Lupron Depot)
3) using a barrier method (such as a condom or diaphragm) along with spermicide during sex

4) female partner having an intrauterine device (IUD) in place

It is important for you to tell the study doctor immediately if sexual activity between the first dose of study drug and 24 hours after the last dose of study drug resulted in pregnancy. If this happens, the study doctor will discuss with you what to do.

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Version Date: October 19, 2021

Master Consent Drug Information Sheet

Study Drug: TXA127

Introduction
The purpose of this addendum to the informed consent document is to tell you about one of the study drugs called **TXA127**. You are being given this drug information sheet about **TXA127** because you might get this drug if you join the study. This addendum is intended to be used with Part 1 (Master Consent) and Part 2 (Study Site Information) of the informed consent document.

About the study drug TXA127
The study drug TXA127 works in the body in what is called the Renin Angiotensin Aldosterone System (RAAS). The RAAS normally helps control blood pressure and the amount of water and salt in the body. The virus that causes COVID-19 (which is called SARS-CoV-2) attacks the RAAS, which likely causes some of the symptoms and lung problems of COVID-19. TXA127 replaces some of the chemicals that are lost due to SARS-CoV-2 infection. TXA127 replaces a chemical called Ang (1-7). We think that by increasing the levels of Ang (1-7), TXA127 might prevent lung problems from COVID-19 and allow people to come off oxygen faster and go home sooner. TXA127 is an investigational drug, meaning that it is not available outside of research studies and has not been approved by the US Food and Drug Administration (FDA). TXA127 has been used in over 100 patients in other studies. Most of these studies were evaluating TXA127 in patients with other health problems besides COVID-19. More recently, TXA127 has been studied in patients with COVID-19. Overall, TXA127 was well tolerated by these patients in other studies, meaning that there were not many serious side effects seen. Possible side effects from TXA127 are listed in detail below in this document.

Will you definitely get TXA127?
No, all patients in the study will not get TXA127. Several drugs are being studied. You will be shown information on all the study drugs that you might get during the study. Each person in the study will be randomly assigned to receive one study drug or to receive one study placebo. This means that you have a chance to get TXA127 or a placebo (salt water that is made to look like TXA127) but are not guaranteed to get either TXA127 or the placebo that looks like TXA127.

How is TXA127 given?
TXA127 is given through your IV line (a small plastic hose in your vein). It will be given for 3 hours each day for 5 days or until you are ready to leave the hospital, whichever happens first.

TXA127 placebo
In this study, you might get a placebo that looks like TXA127. This placebo is sterile saline (salt water) and is not expected to have any effect on your health. The TXA127 placebo given through your IV line (a small plastic hose in your vein) for 3 hours each day for 5 days or until you are ready to leave the hospital,

whichever happens first. You, your doctors and nurses, and the study team will not know if you are getting TXA127 or the placebo that looks like TXA127.

Possible benefits of TXA127 in COVID-19
TXA127 increases the levels of Ang (1-7) in the body. We think this might prevent some problems caused by SARS-CoV-2, which is the virus that causes COVID-19. TXA127 might decrease the amount of swelling (inflammation) in the lungs and prevent the body from making small blood clots. Possible benefits include being able to breathe better, getting off oxygen faster, leaving the hospital sooner and preventing damage from SARS-CoV-2 to the heart and kidneys. We do not know if you will have these benefits or not.

Possible Side Effects and Risks of TXA127
Like all drugs, TXA127 can have side effects, which are problems caused by the drug. We do not expect everyone who takes TXA127 to have side effects. People in the study will be carefully monitored to see if side effects are happening. Most of the information on possible side effects from TXA127 comes from studies in patients who did not have COVID-19. The list below shows the side effects that people have had in other studies. Side effects could be different in patients with COVID-19. During the study, we will carefully monitor for the side effects listed below and other ones.

<u>Common side effects (≥10% of patients):</u>
- Pain in the head (headache)
- Feeling sick to the stomach (nausea)

<u>Uncommon side effects (1-10% of patients):</u>
- Muscle pain (myalgia)
- Bone pain
- Feeling of fullness and tightness in the abdomen (abdominal distension)
- Tiredness (fatigue)
- Feeling symptoms of body pains and feverishness (flu like illness symptoms)
- Difficulty passing stool (constipation)
- Dry mouth
- Infection of the mouth (gingivitis)
- Throwing up (vomiting)
- Mouth pain
- Loose stool (diarrhea)
- Bloated feeling (abdominal bloating)
- Mouth dryness
- Shaking (tremors)

<u>Rare side effects (<1% of patients)</u>

- A low count of the blood cells that fight infection (neutropenia)
- A low count of the blood cells that carry oxygen (anemia) – this can cause tiredness and shortness of breath, and if severe, can be treated with a blood transfusion
- Drop in blood pressure (hypotension)

Pregnancy and Breast Feeding with TXA127

Pregnancy related instructions for women

There have been no studies in pregnant women using this drug. Therefore, the risks of TXA127 in pregnancy are unknown. Women who are pregnant will not be included in this study. Women who have childbearing potential will be able to participate in the study if they have a negative pregnancy test. Women are considered to have childbearing potential unless they have one or more of the following:

4) no menstrual periods for more than one year after menopause (change of life)
5) a prior sterilization surgery (tubes tied)
6) a prior hysterectomy (removal of uterus or womb)

If you are a woman of childbearing potential, you must agree to take medically acceptable steps to not get pregnant between the first dose of study drug and 24 hours after your last dose of study drug. Medically acceptable steps to not get pregnant include any of the following:

1) not having sex with a male partner
2) using an approved hormonal contraceptive medication (such as birth control pills, Depo-Provera, or Lupron Depot)
3) using a barrier method (such as a condom or diaphragm) along with spermicide during sex
4) having an intrauterine device (IUD) in place

It is important for you to tell the study doctor immediately if you become pregnant between the first dose of study drug and 24 hours after the last dose of study drug. If this happens, the study doctor will discuss with you what to do. If you become pregnant during the study, no additional study drug doses will be given. Additional information will be collected about the pregnancy and the baby.

Breast-feeding related instructions

The effects of TXA127 on breastmilk and children who ingest breastmilk with TXA127 are unknown. If you are breastfeeding, you will be excluded from this study.

Pregnancy-related instructions for men

The effects of TXA127 on sperm are unknown. If you are a man and could impregnant a woman, you must agree to take medically acceptable steps to prevent pregnancy between your

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first dose of study drug until 24 hours after your last dose of study drug. Men who have had either of the following procedures are considered not to have the potential to impregnant a woman:

1) vasectomy (cutting of the vas deferens)
2) bilateral orchiectomy (removal of both testicles; castration)

Medically acceptable steps to prevent pregnancy for men who have the potential to impregnant a woman include:

1) not having sex with a female partner
2) female partner using an approved hormonal contraceptive medication (such as birth control pills, Depo-Provera, or Lupron Depot)
3) using a barrier method (such as a condom or diaphragm) along with spermicide during sex
4) female partner having an intrauterine device (IUD) in place

It is important for you to tell the study doctor immediately if sexual activity between the first dose of study drug and 24 hours after the last dose of study drug resulted in pregnancy. If this happens, the study doctor will discuss with you what to do.

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Part 2 of 2: STUDY SITE INFORMATION

Site Name:	Vanderbilt University Medical Center
Site Principal Investigator:	Wesley H. Self, MD, MPH
Site Principal Investigator Contact:	615-936-4790
Site Study Coordinator *(if applicable)*:	Karen Miller
Site Study Coordinator Contact *(if applicable)*:	615-936-4790

This part of the consent form includes information about the site that is asking you to participate in this study and is specific to participation at your site only. Before making your decision, both the site-specific information and the general study information should be reviewed with you. Your medical record will contain a note saying you are in a research study and may contain some research information about you. Anyone you authorize to receive your medical record will also get this information.

Costs to you if you take part in this study:
If you agree to take part in this research study, you and/or your insurance will not have to pay for the tests and treatments that are being done only for research. However, you are still responsible for paying for the usual care you would normally receive for the treatment of your illness. This includes treatments and tests you would receive even if you were not in this study. These costs will be billed to you and/or your insurance.

You have the right to ask what it may cost for the routine (non-research) care you are receiving. If you would like assistance, financial counseling is available through the Vanderbilt Financial Assistance Program. The study staff can help you contact this program. You have the right to contact your insurance company to discuss the costs of your routine (non-research) care further before choosing to be in the study. You may choose not to be in this study if your insurance does not pay for your routine (non-research) care. Your doctor can discuss other treatment plans with you.

Payment in case you are injured because of this research study:
If it is determined by Vanderbilt and the study investigator that an injury occurred as a direct result of the tests or treatments that are done for research, then you and/or your insurance will not have to pay for the cost of immediate medical care provided **at Vanderbilt** to treat the injury.

There are no plans for Vanderbilt to pay for any injury caused by the usual care you would normally receive for treating your illness or the costs of any additional care. There are no plans for Vanderbilt to give you money for the injury.

A new public health declaration, called the Public Readiness and Emergency Preparedness Declaration (PREP), was issued by the Department of Health and Human Services on March 10, 2020.

This declaration may limit the legal rights of a subject taking part in a COVID-19 clinical study that uses a drug, device or vaccine designed to treat, diagnose, cure, or prevent COVID-19. This includes the study drugs used in this study. Subjects using the drugs in this study may have limits on their right to sue the manufacturers, the study sponsor, healthcare providers and others for significant injuries and adverse reactions.

Under some circumstances, compensation may still be available under the PREP Declaration for certain patients who sustain injuries. To find out more, go to https://www.hrsa.gov/cicp/about/index.html or call 1-855-266-2427.

Who to call for any questions or in case you are injured:

If you should have any questions about this research study or if you feel you have been hurt by being a part of this study, please contact Wesley Self M.D. at 615-936-4790.

For additional information about giving consent or your rights as a person in this study, to discuss problems, concerns, and questions, or to offer input, please feel free to call the Vanderbilt University Medical Center Institutional Review Board Office at (615) 322-2918 or toll free at (866) 224-8273.

Confidentiality:

The study funder, [The National Heart, Lung and Blood Institute (NHLBI) of the National Institutes of Health (NIH)] and Vanderbilt University Medical Center may share your information and/or samples, without identifiers, to others or use them for other research projects not listed in this form. NHLBI, Vanderbilt University Medical Center, Dr. Self, and his staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information.

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It is the intent of the study doctor, study staff, and NHLBI that the health data that is sent to NHLBI will not identify you.

You will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

NHLBI and Vanderbilt University Medical Center may use the health data and/or samples sent to them:

1) To develop new tests
2) For other activities (such as development and regulatory)
3) As part of research activities related to the study of diseases and the development of drugs and tests used to treat diseases.
4) To allow outside researchers to use data and specimens that does not identify you.

There is a risk that if people outside the study get your health data, they could misuse it for purposes other than those outlined in this consent. The study team has strict privacy and confidentiality protection procedures in place to prevent this from occurring so the chance of this happening to you is extremely small.

Your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

This study may have some support from the National Institutes of Health (NIH). If so, your study information is protected by a Certificate of Confidentiality. This Certificate allows us, in some cases, to refuse to give out your information even if requested using legal means.

It does not protect information that we have to report by law, such as child abuse or some infectious diseases. The Certificate does not prevent us from disclosing your information if we learn of possible harm to yourself or others, or if you need medical help.

Disclosures that you consent to in this document are not protected. This includes putting research data in the medical record or sharing research data for this study or future research. Disclosures that you make yourself are also not protected.

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Authorization to Use/Disclose Protected Health Information
What information is being collected, used, or shared?
To do this research, we will need to collect, use, and share your private health information. By signing this document, you agree that your health care providers (including both at Vanderbilt University Medical Center and others) may release your private health information to us, and that we may use any and all of your information that the study team believes it needs to conduct the study. Your private information may include things learned from the procedures described in this consent form, as well as information from your medical record (which may include information such as HIV status, drug, alcohol or STD treatment, genetic test results, or mental health treatment).

Members of the study team or other agents of the study [including, but not limited to, several US government groups, such as the Food and Drug Administration (FDA), the Office of Human Research Protections (OHRP), the NIH, the NHLBI, and the research group helping NHLBI run COVID-19 research (CONNECTS)], who will be bound by the same provisions of confidentiality, will have access to the participants' medical information [(including both personal identifiable information (PII) and protected health information (PHI)].

Who will see, use or share the information?
The people who may request, receive, or use your private health information (PHI) include the researchers and their staff. Additionally, we may share your information with other people at Vanderbilt, for example, if needed for your clinical care or study oversight. By signing this form, you give permission to the research team to share your information with others outside of Vanderbilt University Medical Center. This may include study safety monitors, government agencies, data managers and other agents and contractors used by the study team. We try to make sure that everyone who sees your information keeps it confidential, but we cannot guarantee that your information will not be shared with others. If your information is disclosed by your health care providers or the research team to others, federal and state confidentiality laws may no longer protect it.

Do you have to sign this Authorization?
You do not have to sign this Authorization, but if you do not, you may not join the study.

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How long will your information be used or shared?
Your Authorization for the collection, use, and sharing of your information does not expire. Additionally, you agree that your information may be used for similar or related future research studies.

What if you change your mind?
You may change your mind and cancel this Authorization at any time. If you cancel, you must contact the Principal Investigator in writing to let him know by using the contact information provided in this consent form. Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

Send written notice of cancelling your authorization to be in this study to:
Wesley Self, M.D.
1313 21st Ave South
Oxford House 312
Nashville, Tennessee 37232
If you decide not to take part in this research study, it will not affect your treatment, payment or enrollment in any health plans or affect your ability to get benefits. You will get a copy of this form after it is signed.

STATEMENT BY PERSON AGREEING TO BE IN THIS STUDY
I have read this consent form and the research study has been explained to me verbally. All my questions have been answered, and I freely and voluntarily choose to take part in this study.

PARTICIPANT:

Date _____ Signature of patient/volunteer _____

Printed Name of patient/volunteer _____

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CONSENT OBTAINED BY:

Date | Signature

Printed Name and Title

WITNESS/INTERPRETER (if required):

Date | Witness/Interpreter Signature

Printed Witness/Interpreter Name

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Consent via a Surrogate Decision Maker

I, _____ [name of decision-maker/surrogate], am the _____ [state relationship to participant] of _____ [state participant's name]. I have read the informed consent document or it has been explained to me. I have had the opportunity to ask any questions and all of my questions have been answered. I have been informed that an investigational treatment may be administered to _____ [participant's name]. I believe receiving such treatment would be in the interests of _____ [participant's name] and is consistent with what he/she would have decided had he/she been able to do so.

Your decision to allow your family member/friend to participate in this research study is voluntary. You may choose not to allow his/her participation and he/she will receive alternative treatments without affecting his/her healthcare/services or other rights. You are also free to withdraw him/her from this study at any time. In the event new information becomes available that may affect the risks or benefits associated with this research study or your willingness to allow continued participation in this research study, you will be notified so that you can make an informed decision whether or not to continue your family member/friend's participation in this study.

Your family member/friend will periodically be re-evaluated for the capacity to give consent. If he/she is found to be capable, continued participation in this study would only occur with his/her consent.

_____ ___/___/___
Signature of Health Care Decision-Maker/Surrogate Date

_____ ___/___/___
Signature of Witness Date

_____
Name of witness

_____ ___/___/___
Name and Signature of person obtaining consent Date

_____
Name of person obtaining consent