Safety and Tolerability of Escalating Doses of Subcutaneous Elafin (Tiprelestat) Injection in Healthy Normal Subjects

Informed Consent Form

NCT03522935

September 17, 2019

DUKE UNIVERSITY HEALTH SYSTEM

Consent to Participate in a Research Study

Safety and Tolerability of Escalating Doses of Subcutaneous Elafin (Tiprelestat) Injection in Healthy Normal Subjects
DEPRU No.: NP05IRB No.: Pro00100164

CONCISE SUMMARY

The purpose of this study is find out if the study drug, Elafin, is safe in healthy adults. There is no cure for pulmonary arterial hypertension (PAH) at this time, however there are scientific reasons why this study drug may be beneficial for patients with this disease.

Approximately 30 healthy adults will be enrolled in this study. If you qualify for this study, your participation in the study will last for approximately 4-8 weeks. You will be given the study drug on each day for 7 days, and come back for follow up visits approximately 2 weeks and 4 weeks after the time of the first dose. The study drug or placebo (an inactive substance that looks and is given like the drug, but does not contain any of the drug) will be given as a subcutaneous injection (a shot inserted just under the skin) and you will have tests, exams and procedures performed as part of your care for study purposes.

There are risks to this study drug that are described in this document. Possible common side effects of the study drug (also seen in placebo control) include: headache, nausea and liver function test abnormalities which includes, low counts of red blood cells and high level of bilirubin in the blood.

If you are interested in learning more about this study, please continue reading below.

We are asking healthy individuals like you to participate in a study to see if the study drug, Elafin, is safe. Research studies are voluntary and include only people who choose to take part. Your decision not to participate will not have any negative effect on you or your medical care. You can decide to participate now, but withdraw your consent later and stop being in the study without any loss of benefits or medical care to which you are entitled.

Please read this consent form carefully and take your time making your decision. As your study doctor or study staff discusses this consent form with you, please ask him/her to explain any words or information that you do not clearly understand. We encourage you to talk with your family and friends before you decide to take part in this research study. The nature of the study, risks, inconveniences, discomforts, and other important information about the study are listed below.

Please tell the study doctor or study staff if you are taking part in another research study.

WHO WILL SPONSOR (PAY FOR) THIS STUDY?
This study is funded by the National Institutes of Health (NIH) through a grant awarded to Stanford University. The sponsor of the study, Stanford University, will pay Duke University Health System

(DUHS) to perform this research. Portions of Dr. Jeffrey Guptill, Dr. Kishan Parikh and their research team's salaries will be paid by this grant.

WHO WILL BE MY DOCTOR ON THIS STUDY?
If you decide to participate, Dr. Jeffrey Guptill and Dr. Kishan Parikh will be your doctors for this study and will be in contact with your regular health care provider throughout the time that you are in the study and afterwards, if needed.

WHY IS THIS STUDY BEING DONE?
The purpose of this study is to find out whether an investigational drug is safe and well tolerated. "Investigational" means the drug is being tested for safety and effectiveness and has not been approved by the Food and Drug Administration (FDA) for use in the United States. In this consent form, the investigational drug refers to Elafin. Elafin is being studied as a possible treatment for people with pulmonary arterial hypertension (PAH). Research studies have been done in animals and humans, but the product has not been tested when it is given subcutaneously or as an injection under the skin. The study will measure how the drug is moved to the bloodstream after being administered, and how long it takes for the body to remove the drug from the bloodstream.

There is no cure for PAH at this time, however there are scientific reasons why this study drug may be beneficial for patients with this disease. We are asking healthy individuals like you to participate in this study to see if this study drug is safe given in this manner.

Elafin has previously been given to 24 healthy human volunteers and 51 patients as a single intravenous (into the vein) dose, and there were no significant problems or bad effects in people who received the study drug.

However, before it can be tested in people with PAH, it is important to test Elafin in healthy volunteers. This study will look at the safety and tolerability of subcutaneous Elafin and will look at how the amount of drug in the blood changes over time. This will help the Sponsor determine what doses should be used later on. This is the first time that Elafin has been given as a shot under the skin or subcutaneously.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Approximately 30 people will take part in the active portion of the study at Duke. Additional subjects will be consented and screened in order to identify the 30 subjects needed.

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WHAT IS INVOLVED IN THE STUDY?
Five groups of subjects will be enrolled in the study. Each group will include six (6) subjects. In each group, approximately five (5) subjects will receive the study drug and one (1) subject will be given placebo. Which subjects will be given the study drug and which subjects will be given placebo will be decided using a randomization process (like drawing numbers from a hat) and no one will know which you have been given until the end of the study. This is called a double-blind study. Both the study drug and placebo will be administered by subcutaneous injection. Each group will receive one dose daily for 7 days.

Group 1:
Subjects will receive 0.03 milligram (mg)/kilogram (kg) of either Elafin, or placebo via subcutaneous injection.
Group 2:
Subjects will receive 0.06 mg/kg of either Elafin, or placebo via subcutaneous injection

Group 3:
Subjects will receive 0.1 mg/kg of either Elafin, or placebo via subcutaneous injection

Group 4:
Subjects will receive 0.15 mg/kg of either Elafin, or placebo via subcutaneous injection

Group 5:
Subjects will receive 0.18 mg/kg of either Elafin, or placebo via subcutaneous injection.

If you agree to be in this study, you will be asked to sign and date this consent form. No study procedures will begin until you have read and signed this document. You will have the following tests and procedures to make sure that you are eligible:

The study doctor will talk to you about the things you must do or not do to participate. Please tell your regular health care providers and any emergency care providers that you are in this research study.

The study will begin with a Screening visit. The purpose of the Screening visit is to find out if you meet all of the requirements to take part in this study. The Screening visit usually takes between 2-3 hours.

Summary of the study procedures:
You will have a screening visit approximately 1 to 28 days prior to the study beginning to determine if you are eligible to participate. You will be notified if you are eligible and a date will be set for you to begin study procedures. During your first visit you will be admitted for approximately 36-50 hours at the Duke Early Phase Clinical Research Unit (DEPRU). During that time you will receive the first two

subcutaneous injections of study drug or placebo under your skin and blood and urine samples will be collected for analysis. You will be assigned randomly (like drawing numbers from a hat) to receive either the study drug or placebo injection. Your chance of being in the study drug group is approximately 83%. You will be observed overnight in DEPRU. On the day of the discharge you will have additional tests done.

You will come back to DEPRU on Days 3, 4, 5. On Day 6 you will stay overnight again at DEPRU and be discharged on Day 7. You will have additional follow up visits on days 8, 10 and 28. You will have tests and procedures described below. You will receive a subcutaneous injection each day through day 7. You may get telephone calls from us to check on how you feel. Your final visit will be about 28 days after your first dose, where you will again go over the list of your medical problems with one of us and will tell us how you are feeling compared to when you first started the trial.

Details of the procedures:
Screening (Day -28 to -2) – the following procedures will occur during Screening:

- Before any study procedures are done, we will obtain informed consent and have you sign and date this document.
- We will ask you questions regarding your race, sex and ethnicity.
- We will ask about your current participation in research studies.
- We will ask about your medical history, including your current diagnoses, past diagnoses, surgical history, date of last menses for women, current contraceptive methods, smoking, drug and alcohol history and allergies.
- We will ask you about any current medications that you are taking and any medications taken in the past 30 days (including over the counter medications, herbal supplements and illicit substances).
- We will perform a complete physical exam including a neurological assessment; head, eyes, ears, nose and throat (HEENT); cardiovascular; lung; abdomen; skin; and musculoskeletal (muscle strength) examinations. Genital, rectal and pelvic examinations will not be performed.
- We will collect vital signs (heart rate, blood pressure, temperature, respiratory rate and pulse oximetry), measure height and weight and calculate your body mass index (BMI).
- We will do an Electrocardiogram (ECG) to measure the electrical activity of your heart.
- We will draw blood for laboratory tests (approximately 2 tablespoons); this will include:
    - biomarkers
    - pregnancy test if you are a woman of child-bearing potential
    - Tests for hepatitis B and C, and HIV

As part of this protocol you will be tested for Hepatitis B and C which causes injury to the liver and for HIV (human immunodeficiency virus), which is the virus that causes the acquired immunodeficiency

syndrome (AIDS). You will be notified of the results of the testing and counseled as to the meaning of the results, whether they are positive or negative. If the test indicates that you are infected with Hepatitis or HIV, you will receive additional counseling about the significance of your care and possible risks to other people. We are required to report all positive results to the North Carolina Division of Public Health. The test results will be kept confidential to the extent permissible under the law. If you do not want to be tested for Hepatitis B, Hepatitis C and HIV then you should not agree to participate in this study.

- We will ask for a urine sample for drug testing and a urinalysis (if the urinalysis is positive, we will send it for additional testing, to confirm the results of the test performed in the unit). If the drug screen was confirmed positive for an illicit drug and was subpoenaed or somehow disclosed, an unlikely event, it could be incriminating.
- We will do a breathalyzer test to check for alcohol.
- We will provide you with a list of house rules that goes over what is allowed during the confinement or overnight portion of the study.
- We will review all other inclusion and exclusion criteria and collect demographic information.

Day -1 Admission to DEPRU (overnight confinement unit)
If test results from Screening meet inclusion in the study, we will contact you by phone to schedule you to come in to be a part of the study. On the first day of the study, you will be admitted to the Duke Early Phase Research Unit (DEPRU). You will arrive early in the morning and should expect to be there between 36 and 50 hours.

You will have the following procedures:

- We will collect additional blood (approximately 2 tablespoon) to verify that your safety labs are still acceptable to be a part of the study.
- We will do a breathalyzer alcohol test and collect urine for a drug screen.
- A urine pregnancy test will be done if you are a woman of child-bearing potential.
- We will also collect urine for a urinalysis.
- We will perform a complete physical exam including a neurological assessment
- We will collect vital signs (heart rate, blood pressure, temperature, respiratory rate and pulse oximetry) and measure your weight.
- We will do an ECG.
- We will review your medical history, including your medications and previous medical conditions as well as your surgical history to assure that nothing has changed since your screening visit.
- We will review your current medications and verify that no other prescription medications or over the counter medication (with the exception of acetaminophen or ibuprofen) have been taken 7 days prior to the start of study drug.
- We will review the inclusion and exclusion criteria to confirm your eligibility

- Once all eligibility criteria have been confirmed, you will be randomized to receive study drug or placebo.
- You will be told what to expect on the following day – also known as the dosing day.

Day 1 pre-dose – Confinement Visit

- You will be awakened early and an IV line will be established (a small tube will be placed in your arm that will be used to collect blood from – approximately 1 teaspoon). This line will need to remain in place while you are in the unit.
- We will measure your vital signs (heart rate, blood pressure, pulse oximetry)
- We will perform an ECG.
- We will collect urine prior to dosing. This must be done within 15 minutes prior to you receiving your injection. This will also begin the 24 hour urine collection.
- We will collect blood prior to dosing. This must be done within 10 minutes prior to you receiving your injection.
- You will receive the first injection of study drug (drug or placebo) under your skin (each site of administration will be documented and observed so that the sites are rotated over the 7 day daily dosing period).

Day 1 (post-dose) – Confinement visit:

- We will draw a small amount of blood about 5, 15, 30, 45, 60 min, and 2, 4, 8, 12 hours after the injection of the study drug (drug or placebo). This is to learn how long the study drug stays in your body. The total amount of blood drawn will be about 4 tablespoons. The blood will be drawn from a small tube that was placed in your arm (IV). Should the IV no longer function, we will need to replace it or draw the blood from another vein in your arm.
- We will monitor your vital signs at 30 min, 1, 2, 4, 8 and 12 hours after the injection.
- We will perform an ECG at 1 and 12 hours after the injection.
- We will collect all of your urine for 24 hours after the injection.
- We will monitor you closely for any reactions or side effects from the study drug.

Day 2 (24 hours post-dose) – Day of Discharge:

- We will draw blood (approximately 2 tablespoons) and collect urine for safety measures.
- We will also draw blood for study purposes. This must be drawn within 10 minutes prior to receiving your second dose of medication.
- We will continue to collect urine until the 24 hour time point or after your injection.
- We will ask you if you have any new symptoms or medical problems since the last visit and we will do a physical exam if needed.
- We will monitor your vital signs.

- We will perform an ECG.
- You will be given your second subcutaneous injection of study drug or placebo.
- You will be discharged once you have been observed for at least one hour after your second injection and there is no medical reason to keep you in the unit for further evaluation. We will give contact information for any questions, concerns or emergencies.
- You will be told what to expect at your next visit.

Days 3, 4 and 5: Follow-up Visits

- We will ask you to report to DEPRU approximately the same time each day to draw blood (approximately 1 teaspoon) and collect urine. The time will be based on when you received your first dose of study drug or placebo
- We will obtain your vital signs.
- We will ask you if you have any new symptoms or medical problems since the last visit. If needed, you will have a physical exam.
- If you have taken any medication, even over the counter medication we will ask that you bring it in and indicate when you took it, what dose, and for how long.
- You will be given your next injection of study drug or placebo
- You will be discharged once you have been observed for at least one hour after your injection if there is no medical reason to keep you in the unit. We will give contact information for any questions, concerns or emergencies.
- You will be told what to expect on your next visit.

Day 6 – 2nd Confinement visit

- You will arrive to the unit at approximately the same time as you did on Days 3-5, but will be admitted to DEPRU for your second overnight stay.
- We will obtain your vital signs.
- We will ask you if you have any new symptoms or medical problems since the last visit. If needed, you will have a physical exam.
- If you have taken any medication, even over the counter medication we will ask that you bring it in and indicate when you took it, what dose, and for how long.
- We will draw blood (approximately 2 tablespoons).
- We will collect a urine sample.
- You will be given your next injection of study drug or placebo

Day 7 pre-dose – Confinement Visit

- You will be awakened early and an IV line will be placed in your arm (a small tube that is placed in your arm that will be used to collect blood). This line will need to remain in place while you are in the unit.

- We will measure your vital signs.
- We will perform an ECG (within 4 hours prior to dosing).
- We will collect urine prior to dosing. This must be done within 15 minutes prior to you receiving your injection. This will also begin the 24 hour urine collection.
- We will collect blood prior to dosing. This must be done within 10 minutes prior to you receiving your injection.
- You will receive the last injection of study drug or placebo under your skin
- You will be told what to expect on your next visit.

Day 7 (post-dose) - Confinement visit:

- We will draw a small amount of blood about 5, 15, 30, 45, 60 min, and 2, 4, 8, 12 hours after the injection of the study drug or placebo. This is to learn how long the study drug stays in your body. The total amount of blood drawn will be about 4 tablespoons. The blood will be drawn from a small tube that was placed in your arm (IV). Should the IV no longer function, we will need to replace it or draw the blood from another vein in your arm.
- We will monitor your vital signs at 30 min, 1, 2, 4, 8 and 12 hours after the injection.
- We will collect all of your urine for 24 hours after the injection.
- We will monitor you closely for any reactions or side effects from the medications.
- After the 12 hour time point is collected, you will be discharged if there is no medical reason to keep you in the unit. We will give contact information for any questions, concerns or emergencies.
- You will be told what to expect on your next visit.

Day 8 – Follow-up visit

- We will ask you to come to DEPRU at approximately the same time as Day 7 to draw blood (approximately 1 teaspoon) and collect urine. The time will be based on when you received your first dose of study drug or placebo.
- We will obtain your vital signs.
- We will ask you if you have any new symptoms or medical problems since the last visit.
- We will perform a complete medical examination including a neurological assessment.
- If you have taken any medication, even over the counter medication we will ask that you bring it in and indicate when you took it, what dose, and for how long.
- You will be told what to expect on your next visit.

Day 10: Follow-up visit

- We will draw blood (approximately 2 tablespoons)
- We will obtain your vital signs.
- We will ask you if you have any new symptoms or medical problems since the last visit. If needed, you will have a physical exam.

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Day 28: Final follow-up visit

- We will draw blood (approximately 4 tablespoons) and collect urine
- You will have a physical examination.
- We will ask you if you have any new symptoms or medical problems since the last visit.
- If you have taken any medication, even over the counter medication we will ask that you bring it in and indicate when you took it, what dose, and for how long
- We will obtain your vital signs
- We will perform an ECG

Blood and Urine Sampling for Research:

Blood and urine collected during this study will be sent to our research laboratory and saved for future testing. Research using blood and urine is an important way to try to understand human disease. You have been given this information because the investigators want to save the samples for future research. There are several things you should know before allowing your tissues to be studied.

Your blood and urine will be stored under a unique identifier (study number) that will be separated from your name. This will protect your identity and preserve anonymity. You have the right to refuse to allow your blood and urine to be studied now or saved for future study. You may withdraw from this study at any time. The investigators might retain the identified samples, e.g., as part of your routine clinical care, but not for additional research.

Please initial next to one of the two options:

_____ I consent to my samples being saved for future research
(initial)

_____ I do not consent to my samples being saved for future research
(initial)

HOW LONG WILL I BE IN THIS STUDY?

Your participation in the study will last for approximately 4-8 weeks. You will be given the study medication on each day for 7 days, and come back for follow up visits approximately 1, 2 and 4 weeks after the time of the first treatment. In total, during this time you will be required to stay DEPRU for 4 days, and visit Duke 6 more times. Confined D-1 - D2 (36-50 h) = 2 days

Confined D6 - D7 (24-40 h) = 2 days

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Total confinement approximately 4 days

FU Visits: D3, D4, D5, D8, D10, D28 = 6 days

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled. However, if you decide to stop participating in the study, we encourage you to talk to your doctor first.

Clinically relevant results of this research will not be communicated with you.

WHAT ARE THE RISKS OF THE STUDY?
As a result of your participation in this study, you are at risk for the following side effects. You should discuss these with the study doctor and your regular health care provider if you choose.

It is possible for any drug to cause side effects. In addition to the risks below, there may be risks that are currently unknown. If further risks are identified during the study, you will be told about them in a timely manner.

Risks of study drug Elafin:
This is the first study to inject a small dose of Elafin under the skin for a 7-day period. Current data shows that Elafin is safe and tolerated as a one-time large infusion. The following side effects were observed in other studies involving Elafin. However, it was not determined that they were related to Elafin more than they were to the placebo.

Possible rare side effects of Elafin, also seen with control placebo

- Lower hemoglobin / hematocrit – lower red blood count.
- Reduction in liver function
- Heart problems (myocardial hypertrophy or enlarging of the heart) – dysrhythmias (or abnormal beating of the heart)

Possible common side effects of Elafin, also seen with control placebo

- Headache
- Nausea
- Liver function test abnormalities
- Anemia – fatigue or paleness related to low red blood cell counts
- High level of total bilirubin in the blood which may indicate liver dysfunction

Possible side effect of Elafin, not seen in previous studies: Increased risk of Infection

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Elafin is a drug that may lower the ability of cells that fight infection and cause inflammation. Call you doctor right away if you have symptoms of any infection such as:

- Fever
- Sweats or chills
- Cough or flu-like symptoms
- Muscle aches
- Warm, red, or painful areas on your skin

Reproductive Risks:

For Women:

The study drug involved in this trial may have unknown risks for a developing pregnancy.

Women Who Are Able to Have Children

If you are a woman who has not had a hysterectomy or completed menopause, and have a partner who is capable of fathering a child, there are additional requirements to participate in this study.

Pregnancy Testing
A blood pregnancy test will be performed at screening and at your baseline visit and it must be negative prior to beginning other study activities. If the test is positive or indeterminate, you will be unable to continue in the study.

Although pregnancy tests are very accurate, it is still possible to have a negative test in very early pregnancy. If you think that there is a chance you could be pregnant, it is important that you contact your study doctor right away even if your last pregnancy test was negative.

Women who could possibly become pregnant must use two effective methods of birth control starting 28 days prior to the first dose of study drug, for the duration of the study.

One option is to abstain completely from vaginal intercourse for the duration of the study for 28 days prior to first dose of study drug, for the duration of the study and for the duration of the study.

If you and your partner are not currently using any method of birth control and abstinence is not an option for you, your study doctor will discuss options for you, other medications, personal preferences and the level of pregnancy prevention required by the study. Because some methods take several weeks to become fully effective, you may need to delay starting the study.

Highly effective methods of birth control are more than 99% effective in preventing pregnancy and include (a) partner vasectomy, (b) bilateral tubal sterilization, (c) intrauterine devices (IUDs), and (d)

hormonal implants. If you and your partner are currently using one of these methods, you should continue to use them along with some other method of birth control such as one of the barrier methods listed below (male or female condom or diaphragm). If you are using an IUD or implant and it is due to be changed during the planned duration of the study, you should discuss this with your study doctor.

Other hormonal methods of birth control, including birth control pills, patches, and vaginal rings, are approximately 90-95% effective in preventing pregnancies, while barrier methods (male condom or female condom or diaphragm) when used with a spermicide are approximately 85% effective. You and your partner must use two methods e.g.(birth control pills along with a diaphragm) of birth control for this study.

If pregnancy occurs
If you do become pregnant during the study, you should notify your study doctor immediately.

Men Who Are Able to Father Children
The study drug involved in this study may have risks for a developing pregnancy. Therefore, men who participate in the study who are able to father children and have a female partner who is able to become pregnant need to follow additional requirements in order to participate.

Some drugs may be present in semen, and it is possible that the drug may be absorbed during sexual activity and then be transmitted to a developing pregnancy. In order to minimize this risk, you will be asked to use a condom with spermicide every time you have intercourse for 28 days before your first dose of study drug, and to continue using these methods for the duration of the study. This is especially important if your partner is already pregnant. If she is not pregnant, you should use condoms with spermicide even if you and your partner are already using another method of birth control, including vasectomy (because drug may still be present in semen after vasectomy).

Being a part of this study while pregnant may expose the unborn child to significant risks, some of which may be currently unforeseeable. Therefore, pregnant women will be excluded from the study. If you are a woman of childbearing potential, a blood pregnancy test will be done (using 1 teaspoon of blood drawn from a vein by needle-stick), and it must be negative before you can continue in this study. If sexually active, you must agree to use appropriate contraceptive measures 28 days before your first dose of study drug, and continue using these methods for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a tubal ligation or hysterectomy), (2) approved hormonal contraceptives (such as birth control pills, patches, implants or injections), (3) barrier methods (such as a condom or diaphragm) used with a spermicide, or (4) an intrauterine device (IUD). Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. If you do become pregnant during this study or if you have unprotected sex, you must inform your study physician immediately.

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Risks to Male:
Your participation in this research may damage your sperm, which could cause harm to a child that you may father while on this study. Such harm may be currently unforeseeable. If you are sexually active, you must agree to use a medically acceptable form of birth control in order to be in this study for 28 days before your first dose of study drug, and continue using these methods for the duration of the study. Medically acceptable contraceptives include: (1) surgical sterilization (such as a vasectomy), or (2) a condom used with a spermicide. Contraceptive measures such as Plan B (TM), sold for emergency use after unprotected sex, are not acceptable methods for routine use. You should inform your partner of the potential for harm to an unborn child. She should know that if pregnancy occurs, you will need to report it to the study doctor, and she should promptly notify her doctor.

Risks of Drawing Blood:
Risks associated with drawing blood from your arm include momentary discomfort and/or bruising. Infection, excess bleeding, clotting, or fainting are also possible, although unlikely.

Risks of Electrocardiogram (ECG):
Possible side effects of the ECG are skin irritation, itching and redness from the ECG electrode pads. There may be risks, discomforts, drug interactions or side effects that are not yet known.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
If you agree to take part in this study, there may not be direct medical benefit to you. We hope that in the future the information learned from this study will further the research on treatment for PAH.

WILL MY INFORMATION BE KEPT CONFIDENTIAL?
Participation in research involves some loss of privacy. We will do our best to make sure that information about you is kept confidential, but we cannot guarantee total confidentiality. Your personal information may be viewed by individuals involved in this research and may be seen by people including those collaborating, funding, and regulating the study. We will share only the minimum necessary information in order to conduct the research. Your personal information may also be given out if required by law.

The purpose of this research study is to obtain information on the safety of Elafin (Tiprelestat); the results will be provided to the manufacturer, Proteo. As part of the study, results of your study-related laboratory tests, and procedures may be reported to the NIH and its affiliates. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the Food and Drug Administration, representatives and affiliates of the NIH**,** Stanford University, the Duke University Health System Institutional Review Board, the Data Safety and Monitoring Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

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The Department of Health and Human Services (HHS) has issued a Certificate of Confidentiality to further protect your privacy. With this Certificate, the investigators may not disclose research information that may identify you in any Federal, State, or local civil, criminal, administrative, legislative, or other proceedings, unless you have consented for this use. Research information protected by this Certificate cannot be disclosed to anyone else who is not connected with the research unless:

1) there is a law that requires disclosure (such as to report child abuse or communicable diseases but not for legal proceedings);

2) you have consented to the disclosure, including for your medical treatment; or

3) the research information is used for other scientific research, as allowed by federal regulations protecting research subjects.

Disclosure is required, however, for audit or program evaluation requested by the agency that is funding this project or for information that is required by the Food and Drug Administration (FDA).

You should understand that a Confidentiality Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If you want your research information released to an insurer, medical care provider, or any other person not connected with the research, you must provide consent to allow the researchers to release it. This means that you and your family must also actively protect your own privacy.

Finally, you should understand that the investigator is not prevented from taking steps, including reporting to authorities, to prevent serious harm to yourself or others.

All of the blood, urine and study procedures are being done only because you are in this study. The study results will not be provided to you OR sent to your physician.

The study results will be retained in your research record for at least six years after the study is completed. At that time either the research information not already in your medical record may be destroyed or information identifying you will be removed from such study results at DUHS. Any research information in your medical record will be kept indefinitely.

Some information collected in research studies is maintained in your medical record. However, for this study that information will be inaccessible until the end of the study, unless your physician(s) decide that it is necessary for your care.

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Safety and Tolerability of Escalating Doses of Subcutaneous Elafin (Tiprelestat) Injection in Healthy Normal Subjects
DEPRU No.: NP05IRB No.: Pro00100164

This information may be further disclosed by the sponsor of this study. If disclosed by the sponsor, the information is no longer covered by federal privacy regulations. If this information is disclosed to outside reviewers for audit purposes, it may be further disclosed by them and may not be covered by federal privacy regulations.

While the information and data resulting from this study may be presented at scientific meetings or published in a scientific journal, your name or other personal information will not be revealed.

Some people or groups who receive your health information might not have to follow the same privacy rules. Once your information is shared outside of DUHS, we cannot guarantee that it will remain private. If you decide to share private information with anyone not involved in the study, the federal law designed to protect your health information privacy may no longer apply to the information you have shared. Other laws may or may not protect sharing of private health information.

WHAT ARE THE COSTS TO YOU?
You or your insurance provider will be responsible and billed for all costs related to your routine medical care, including copayments and deductibles. Routine medical care services are those that you would have received for your condition if you were not participating in this research study. Not all services are covered by insurance. Some procedures or scans may require pre-authorization by your insurance plan. We will notify you if we learn that a service is not covered by your insurance plan as part of the pre-authorization process. If it is not covered, you will be responsible for paying for it. The amount of your out-of-pocket expense will depend on your insurance plan. For beneficiaries with Medicare Advantage Plans, traditional Medicare is billed for the routine cost of a research study. You may have more or higher co-pays than with a Medicare Advantage plan. Please discuss the costs of the study with Drs. Parikh and Guptill**.** At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

If you participate in this study, the study will pay for those services, supplies, procedures, and care associated with the study. However, there may be additional costs to you. These include basic expenses like transportation and the personal time it will take to come to the study visits. You and/or your health insurance must pay for services, supplies, procedures, and care that are required during this study for routine medical care. You will also be responsible for any co-payments and/or deductibles as required by your insurance. Participation in this study is not a substitute for health insurance.

We will monitor your DUHS patient care charges to make sure that costs are directed appropriately. If you have any questions or concerns about appropriate billing, contact your study team coordinator so that he/she can help find a resolution.

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Proteo Inc**.** will provide the study drug free of charge to you. If you decide to withdraw from the study, your study doctor may request that you return for a checkup and may ask you to complete the tests that would ordinarily occur when a person completes the study.

WHAT ABOUT COMPENSATION?
You will be paid $[redacted] for taking part in the study, to compensate for your time and for travel expenses associated with study participation.

Screening Visit	[redacted]
Day -1	
Day 1	
Day 2	
Day 3	
Day 4	
Day 5	
Day 6	
Day 7	
Day 8	
Day 10	
Day 28	

Payment received as compensation for participation in research is considered taxable income to the research subject. If payment to an individual exceeds $[redacted] in any one calendar year, Duke University is required to report this information to the Internal Revenue Service (IRS). Research subject payments to a non-employee of Duke University exceeding $[redacted] during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the individual and a copy sent to the IRS.

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WHAT ABOUT RESEARCH RELATED INJURIES?
All forms of medical diagnosis and treatment – whether routine or experimental – involves some risk of injury. In spite of all precautions, you might develop medical complications from participating in this study. If such complications arise, the Principal Investigator and the research study staff will assist you in obtaining appropriate medical treatment. In the event that you have an injury or illness that is directly caused by your participation in this study, care will be provided to you. You will **not** be responsible for any of these costs..

If you receive Medicare benefits, and if the sponsor of this study pays for any study-related treatment, complications or injuries, personal information about you, your treatment, and your participation in this study will be provided to the sponsor, who is required by law to provide it to Medicare.

You do not waive any liability rights for personal injury by signing this form.

For questions about the study or research-related injury, contact Dr. Jeffrey Guptill and Dr. Kishan Parikh at [redacted] during regular business hours and by pager at [redacted] after hours and on weekends and holidays.

WHAT ABOUT MY RIGHTS TO DECLINE PARTICIPATION OR WITHDRAW FROM THE STUDY?
You may choose not to be in the study, or, if you agree to be in the study, you may withdraw from the study at any time. If you withdraw from the study, no new data about you will be collected for study purposes unless the data concern an adverse event (a bad effect) related to the study. If such an adverse event occurs, we may need to review your entire medical record. All data that have already been collected for study purposes, and any new information about an adverse event related to the study, will be sent to the study sponsor.

Your decision not to participate or to withdraw from the study will not involve any penalty or loss of benefits to which you are entitled, and will not affect your access to health care at Duke. If you do decide to withdraw, we ask that you contact Dr. Jeffrey Guptill or Dr. Kishan Parikh in writing and let them know that you are withdrawing from the study. The mailing address is [redacted] Durham, NC 27710.

If you withdraw from the study, or the study drug is stopped for any reason, we ask that you keep your follow-up visits with us as scheduled. Remember that the decision to participate is totally yours to make, and there are no penalties for not wanting to participate.

Dr. Parikh may ask you to return for a checkup before you stop your study drug if he thinks that stopping the drug suddenly may harm you. He may also ask you to complete the tests that would ordinarily occur when a person completes the study.

We will tell you about new information that may affect your health, welfare, or willingness to stay in this study.

Your doctor may decide to take you off this study if your condition gets worse, if you have serious side effects, or if your study doctor determines that it is no longer in your best interest to continue. The sponsor or regulatory agencies may stop this study at any time without your consent. Reasons why this might occur include:

- Failure to follow the instructions of the PI and study staff.
- The PI decides that continuing your participation could be harmful to you.
- Pregnancy
- You need treatment not allowed in the study.
- The study is cancelled.
- Other administrative reasons.
- Unanticipated circumstances.

If this occurs, you will be notified and your study doctor will discuss other options with you.

If you agree to allow your blood and urine to be kept for future research with identifying information that could link your sample to you, you are free to change your mind at any time. We ask that you contact Dr. Parikh in writing and let him know you are withdrawing your permission for your identifiable blood and urine to be used for future research. His mailing address is [redacted] Durham, NC 27710. At that time we will ask you to indicate in writing if you want the unused identifiable blood and urine destroyed or if your samples (having all identifying information removed that would link the sample to you) could be used for other research.

Your samples and/or may be stored and shared for future research without additional informed consent if identifiable private information, such as your name and medical record number, are removed. If your identifying information is removed from your samples or data, we will no longer be able to identify and destroy them.

The use of your samples may result in commercial profit. You will not be compensated for the use of your samples other than what is described in this consent form.

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A description of this clinical trial will be available on https://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.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?
For questions about the study or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Jeffrey Guptill or Dr. Kishan Parikh at [redacted] during regular business hours and by pager at [redacted] after hours and on weekends and holidays.

For questions about your rights as a research participant, or to discuss problems, concerns or suggestions related to the research, or to obtain information or offer input about the research, contact the Duke University Health System Institutional Review Board (IRB) Office at (919) 668-5111.

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STATEMENT OF CONSENT
"The purpose of this study, procedures to be followed, risks and benefits have been explained to me. I have been allowed to ask questions, and my questions have been answered to my satisfaction. I have been told whom to contact if I have questions, to discuss problems, concerns, or suggestions related to the research, or to obtain information or offer input about the research. I have read this consent form and agree to be in this study, with the understanding that I may withdraw at any time. I have been told that I will be given a signed and dated copy of this consent form."

_____	_____	_____
Signature of Subject	Date	Time

_____	_____	_____
Signature of Person Obtaining Consent	Date	Time