Wake Forest™
School of Medicine

Section on *Hematology and Oncology*

A PILOT STUDY OF CPI-613 IN PATIENTS WITH MYELODYSPLASTIC SYNDROME WHO HAVE FAILED PREVIOUS THERAPY

Informed Consent Form to Participate in Research
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INTRODUCTION

You are invited to be in a research study. Research studies are designed to gain scientific knowledge that may help other people in the future. You are being asked to take part in this study because you have myelodysplastic syndrome (MDS) and prior treatments have not been successful. Your participation is voluntary. Please take your time in making your decision as to whether or not you wish to participate. Ask your study doctor or the study staff to explain any words or information contained in this informed consent document that you do not understand. You may also discuss the study with your friends and family.

WHY IS THIS STUDY BEING DONE?

An investigational drug is one that has not been approved by the U.S. Food and Drug Administration (FDA). CPI-613 is an investigational drug that has not been approved by the FDA for any type of tumor or cancer, and it is currently being studied for the treatment of cancer and related conditions, such as MDS.

The purpose of this study is to test the safety and effectiveness of an investigational drug called CPI-613 ("study drug") when used to treat MDS. In MDS, the blood-forming cells in your bone marrow are damaged and have difficulty making new blood cells. If MDS does not respond to treatment, it can turn into a type of blood cancer known as acute myeloid leukemia. CPI-613 is thought to kill cancer cells by turning off their mitochondria. Mitochondria are used by cells to produce energy and are the building blocks needed to make more cells. By shutting off these mitochondria, CPI-613 deprives the cells of energy and other supplies that they need to survive and grow in your body. In other studies, CPI-613 has been shown to kill cancer cells in some types of cancer. We want to find out what effects, good and/or bad, CPI-613 has on MDS.

HOW MANY PEOPLE WILL TAKE PART IN THE STUDY?

Twenty (20) people at Wake Forest Baptist Health will take part in this study.

WHAT IS INVOLVED IN THE STUDY?

After your study doctor has answered all your questions about this study and you have given written consent by signing this form, several tests will be done to be sure you are able to enter this study. Many of the tests are the same as those you have had in the past to diagnose and treat your disease. Some of these same tests will also be done during the study to follow your progress.

Your participation in this study is divided into different visits:

Pre-Study Screening Tests (To see if you are eligible to participate in this study)

The following tests will be done in order to determine if you are eligible to participate in this study.

Within 4 weeks before receiving CPI-613: You will have a bone marrow biopsy

Within two weeks before receiving CPI-613.

- The study doctor or study nurse will ask you about your medical history, and obtain a list of all medications that you are currently taking.
- The study doctor or study nurse will examine you and determine your performance status.
- A physical examination with your vital signs (heart rate, blood pressure, breathing rate, and body temperature), height, and body weight will be recorded.
- Approximately 10 teaspoons of blood will be drawn for routine lab tests.

Within one week before receiving CPI-613:

- Pregnancy test for female subjects who can become pregnant. This must be done within one week of starting treatment.

Study-Related Treatment Procedure and Tests

This clinical research study consists of treatment with CPI-613. Treatment will be given over a 4-week period known as a "cycle." The number of cycles you receive will be determined by how well your cancer responds to the therapy. The following table shows a schedule of the treatment, tests and procedures you will have:

Treatment, tests, and procedures	Each Treatment Cycle					
	Week 1					Weeks 2-4
	D1	D2	D3	D4	D5	
Physical Exam (within 24 hours of receiving CPI-613)	√					
Evaluation of symptoms and vital signs	√	√	√	√	√	
Performance status	√	√	√	√	√	
10 tablespoons of blood drawn for routine lab tests	√					
1 teaspoon of blood drawn to check kidney function		√	√	√	√	
Treatment with CPI-613	√	√	√	√	√	
Bone Marrow Biopsy						√[1]
Definitions of abbreviations used in this table: D1 = Day 1; D4 = Day 4 [1] Week 4 of cycles 3 and 6 and then as recommended by your doctor until your MDS has failed to respond						

Additional Evaluations and Procedures

During week 4 of cycle 3, you will undergo a bone marrow biopsy to see if your MDS has responded to treatment with CPI-613. If the results show that your MDS has responded, you will continue with another 3 cycles of treatment with CPI-613 and having your bone marrow examined at the end of cycle 6. If your MDS has failed to respond, you will be removed from the study.

HOW LONG WILL I BE IN THE STUDY?

You will be given CPI-613 5 times each week for 1 week, followed by 3 weeks of rest (a cycle). CPI-613 will be given over a 2-hour infusion into your vein through a central venous catheter (a catheter that is put into a larger vein in your body and will remain in place for the duration of the

treatment).The length of participation in this study will vary for each person and will be determined by the number of treatment cycles you receive. All participants will be in the study for at least 2 months, which is the amount of time required to complete 2 treatment cycles. The following details how long you will be in the study based on the total number of cycles you receive:

- 2 cycles: you will be on the study for 8 weeks (2 months)
- 4 cycles: you will be on the study for 16 weeks (4 months)
- 6 cycles: you will be on the study for 24 weeks (6 months)
- Etc.

You can stop participating at any time. It is important to tell the study doctor if you are thinking about stopping so that any risks from CPI-613 can be evaluated by your study doctor. Another reason to tell your study doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

WHAT ARE THE RISKS OF THE STUDY?

Being in this study involves some risk to you. You should discuss the risk of being in this study with the study staff.

Risks Related to CPI-613

The study drug is in the very early stages of development for use in humans. The main purpose of this study is to learn about the safety and effectiveness of the drug when used to treat MDS. Please carefully read the sections on risk and benefits below. Not all of the side effects are known at this time. If you choose to take part in this study, it is very important that you let the study team know of any symptoms you have.

Some potential risks associated with CPI-613 have been determined from previous animal studies. These side effects include vomiting and some temporary heart damage. CPI-613 has also caused inflammation around the area where the experimental drug is given, causing swelling, redness, and pain. To avoid this potential side effect, CPI-613 will be given to you through a central venous catheter. There may be other more severe side effects such as significant inflammation throughout your body. The study drug could cause changes in certain chemicals in your blood that could indicate liver problems. Significant side effects have also caused some deaths in test animals at dose levels that are higher than those to be used in this study. Many side effects may go away shortly after being given CPI-613 but in some cases, side effects may be severe, long lasting, or may not go away. Although not yet reported in any human subjects, it remains possible that CPI-613 might cause your disease to progress or produce a fatal side effect. CPI-613 may also cause side effects that we have not yet seen and cannot predict.

Some common side effects observed in patients taking CPI-613 include:

- Allergic reaction at the place where you receive your drug
- Vomiting

- Diarrhea
- Fatigue
- Headache
- Constipation
- Nausea
- Light-headedness
- Abdominal pain
- Changes in liver function
- Changes in kidney function
- Jaundice (temporary yellowing of the skin and eyes)
- Too much or too little calcium in the blood
- Flushing
- Anemia
- Low levels of white blood cells
- Low levels of platelets (blood cells that help to form clots)
- Electrolyte imbalance
- Abnormal heartbeat (changes in heart rhythm that may require placement of a pacemaker)

There may be other, more severe side effects, such as inflammation throughout your body. The study drug could case changes in certain chemicals

Pregnancy Risks

The effects of CPI-613 on a fetus are unknown. You should not become pregnant or father a child while on this study. If you are able to become pregnant or father a child, BOTH you and your partner must use effective birth control methods during the study period. Effective birth control methods are outlined below.

Women subjects who have never been pregnant can use one of the following methods:

- Abstinence
- A barrier method (diaphragm, cervical cap, sponge, or condom with a spermicidal foam or jelly) plus hormonal birth control (oral, patch or injectable).
- A barrier method (diaphragm, cervical cap, sponge, or condom with a spermicidal foam or jelly) plus and intrauterine device (IUD).

Women subjects who have previously been pregnant at least once can use one of the following methods:

- Abstinence
- A barrier method (diaphragm or condom with a spermicidal foam or jelly) plus hormonal birth control (oral, patch or injectable).
- A barrier method (diaphragm or condom with a spermicidal foam or jelly) plus and intrauterine device (IUD).

Male subjects can use one of the following methods:

- Abstinence
- Condom with spermicide

For male subjects, you should also advise your partner to use an effective birth control method such as those outlined above for women subjects.

If you suspect that you have become pregnant, you must notify the study doctor immediately.

Female subjects should avoid becoming pregnant for at least 10 weeks following completion of the study. Male subjects should avoid fathering a child for at least 10 weeks following study completion.

Other Risks

It is possible that you could experience an allergic reaction to CPI-613. An allergic reaction can be mild, or it can be serious, leading to shock with loss of consciousness, or it can be life-threatening.

Certain drugs, when taken together with the study drug, may increase side effects. It is important that you inform your study doctor of any prescription, over-the-counter, or alternative medications you are taking while in this study.

Drawing blood may cause pain, bruising, lightheadedness, or, on rare occasions, infection.

Risks of a central venous catheter may include pain, bleeding, infection, and damage to lungs or other tissue.

Your condition may not get better or may become worse during this study.

If you have questions about risks and side effects, ask your study doctor. ***You should talk to your study doctor about any side effects that you have while taking part in this study.*** The study doctor will take steps to try to treat any side effects, if they appear. If the study drug causes severe side effects or if your disease worsens, the study drug will be discontinued. In that case, your study doctor will discuss treatment options with you.

Taking part in this research study may involve providing information that you consider confidential or private. Efforts, such as coding research records, keeping research records secure and allowing only authorized people to have access to research records, will be made to keep your information safe.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?

If you agree to take part in this study, there may or may not be direct benefit to you. We hope the information learned from this study will benefit other people in the future. The benefits of participating in this study may be: improvement in your cancer.

WHAT OTHER CHOICES ARE THERE?

You do not have to be in this study to receive treatment. You should talk to your doctor about all the choices you have. Instead of being in this study, you have these options:

- Other chemotherapies
- Comfort care, which is an option if you decide that you do not want any more active treatment for your cancer. Comfort care includes pain medication and other types of support. It aims to maintain your comfort and dignity rather than cure disease. Usually this care can be provided at home. If you think you might prefer comfort care, please discuss this with your family, friends, and your doctor.

WHAT ABOUT MY HEALTH INFORMATION?

In this research study, any new information we collect from you about your health or behaviors is considered Protected Health Information. The information we will collect for this research study includes: your health history, bone marrow biopsy information, how you respond to study procedures, laboratory and other test results, and physical examinations.

If this research study involves the diagnosis or treatment of a medical condition, then Protected Health Information collected from you during this study will be placed in your medical record, and may be used to help treat you, arrange payment for your care, or assist with Medical Center operations.

We will make every effort to keep your Protected Health Information private. We will store records of your Protected Health Information in a cabinet in a locked office or on a password protected computer.

Some of the people, agencies and businesses that may receive and use your health information are the research sponsor; representatives of the sponsor assisting with the research; investigators at other sites who are assisting with the research; central laboratories, reading centers or analysis centers; the Institutional Review Board; representatives of Wake Forest University Health Sciences and North Carolina Baptist Hospital; representatives from government agencies such as the Food and Drug Administration (FDA) or the Office of Human Research Protections (OHRP), the Department of Health and Human Services (DHHS) and similar agencies in other countries.

Some of these people, agencies and businesses may further disclose your health information. If disclosed by them, your health information may no longer be covered by federal or state privacy regulations. Your health information may be disclosed if required by law. Your health information may be used to create information that does not directly identify you. This information may be used by other researchers. You will not be directly identified in any

publication or presentation that may result from this study unless there are photographs or recorded media which are identifiable.

If required by law or court order, we might also have to share your Protected Health Information with a judge, law enforcement officer, government agencies, or others. If your Protected Health Information is shared with any of these groups it may no longer be protected by federal or state law.

Any Protected Health Information collected from you in this study that is maintained in the research records will be kept for an indeterminate period of time. This authorization does not expire. Any research information entered into your medical record will be kept for as long as your medical record is kept by the Medical Center. You will not be able to obtain a copy of your Protected Health Information in the research records until all activities in the study are completely finished.

You can tell Dr. Bayard Powell that you want to take away your permission to use and share your Protected Health Information at any time by sending a letter to this address:

Bayard Powell, MD,
Medical Center Boulevard
Winston-Salem, NC 27157

However, if you take away permission to use your Protected Health Information you will not be able to be in the study any longer. We will stop collecting any more information about you, but any information we have already collected can still be used for the purposes of the research study.

By signing this form you give us permission to use your Protected Health Information for this study.

If you choose to participate in this study, your medical record at Wake Forest University Baptist Medical Center will indicate that you are enrolled in a clinical trial. Information about the research and any medications or devices you are being given as a participant may also be included in your medical record. This part of the medical record will only be available to people who have authorized access to your medical record. If you are not a patient at this Medical Center, a medical record will be created for you anyway to ensure that this important information is available to doctors in case of an emergency.

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

Laboratory test results and other medical reports created as a result of your participation in the research study may be entered into the computer systems of Wake Forest University Health

Sciences and North Carolina Baptist Hospital. These will be kept secure, with access to this information limited to individuals with proper authority, but who may not be directly involved with this research study.

A North Carolina Baptist Hospital (NCBH) medical record will be created for all study participants. Information about your participation in the study will be placed in the NCBH medical record, along with any routine medical test results that were obtained at NCBH as part of this study.

WHAT ARE THE COSTS?

There are no costs to you for taking part in this study. All study costs, including any study medications and procedures related directly to the study, will be paid for by the study. Costs for your regular medical care, which are not related to this study, will be your own responsibility.

WILL YOU BE PAID FOR PARTICIPATING?

The investigational study drug, CPI-613, is being provided to you at no cost from the pharmaceutical company (Cornerstone Pharmaceuticals, Inc.). You will receive no payment for your participation in this study. Parking validation will be provided for all study-related visits.

WHO IS SPONSORING THIS STUDY?

This study is being sponsored by Wake Forest University Health Science. Cornerstone Pharmaceuticals, Inc. is providing the investigational drug (CPI-613) to Wake Forest University Health Sciences to help conduct this study. Boris Pasche, MD, the Director of the Comprehensive Cancer Center of Wake Forest Baptist Medical Center serves on the board of directors for Rafael Holdings, Inc., which owns the manufacturer of the drug that is being studied. Timothy Pardee, MD holds a part-time position as Chief Medical Officer for Rafael Pharmaceuticals, Inc, the study drug manufacturer. Dr. Bayard Powell serves on the Scientific Advisory Board for Rafael Pharmaceuticals, Inc.

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WHAT HAPPENS IF YOU EXPERIENCE AN INJURY OR ILLNESS AS A RESULT OF PARTICIPATING IN THIS STUDY?

Should you experience a physical injury or illness as a direct result of your participation in this study, Wake Forest University School of Medicine maintains limited research insurance coverage for the usual and customary medical fees for reasonable and necessary treatment of such injuries or illnesses. To the extent research insurance coverage is available under this policy the reasonable costs of these necessary medical services will be paid, up to a maximum of $25,000. Wake Forest University Baptist Medical Center holds the insurance policy for this coverage. It provides a maximum of $25,000 coverage for each claim and is limited to a total of $250,000 for all claims in any one year. The Wake Forest University School of Medicine, and the North Carolina Baptist Hospitals, Incorporated do not assume responsibility to pay for these medical services or to provide any other compensation for such injury or illness. Additional information may be obtained from the Medical Center's Director of Risk and Insurance Management.

If you are injured, the insurer may require information such as your name, social security number, and date of birth in order to pay for your care. This is because the insurer is required by law to report any payments made to cover the care of any persons who are members of a government insurance plan to the Department of Health and Human Services.

You do not give up any legal rights as a research participant by signing this consent form. For more information on medical treatment for research related injuries or to report a study related illness, adverse event, or injury you should call Dr. Bayard Powell.

ARE MY RIGHTS AS A RESEARCH STUDY PARTICIPANT?

Taking part in this study is voluntary. You may choose not to take part or you may leave the study at any time. Refusing to participate or leaving the study will not result in any penalty or loss of benefits to which you are entitled. If you decide to stop participating in the study we encourage you to talk to the investigators or study staff first to learn about any potential health or safety consequences. The investigators also have the right to stop your participation in the study at any time. This could be because it is in your best interest, you do not follow the study rules, the study is stopped, you do not later consent to any future changes that may be made to the study plan, or your become pregnant.

You will be given any new information we become aware of that would affect your willingness to continue to participate in the study.

WHOM DO I CALL IF I HAVE QUESTIONS OR PROBLEMS?

For questions about the study or in the event of a research-related injury, contact the study investigator, Dr. Bayard Powell.

The Institutional Review Board (IRB) is a group of people who review the research to protect your rights. If you have a question about your rights as a research participant, or you would like to discuss problems or concerns, have questions or want to offer input, or you want to obtain additional information, you should contact the Chairman of the IRB.

You will be given a copy of this signed consent form.

SIGNATURES

I agree to take part in this study. I authorize the use and disclosure of my health information as described in this consent and authorization form. If I have not already received a copy of the Privacy Notice, I may request one or one will be made available to me. I have had a chance to ask questions about being in this study and have those questions answered. By signing this consent and authorization form, I am not releasing or agreeing to release the investigator, the sponsor, the institution or its agents from liability for negligence.

Subject Name (Printed):_____

Subject Signature: _____ Date: _____Time:_____ am pm

Person Obtaining Consent:_____ Date:_____ Time:_____ am pm