INSTITUTE: National Cancer Institute

STUDY NUMBER: 14-C-0037 PRINCIPAL INVESTIGATOR: Ramaprasad Srinivasan, M.D., Ph.D.

STUDY TITLE: A Phase 2 Study of the MET Kinase Inhibitor INC280 in Papillary Renal Cell Cancer

Continuing Review Approved by the IRB on 05/26/21

Amendment Approved by the IRB on 04/29/20 (I) Date Posted to Web: 06/02/21

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

INC280 is a medicine which has not been approved by the US Food and Drug Administration. It is not currently "on the market" (available for you to buy) in any country. Preliminary results from a first in human study however have shown that INC280 is generally tolerated with few

serious side effects. INC280 has been shown in laboratory studies to block a certain protein called MET that is important to the growth and multiplication of cells. This protein has been shown to be highly activated in certain cancers, including some forms of papillary renal cell carcinoma. The purpose of this study is to measure what effect if any, treatment with INC280, has on the tumors of patients with papillary renal cell carcinoma. We will also try to determine how long patients using INC280 survive without cancer, how long patients survive overall and determine the types of side effects they have from using INC280.

Why are you being asked to take part in this study?

You are being asked to take part in this study because you have been diagnosed with papillary renal cell carcinoma, either hereditary or sporadic (not inherited).

How many people will take part in this study?

Approximately 20 people will be enrolled in this study.

Description of Research Study

Before you begin the study

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. However, there are some extra exams, tests and procedures that you will need to have if you take part in this study. If you have had some of them recently, they may not need to be repeated.

These tests include:

- History and physical evaluation including vital signs
- Tests to check your blood counts and blood chemistries
- Urine tests
- Serum pregnancy test (if you are female and can have children)
- CT scan of chest/abdomen/pelvis or MRI
- Brain MRI or brain CT
- Bone scan (if it is suspected that your tumor has spread to your bones)
- FDG-PET if your cancer is known or suspected to have spread outside the kidneys

During the study

If you meet the "entry criteria" of the study, you will have your blood pressure and heart rate measured, an ECG will be performed and you will be asked again about any medications you have been taking. You may also need to have some of the tests that were done at screening repeated depending on how much time has passed. Your study team will let you know if any of the above tests need to be repeated. In addition, your study doctor may also discuss enrolling you in another study, in order to determine if your cancer is associated with any genetic changes.

INC280 is provided free of charge by Novartis Pharmaceuticals for a time span of one year or so long as you remain on study (if more than one year).

You will take INC280 (2 tablets) twice a day by mouth and will continue taking INC280 until your disease gets worse or you experience intolerable side effects. You will return to your doctor's office at regular intervals so that your condition can be monitored. The Study Doctor will ask you how you are feeling. It is very important that you take the medicine given to you just as the doctor tells you to.

You will take the study medication at about the same time each day for the entire time you are participating in the study. For seven (7) days prior to your first dose, and while you are taking INC280, you should not drink grapefruit juice or Seville orange juice. INC280 should be taken at least 8 hours apart. The morning dose may be taken 2 hours after a light breakfast, and a 2 hour fast must occur following this dose. For the evening dose, you must not have eaten anything 2 hours before or 2 hours after taking the evening dose. Each dose should be taken with at least 8 ounces of water and you should drink at least another 8 ounces of water within 2 hours after taking the medication. If necessary, you may have some ginger ale, apple juice or cranberry juice. Do not miss any tablets; however, if you do forget to take a dose, do not replace if you are more than 4 hours past the planed dosing time. Resume your normal schedule the next day.

Tell the study staff about any medications you are taking during the study. This includes prescriptions drugs, over-the-counter medicines, vitamins, nutritional supplements or herbal remedies. This is very important. Some over-the-counter and prescription medications can reduce the effectiveness or increase the side effects of INC280. Likewise, INC280 can increase the side effects or lessen the effectiveness of some medications.

You must tell your doctor, or his/her delegate, if you are taking aluminium hydroxide and magnesium hydroxide, (e.g., Maalox®) or calcium carbonate (e.g., TUMS®). If you need to take one of these medications, you must do so 4 hours before or after you have taken the study drug.

Medications such as cimetidine (Tagamet), famotidine (Pepcid), nizatidine (Axid), ranitidine (Zantac) should be avoided when possible. If you need to take one of these medications, you have to take it at least 2 hours after the study drug. The next scheduled dose of the study drug should be taken at least 8 hours after you have taken the medication. Proton pump inhibitors such as Prevacid, Nexium, Protonix and Prilosec should not be used when you are on this study.

A variety of other medications can result in harmful interactions with INC280. Since it is not possible to list all of them here, your research team will carefully go over all the medications you are taking to ensure that you do not take medications that could result in potential harm. Please do not take any new medications during the study without consulting your research team at the NIH.

In order to monitor your progress during the study, we will divide the time you are on the study into cycles. One cycle = 4 weeks or 28 days.

You will need the following tests and procedures that are part of regular cancer care.

- History and physical evaluation will be done during week 1 of each cycle
- Serum pregnancy test (if you are female and can have children) will be done during week 1 of each cycle
- Vital signs will be taken during weeks 1 and 3 of the first cycle, and during week 1 of the following cycles.
- Tests to check your blood counts and blood chemistries will be performed during week 1 and week 3 of each cycle
- CT or MRI of the abdomen if tumors are only in the kidney; CT of the chest if indicated; CT or MRI of the pelvis if indicated; and a bone scan if disease in the bone. These tests will be performed during week 1 of every other cycle until cycle 8 (week 32). After that they will be performed during week 1 of every third cycle.
- Urine tests will be performed on the same schedule as CT or MRI scans
- FDG-PET if your cancer is known or suspected to have spread outside the kidney

You will need the following tests or procedures that are not usually part of regular cancer care to help us monitor your safety

- Record when you take your medication and any symptoms that you experience in a diary provided by the study team

- An electrocardiogram (ECG), a test for your heart will be performed during week 1 and week 3 of cycle 1, then during week 1 of the following cycles
- A series of eye examinations ~ 4 -5 hours in total will be performed at the beginning of the study, as needed, before you have taken any drug. Additional eye examinations may also be performed if you complain of any symptoms.

You will also need the following tests for research to see how the drug is affecting your body and other research studies.

- Tumor biopsy (optional) will be collected at the beginning of the study before you have taken any study drug and then at approximately 8 weeks (the end of cycle 2). The tumor samples we obtain will be used to look for special markers that may be helpful in the study of kidney cancer and in understanding the effect of the study drugs on the tumor. We may also use the samples to grow tumor cell lines (cells which keep dividing and growing in the laboratory, sometimes for years allowing us to continually study those cells). Results of research done on your specimens and data will not be available to you or your doctor. **A separate consent form will be provided to you at the time of the biopsy for you to grant permission to that procedure if you agree to the biopsy.**
- ~ 2 teaspoons of blood will be collected at the beginning of the study and every restaging after while you are taking INC280 so that we can measure the level of certain proteins, that may help to determine how much tumor you have in your body and to determine if these protein levels are changing when you are receiving treatment
- ~2 -4 teaspoons of urine will be collected at the beginning of the study and every restaging after while you are taking INC280 so that we can measure the level of certain protein(s), that may help to determine how much tumor you have in your body and to determine if these protein levels are changing when you are receiving treatment
- At the beginning of the study, we would like to obtain your previously collected tumor tissue if it is available. We would like to test your tissue for genes that may be linked to cancer.

When you are finished taking the drugs (treatment)

We would like to see you again within 4 to 5 weeks after you have finished taking the study drug in order to perform the following tests:

- Medical history physical examination
- Tests to check your blood counts and blood chemistries
- Eye examinations

After you have completed this visit, we would also like to contact you by telephone approximately once per year to find out how you are doing.

Birth Control

The risks to an unborn human fetus or a nursing child from INC280 are not known. Animal studies have shown that the offspring of female rabbits treated with INC280 had defects in the muscles of their legs and of the tongue. Therefore, it must be considered that INC280 could cause similar or other defects during a human pregnancy. Therefore, it is important that you do not become or attempt to become pregnant or father a child while you are taking INC280 and for at least three months after your last dose of the drug.

Women who are pregnant or nursing a child may not participate in this study. You must confirm that, to the best of your knowledge, you are not now pregnant, and that you do not intend to become pregnant during the study. If there is any possibility that you may become pregnant during the study, the Study Doctor will discuss appropriate birth control measures with you. If you suspect that you have become pregnant during the study, you must notify the Study Doctor immediately, and you have to stop study treatment immediately. You will not be able to continue in the study if you become pregnant. Although you will not be able to receive medical care related to your pregnancy at the NIH Clinical Center, your study doctors will ask you and the doctor(s) managing your pregnancy to provide relevant medical information until delivery to monitor you and your child's safety.

As a male participant in the study you must agree to use a condom during intercourse and not to father a child during the study and for the period of 3 months following stopping of study treatment. In addition, it is advised that your female partner uses a highly effective form of birth control method (contraception) if she is sexually active and may become pregnant. In case you father a child while in this study you will be asked to report the pregnancy to the study doctor. Your study doctor will seek your partner's permission to obtain relevant medical information relating to this pregnancy until delivery to monitor the mother's and child's safety.

Effective forms of birth control include:

- abstinence

- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Risks or Discomforts of Participation

What side effects or risks can I expect from being in this study?

Risks are possible side effects of study medicine or another medicine, those of taking blood, those associated with scans or other tests/procedures associated with the study, and those of taking a piece of tumor during the biopsies. Although blood samples will be taken throughout the trial, the Study Doctor may decide that you may need to have additional blood tests for your safety to follow up on any side effects.

Risks of INC280

The early results from INC280 single agent human studies have reported common side effects possibly related to INC280 (in at least 10% of patients) such as nausea (feeling like vomiting), vomiting, peripheral edema (swelling in arms and legs), decreased appetite, fatigue, headache, tremor, diarrhea, malaise (feeling of general discomfort), distortion of the sense of taste and decrease in blood chemistry parameter (albumin). Very common side effects related to INC280 (in at least 52% of patients) include blood creatinine increase. This could be an indication of kidney damage or kidney failure. Other side effects that have been seen in patients taking INC280 include pancreatitis (inflammation of the pancreas), cellulitis (inflammation of tissue), pruritus (itching of the skin), urticaria (a rash on the skin that will be itchy and possibly cause swelling), amylase increase lipase increase (molecules that help digest and are produced in your pancreas increase), abdominal pain (stomach pain), arthralgia (joint pain), constipation, dizziness, heartburn or GI reflux, musculoskeletal pain, pain in extremity (arm or leg), changes in the levels of phosphorus, and potassium in the blood, low blood pressure, eye redness, sensitivity to light, neuropathy (damage to nerves that can lead to numbness, tingling or impaired muscle function), altered gait, rash, dry skin, changes in skin color, fever, urinary tract infection, hyponatremia (decreased sodium levels), abnormalities in liver enzymes that may indicate inflammation of or damage to the liver, allergic reaction, decreased white blood cells, and elevated triglycerides. One case of cough that got worse and notable shortness of breath leading to death has been reported by one patient with lung cancer, possibly related to INC280 in a trial

of INC280 combined with another anticancer medication. In addition, reports of inflammation of the lung tissue have occurred in patients receiving INC280, which may cause coughing and difficulty breathing.

In preclinical experiments, INC280 absorbs light in the UVA-range (sunlight), and caused skin sensitization to sunlight in animals; it may be advisable not to sunbathe intensively or use a solarium intensively whilst taking INC280.

In some ongoing clinical studies, an uncommon side effect of temporary hearing impairment has been observed in some patients treated with either INC280 single agent or combined with other anticancer medication. The majority of the events were mild to moderate in severity.

It is important to report any side effects to the treatment team promptly so interventions can be initiated. This will help avoid stopping the drug due to side effects or hospitalizations.

Blood sampling risks

Taking blood may cause some discomfort, bleeding or bruising where the needle enters the body, and in rare cases, it may result in fainting. There is a small risk of infection. Some people have not felt well when having their blood taken. Some people have felt dizzy while having their blood drawn or after. Let the nurse know if you would prefer to lie down while you have your blood drawn.

Biopsy risks

The biopsy will be performed by physicians specially trained in the necessary procedures. We will only ask you to undergo the biopsies if we feel that the tumor can be easily accessed and there are no major risks associated with the procedure.

The biopsy procedure usually causes only brief discomfort at the site from which the biopsy is taken. Rarely, infection or bleeding may occur at the needle site.

The biopsy may be done under CT guidance. If that is the case, then this research study involves exposure to radiation from up to 2 CT scans. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 1.6 rem which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun,

outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material, you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults.

Eye examination risks

- Dilating drops or anesthetic drops may sting. They can cause an allergic reaction, or if contaminated, can cause an infection, but neither of these problems is very likely to occur. Dilating drops can also cause a sudden increase of pressure (acute glaucoma) in eyes that are already predisposed to develop this condition. There is little risk of glaucoma being triggered in this way, but if it is, treatment is available. You will be tested at each eye examination to determine whether there is an increased risk of developing glaucoma.

- Taking photographs of the retina (located at the back of your eye) will involve a bright flash. This brief flash may cause temporary discomfort but does not damage the eye.

- In rare instances, the cornea (the transparent covering of the colored part of your eye) may be scratched during measurement of intraocular pressure or use of a contact lens during one of the exams. A corneal abrasion of this sort may be painful, but it heals quickly with no lasting effects.

- Testing to determine how well you adapt to darkness may cause fatigue or loss of motivation or attention due to the length of the procedure (~ 2 – 3 hours)

Other risks

The side effects that may occur when INC280 is taken with other medicines or alcohol are unknown. Combining INC280 with other medicines and/or alcohol might result in serious reactions. Some over-the-counter and prescription medications can reduce the effectiveness or increase the side effects of INC280. INC280 can also increase the side effects or lessen the effectiveness of some over-the counter or prescription medications. Throughout the study, you should always discuss the use of alcohol or any medicines (over-the-counter, health food supplements, prescription, illegal) with the study doctor before taking INC280. In addition, some fruit and fruit juice/products (grapefruit and Seville orange juice) should be avoided while taking INC280, because they can possibly increase the side effects of INC280.

Since INC280 is a new drug that is still in the early stages of being studied, problems or side effects that are not now known, including serious or life-threatening side effects or death, could also occur. You will be given any new information that may affect your willingness to start or continue in the study.

Side Effects Diary

You will be asked to keep a diary of any side effects, when they occurred, how long they lasted, and what if anything helped to relieve the side effect. This diary will be reviewed by the study team during each visit.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking or decreasing the growth of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study. Some studies suggest that medications used in the more common (clear cell) form of kidney cancer such as sunitinib and temsirolimus may be beneficial in some patients with papillary kidney cancer and your oncologist may offer you treatment with one or more of these agents.
- Taking part in another study
- Continued observation or surgery, if appropriate
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.

- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

In the event that you are injured as a result of taking part in this study, Novartis will not pay any money to you or your medical bills.

Will your medical information be kept private?

For purposes of this study, NCI and Dr. Srinivasan will use medical information collected or created as part of the study, such as medical records and test results, which identifies you by name or in another way. Your consent to participate in the study means you agree that NCI and Dr. Srinivasan may obtain your medical information that they request for study purposes from your physicians and your other health care providers. You are also agreeing that NCI and Dr. Srinivasan may use and share this information with the parties described below. In addition, you agree that, during the study, you may not have access to some of your medical information obtained or created as part of this study. You will be allowed to access this information once the study is finished.

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- Governmental agencies in other countries where the study drug may be considered for approval
- National Institutes of Health Intramural Review Board
- Qualified representatives from Novartis, the pharmaceutical company who supplies INC280, or its authorized representatives.

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

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your tumor grows during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if the company who makes the drug can no longer supply INC280

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to Novartis or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed. Unless and until you do withdraw your consent to participate in this study, it will remain valid and effective.

Certificate of Confidentiality

To help us protect your privacy, we have obtained a Certificate of Confidentiality. The researchers can use this Certificate to legally refuse to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings, for example, if there is a court subpoena. The researchers will use the Certificate to resist any demands for information that would identify you, except as explained below.

You should also know that there are several circumstances in which the Certificate does not provide coverage. These include when information:

- will be used for auditing or program evaluation internally by the NIH; or

- must be disclosed to meet the legal requirements of the federal Food and Drug Administration (FDA).
- is necessary for your medical treatment and you have consented to this disclosure;
- is for other research.

In addition, identifiable, sensitive information protected by this Certificate cannot be admissible as evidence or used for any purpose in any action, suit, or proceeding without your consent.

You should understand that a Certificate of Confidentiality does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers will not use the Certificate to withhold that information.

The Certificate of Confidentiality will not protect against the required reporting by hospital staff of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using a drug developed by Novartis through a joint study with your researchers and the company. The company also provides financial support for this study.

Use of Specimens and Data for Future Research

To advance science, it is helpful for researchers to share information they get from studying human samples. They do this by putting it into one or more scientific databases, where it is

stored along with information from other studies. A researcher who wants to study the information must apply to the database and be approved. Researchers use specimens and data stored in scientific databases to advance science and learn about health and disease.

We plan to keep some of your specimens and data that we collect and use them for future research and share them with other researchers. We will not contact you to ask about each of these future uses. These specimens and data will be stripped of identifiers such as name, address or account number, so that they may be used for future research on any topic and shared broadly for research purposes. Your specimens and data will be used for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you do not want your stored specimens and data used for future research, please contact us in writing and let us know that you do not want us to use your specimens and/or data. Then any specimens that have not already been used or shared will be destroyed and your data will not be used for future research. However, it may not be possible to withdraw or delete materials or data once they have been shared with other researchers.

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Ramaprasad Srinivasan, M.D., Ph.D. Building 10, Room 2W-5940, Telephone: 240-760-6251. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 240-760-6070.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/ Legal Representative — Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/ Guardian — Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian — Date — Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM MAY 26, 2021 THROUGH MAY 24, 2022.

Signature of Investigator — Date

Print Name

Signature of Witness — Date

Print Name