DUKE UNIVERSITY HEALTH SYSTEM

**Consent to Participate in a Research Study**

**A Phase Ib/II Safety and Efficacy Study of ABC294640 in Patients with Refractory or Relapsed Multiple Myeloma Who Have Previously Been Treated with Proteasome Inhibitors and Immunomodulatory Drugs**

You are being asked to take part in this research study because you have multiple myeloma that has become resistant to or gotten worse on previous treatments. Research studies are voluntary and include only people who choose to take part. 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.

Dr. Yubin Kang will conduct the study and it is sponsored by RedHill Biopharma Ltd. The study is funded by a grant from the National Institutes of Health (NIH). Portions of Dr. Yubin Kang and his research team's salaries will be paid by this grant. Apogee Biotechnology Corporation and its partner (RedHill Biopharma) will provide the study drug (ABC294640).

**WHO WILL BE MY DOCTOR ON THIS STUDY?**

If you decide to participate, Dr. Yubin Kang will be your doctor for the 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 determine the safety and efficacy of an investigational drug, ABC294640 (Yeliva[tm]), in subjects with refractory or relapsed multiple myeloma that have previously been treated with proteasome inhibitors such as bortezomib and carfilzomib and immunotherapy drugs such as lenalidomide and pomalidomide. The word "investigational" means the study drug is still being tested in research studies and is not approved by the U.S. Food and Drug Administration (FDA).

Yeliva is an oral drug which stops the enzyme sphingosine kinase-2 (SK2), which is known to regulate tumor cell death and growth. SK2 is a new target for anti-cancer therapy. Studies done in the laboratory by Dr. Kang and his staff show that SK2 is overexpressed in multiple myeloma (MM) cells. Treatment with Yeliva kills the SK2 positive cells in MM cell lines and stops the growth of primary (isolated from patients) human myeloma cells. Yeliva was effective at stopping myeloma tumor growth in mice. Therefore, we think that Yeliva might be a potential treatment option for refractory/relapsed MM patients.

Yeliva has recently completed a Phase I safety study in patients with solid tumors, and was shown to be safe. In this current phase Ib/II study, Yeliva will be studied for its safety and efficacy in treating refractory or relapsed multiple myeloma.

**HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?**

Up to 74 people will take part in this study at Duke and through the Duke Cancer Network.

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**WHAT IS INVOLVED IN THE STUDY?**
If you agree to be in this study, you will be asked to sign and date this consent form. If you do not sign and date this consent form, you will continue to receive care, but not as a part of this study. You will have the following tests and procedures to make sure that you are eligible:

- Physical exam including vital signs and medical history
- Review of current medications (prescription and non-prescription)
- Eastern Cooperative Group (ECOG) Performance Status to determine how active you are
- Blood tests including screening for HIV and hepatitis B and C
- Serum pregnancy test for women of child-bearing potential
- Urinalysis
- Electrocardiogram (EKG), a tracing of the electrical activity of the heart
- Echocardiogram (ECHO), ultrasound of your heart
- Bone marrow biopsy and aspirate.
- Skeletal survey

As part of this study, you will be tested for HIV (human immunodeficiency virus, which is the virus that causes the acquired immunodeficiency syndrome [AIDS]). You will also be tested for hepatitis B and C. 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 tests indicate that you are infected with HIV or hepatitis B or C, 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 HIV or hepatitis B or C then you should not agree to participate in this study.

You will also have a bone marrow biopsy and aspirate done during screening, at the end of cycle 3 and at the end of cycle 6. Bone marrow samples will be important to determine the effectiveness of the drug in killing the myeloma cells and in hitting the right targets.

This study has two phases. The first phase is to assess the unacceptable side effects and determine the maximum tolerated dose (MTD) of Yeliva. Up to 18 subjects will take part in this phase of study. Once the MTD is determined, the study will proceed to the second phase. The second phase of the study is to assess the overall treatment response rate and overall survival with Yeliva in subjects with refractory or relapsed MM that have been previously treated with proteasome inhibitors and immunomodulatory agents. Up to 56 subjects will take part in the second phase of study.

The study drug Yeliva will be given orally in capsules twice a day every day for 28 days as one cycle. The study drug will be taken under fasting conditions or after a light to moderate meal. You will be given a diary to keep track of the number of pills you took each day, the time of day you took them, and any side effects you experienced when taking the study drug.

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The study regimen will continue until unacceptable side effects develop or the myeloma relapses. If you take part in the study, you will have the following procedures performed during each cycle:

**Cycle 1 (weekly)**

- Physical exam including vital signs
- Eastern Cooperative Group (ECOG) Performance Status to determine how active you are
- Blood draw for routine testing,
- Urine sample for routine testing
- Review Diary and pill count
- Review adverse events
- Yeliva administration (daily)
- Blood draw for pharmacokinetic (PK) testing immediately before dosing and at approximately 1, 2, 4, and 8 hours after dosing (Day 1 only). PK testing is to measure the drug level in your blood at different time-points
- Blood draw for pharmacodynamic (PD) testing (Day 1 only). PD testing is to measure if the drug hits the target.

**Cycles 2-4 (Weeks 1 and 3 only)**

- Physical exam including vital signs
- Eastern Cooperative Group (ECOG) Performance Status to determine how active you are
- Blood draw for routine testing,
- Urine sample for routine testing
- Review Diary and pill count
- Review adverse events
- Yeliva administration (daily)
- Blood draw for pharmacodynamic (PD) testing (Day 1 only)

*At the end of Cycle 3, you will have a bone marrow biopsy and aspirate.

**Future Cycles (Day 1 only)**

- Physical exam including vital signs
- Eastern Cooperative Group (ECOG) Performance Status to determine how active you are
- Blood draw for routine testing,
- Urine sample for routine testing
- Review Diary and pill count
- Review adverse events
- Yeliva administration (daily)
- Blood draw for pharmacodynamic (PD) testing (Cycles 5 and 6, Day 1 only)

*At the end of Cycle 6, you will have a bone marrow biopsy and aspirate.

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**End of Study Drug Regimen**

- Physical exam including vital signs
- Eastern Cooperative Group (ECOG) Performance Status to determine how active you are
- Blood draw for routine testing,
- Urine sample for routine testing
- Review Diary and pill count
- Review adverse events
- Blood draw for pharmacodynamic (PD) testing
- Skeletal survey

**Follow-up**
If you are in phase 2 of the study, you will be followed every three months by telephone for two years from the time of your End of Study Drug Regimen visit.

**HOW LONG WILL I BE IN THIS STUDY?**
You may be in the study for about 3 years. You will continue to receive the study drug until unacceptable side effects develop or your myeloma disease progresses or the study is terminated. We will collect data and follow-up information for 2 years from the day you first take part in the study. 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.

**WHAT ARE THE RISKS OF THE STUDY?**
While on this study, you are at risk for the side effects listed below. Not everyone will get these side effects. You may have none or several. Most people do not experience all of the side effects listed. A side effect may get worse while on study drug, or more side effects may develop as the longer you stay on study. This depends on your general health and the amount of the study drug you receive (the dose).

Many side effects are inconvenient but not damaging to your health. They are almost always reversible and usually go away shortly after study drug is complete. However, some side effects are serious medical conditions that may cause your death or cause your condition to deteriorate. The study doctor will closely monitor and treat/prevent the side effects you might have through the study period. Other drugs and procedures may be given to make side effects less serious and less uncomfortable.

**Risks and side-effects of ABC294640 (**Yeliva$^{TM}$**):**
ABC294640 may cause some, all or none of the side-effects listed below.

Common adverse events occurring in greater than or equal to 10% of subjects:

- Nausea
- Fatigue

- Vomiting
- Diarrhea
- Feeling of sleepiness or drowsiness
- Muscles spasms
- Hot flashes
- Change in taste
- Dizziness
- Acute kidney injury
- Vision changes including visual disturbances and blurred vision
- General change in mood and mood swings

Less common adverse events occurring in less than 10% of subjects:

- Urinary retention or inability to completely empty the bladder
- Ringing in the ears
- A fungal infection in the mouth and throat called thrush
- Rapid heart rate
- Sweating
- A feeling of unusual tightness, stiffness or pull in the muscles
- Acid reflux or gastroesophageal reflux disease (GERD)
- Rash
- Damage to the nerve s that causes weakness, numbness and pain in the hands and feet
- Feeling of pins and needles in the legs and arms
- Pain, including pain the pelvic area
- Numbness
- Mood changes, mood swings
- Memory loss
- Lower extremity (leg) weakness
- High blood pressure
- Increase in lipid levels or fat particles in the blood
- Increase in blood glucose (sugar) levels
- Hearing impairment
- Hallucinations
- Generalized muscle weakness
- Excess gas
- Fingernail changes
- Pain, burning or tingling of the skin when touching part of the body
- Shortness of breath
- Difficulty speaking
- Dry mouth

- Drowsiness
- Choking sensation
- Chest discomfort
- Changes in liver function tests (AST, ALT and bilirubin)
- Anxiety
- Loss of appetite
- Anemia or reduction in hemoglobin in the blood that may cause shortness of breath and tiredness
- Agitation
- Abnormal reflexes
- Abdominal discomfort

For Those of Reproductive Potential

**Female**

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 within 48 hours prior to the first dose of study drug before you can continue in this study. If sexually active, you must agree to use appropriate contraceptive measures for the duration of the study and for 12 weeks afterwards.

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.

The study drug ABC294640 may pass the placenta and be secreted in milk, and may be harmful to fetal and infant development. Therefore, breast-feeding women are not allowed to take part in the study.

**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 and for **12 weeks** afterward.

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 bone marrow biopsy and aspirate:**
A bone marrow aspiration is a procedure in which an area of the hip (either one hip or both hips) is numbed and a small sample of bone marrow is withdrawn. When the local anesthesia (numbing medication) is given, you may initially feel a burning sensation in your skin and bone surface for several seconds. During the procedure, you may temporarily feel pressure and/or pain of varying degrees. If necessary, you may ask your physician for additional local anesthesia or a medication to ease your stress. You also may experience bleeding, and/or bruising after the procedure is completed and you may experience soreness in the area for a few days afterwards. Rarely, infection can develop.

**Drug and Food Interactions:**
For your safety, you must tell the study doctor or nurse about all the prescribed medical foods and drugs, herbal products, over-the-counter (OTC) drugs, vitamins, natural remedies, and alcohol that you are taking before you start the study and before starting to take any of these products while you are on the study.

**Risks of Washout:**
If you are in chemotherapy except for low-dose dexamethasone alone or in a clinical trial, you will need to wait for at least 2 weeks before you can start Yeliva. During the washout period (time during which your current chemotherapy drugs are being discontinued), your symptoms of myeloma may get worse. Please discuss the washout period with the study doctor.

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 be direct medical benefit to you. Based on our preclinical data and the phase I study in solid tumors, we believe that ABC294640 is safe. We hope that subjects will benefit from the study drug, achieving response and longer progression free survival. However, there is no guarantee that you will benefit from the study drug and your disease may not improve and may even get worse. We hope that in the future the information learned from this study will benefit other people with your condition.

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**WHAT ALTERNATIVES ARE THERE TO PARTICIPATION IN THIS STUDY?**
Instead of being in this study, you may receive bone marrow stem cell transplantation, other investigational drugs or standard drugs given for patients with your disease. Please talk to your doctor about these and perhaps other options.

**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.

As part of the study, results of your study-related laboratory tests, x-rays, and procedures may be reported to representatives and affiliates of RedHill Biopharma, Ltd and its partner Apogee Biotechnology Corporation. 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, the National Institutes of Health, representatives of Apogee Biotechnology Corporation and its partner, RedHill Biopharma, the Duke University Health System Institutional Review Board, Duke University Office of Audit, Risk and Compliance - Human Subjects Research Compliance office, and representatives of the Duke Cancer Institute. If any of these groups review your research record, they may also need to review your entire medical record.

As part of the study, you will be asked to have certain tests and/or procedures performed. Some of these tests and/or procedures would have been done as part of your regular care. The study doctor will use these test results both to treat you and to complete this research. These test results will be recorded in your medical record and will be reported to representatives and affiliates of RedHill Biopharma, Ltd and its partner Apogee Biotechnology Corporation. Results of tests and studies done solely for this research study and not as part of your regular care will not be included in your medical record. The purpose of collecting and sharing this information is to learn about how the study drugs affects your disease and any side effects you experience.

The study results will be retained in your research record forever. Any research information in your medical record will also be kept indefinitely.

If you decide to take part in the study, you give us permission to use information about you and share it with RedHill Biopharma, Ltd and its partner, Apogee Biotechnology Corporation. Medical monitors, trial managers, auditors of the sponsor and representatives contracted through the sponsor will be able to check your medical records, which means they may have access to your name, medical record number, address, and telephone number. This permission continues until the study is over, including the length of time that we are required to keep records about the study.

This information may be further disclosed by the sponsor of this study, RedHill Biopharma and its partner, Apogee Biotechnology Corporation, and the NIH. If disclosed by the sponsor, the information is no longer covered by the 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 the 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.

**Potential Risks and the Genetic Information Non-Discrimination Act (GINA):** There is a potential risk of loss of confidentiality. Every effort will be made to protect your confidential information, but this cannot be guaranteed. The genetic information obtained as a result of your participation in this research will not be included in your medical record. Information from which you may be personally identified will be maintained in a confidential, secure location at DUHS, accessible only by authorized members of the study team, and will not be disclosed to third parties except as described in this consent form, with your permission, or as may be required by law.

The Genetic Information Nondiscrimination Act (GINA) is a Federal law that will protect you in the following ways:

- Health insurance companies and group plans may not request genetic information from this research;
- Health insurance companies and group plans may not use your genetic information when making decisions regarding your eligibility or premiums;
- Employers with 15 or more employees may not use your genetic information when making a decision to hire, promote, or fire you or when setting the terms of your employment.

GINA does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. GINA also does not protect you against discrimination based on an already-diagnosed genetic condition or disease.

**WHAT ARE THE COSTS?**
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 Dr. Kang**.** At your request, a Financial Counselor in the clinic may provide you with an estimate of costs for routine services.

The study sponsor, RedHill Biopharma and its partner Apogee Biotechnology Corporation have agreed to pay for services and procedures that are done solely for research purposes. Please talk with the PI/study team about the specific services and procedures that the sponsor will pay for, and the ones for which you or your insurance will be responsible.

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.

RedHill Biopharma, Ltd and its partner Apogee Biotechnology Corporation will provide the study drug free of charge to you. At the end of the study, or if you decide to withdraw from the study before it ends, you may be asked to return all unused study drug. Your study doctor may request that you return for a checkup before you stop your study drug if he/she thinks that stopping the drug suddenly may harm you and may ask you to complete the tests that would ordinarily occur when a person completes the study.

**WHAT ABOUT COMPENSATION?**
You will not be compensated or reimbursed for your participation in this trial.

**WHAT ABOUT RESEARCH RELATED INJURIES?**
Immediate necessary medical care is available at Duke University Medical Center in the event that you are injured as a result of your participation in this research study. However, there is no commitment by Duke University, Duke University Health System, Inc., or your Duke physicians to provide monetary compensation or free medical care to you in the event of a study-related injury.

For questions about the study or research-related injury, contact Dr. Kang at (919) 668-2331 during regular business hours and through the Duke University Medical Center paging operator at (919) 684-8111 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.

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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. Kang in writing and let him know that you are withdrawing from the study. His mailing address is DUMC 3961, Durham, NC 27710. You will be asked to come into the clinic for a final assessment, including a physical, blood tests, urinalysis, Echo, and bone marrow biopsy. In addition, you must return all unused study drug to Dr. Kang or his staff.

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 anytime without your consent. Reasons why this might occur include the study drug or combination of drugs is determined not to be effective, or if the study does not have enough patients to complete the study. If this occurs, you will be notified and your study doctor will discuss other options with you.

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

**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. Kang at (919) 668-2331 during regular business hours and through the Duke University Medical Center paging operator at (919) 684-8111 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 |

_____
Printed Name of Person Obtaining Consent