DUKE UNIVERSITY HEALTH SYSTEM

A Phase I, Open Label Study in Healthy Adults to Evaluate the Safety and Pharmacokinetics of AVYCAZ® in Combination with Aztreonam (COMBINE)
DEPRU# NJ07

Consent to Participate in a Research Study

CONCISE SUMMARY

The purpose of this study is to find out if ceftazidime-avibactam (AVYCAZ®) given in combination with aztreonam (ATM) is safe and to determine the concentration (amount) of the drugs in the body in healthy adults. AVYCAZ and ATM are both currently Federal Drug Administration (FDA) approved as individual antibiotics for the treatment of patients with various infections due to gram-negative bacteria, but giving both drugs at the same time requires further testing.

Healthy adults ages 18-45 are able to participate in this the study. AVYCAZ and ATM will be given by a catheter through a vein in your arm in the clinic at Duke. If you qualify for this study, your participation will last approximately 2 months. The study includes 2-3 outpatient visits and an 8-night inpatient visit during which you will have an intravenous catheter placed. Prior to receiving the study antibiotic(s), you will be evaluated at the Duke Early Phase Clinical Research Unit (DEPRU). If you qualify to continue participating in the study, you will receive the study antibiotic(s) assigned to you by the staff at the DEPRU. You may be able to continue in the study if you have no bad reactions(s) to the study drug(s). Tests, exams and procedures will be performed on you as part of the study.

The greatest risks of this study are side effects of the study drug including allergic reactions. Please notify the study team if you are allergic to medicines like penicillin. There is no anticipated direct benefit to you for participation in the study.

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

You are being asked to take part in this research study to help develop better antibiotic treatment plans for patients with serious Gram-negative bacteria (GNB) infections. 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. When your study doctor or the 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.

This study is being conducted by the Antibiotic Resistance Leadership Group (ARLG) (coordinated by Duke University). The ARLG is funded by a grant from the National Institutes of Health (NIH). Portions of Dr. Guptill's and his research team's salaries will be paid by this grant.

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

WHY IS THIS STUDY BEING DONE?
Treatment of patients with serious infections due to highly resistant GNB is a worldwide problem and is a major public health concern. Also, there are increases in resistance to certain antibiotics and combinations of antibiotics among patients with certain GNB infections. New antibiotics are being developed to treat these GNB infections that are resistant to multiple antibiotics, but they are not likely to be available for several years. Until new antibiotics are available, one way to treat patients with these antibiotic resistant GNB infections is to give ceftazidime-avibactam (AVYCAZ) in combination with aztreonam (ATM). AVYCAZ and ATM are both currently FDA approved to treat patients with various infections due to GNB. Although AVYCAZ and ATM appear to be safe, there are limited data on the safety of these antibiotics when they are given together. The purpose of this study is to evaluate the safety and the concentration (amount) of the drugs in the body when each antibiotic is given alone and when the antibiotics are given together in healthy adults ages 18-45. The antibiotics will be given by a catheter through a vein in your arm in the clinic at Duke. A catheter will stay in your arm until you have completed the study. You may receive only one antibiotic or you may be given the two antibiotics at the same time. You will have tests, exams and procedures to determine the safety of the antibiotics. Blood and urine will also be collected to measure the levels of the antibiotics as part of this study.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?
Participants who are 18-45 years old will be enrolled into the study. Approximately 120 participants will be screened to enroll 48 people will participate at Duke.

WHAT IS INVOLVED IN THE STUDY?
You will come to the Duke Early Phase Clinical Research Unit (DEPRU) at least three times over the next two months. The visits include the screening visit, an inpatient visit for 8 nights and 9 days in the DEPRU's confinement (research) unit when you are enrolled into the study and the study drug(s) are being administered, and for one follow-up visit. If you have side effects from the drug(s), you will be asked to return to the clinic for additional visits to be sure the side effect has resolved or has stabilized. You will not be allowed to leave the DEPRU confinement unit during your inpatient visit. The research staff will explain each visit to you. You will be able to ask questions to make sure that you understand what will happen.

Visit 1: Screening Visits (Days -30 to Day -2)
If you agree to be in this study, you will be asked to sign and date this consent form. You will then have the following tests and procedures to make sure that you are eligible:

- Sign this informed consent form before any tests or procedures will be completed

Consent to Participate in a Research Study

- Ask you questions about your age, race, sex, and ethnic group
- Ask you about any past or present illnesses and medications and supplements you are taking
- Complete physical examination
- Collect vital signs (height, weight, blood pressure, heart rate, respiratory rate, temperature)
- 12-lead electrocardiogram (ECG) in triplicate, which is a test used to measure the electrical activity of the heart
- Blood collection (approximately 2 tablespoons/30mL) to test the following:
  - Routine lab tests to check your health
  - Hepatitis B and C
  - HIV infection*

  **Note: As part of this protocol, you will be tested 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 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 HIV, then you should not agree to participate in this study.*
- Collect urine for drug screening, nicotine use and routine lab test
- If you are a female of child bearing potential, we will test your blood to make sure you are not pregnant
- Alcohol screen breathalyzer

Visit 2: Admission to Research Unit Visit (Enrollment) (Day -1-Day 8)
Day -1
If you qualify and agree to participate in the study, you will be asked to return to the clinical unit (DEPRU) on Day -1 (one day before drug dosing starts). After you complete the following tests and are confirmed eligible to participate, you will stay at the DEPRU for 9 days and 8 nights.

- You will be asked about any past or present illnesses and medications or supplements you are taking
- Complete physical examination
- Collect vital signs (height, weight, blood pressure, heart rate, respiratory rate, temperature)
- 12-lead electrocardiogram (ECG)
- Blood collection (approximately 1 tablespoons/15mL) for routine lab tests
- Collect urine for drug screen, nicotine use and routine lab tests
- If you are a female of child bearing potential, we will test your blood, if not already performed within the past 48 hours to make sure you are not pregnant
- Alcohol screen breathalyzer

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If you are enrolled you will be assigned into one of the following groups (cohorts) depending on when you are screened. You will know which group you are being assigned at the time of your screening visit.

Cohort 1: AVYCAZ 2.5 g IV as a 2-hour infusion every 8 hours for 7 days

Cohort 2: AVYCAZ 2.5 g IV as a 2-hour infusion x 1, then 0.32 g per hour IV daily as a continuous infusion (CI) (7.5 g/day) for 7 days

Cohort 3: ATM 2 g IV as a 2-hour infusion every 6 hours for 7 days

Cohort 4: ATM 2 g IV as a 2-hour infusion x 1, then 0.33 g per hour IV daily as a CI (8 g/day) for 7 days

Cohort 5: AVYCAZ 2.5 g IV as a 2-hour infusion every 8 hours for 7 days combined with ATM 1.5 g IV as a 2-hour infusion every 6 hours for 7 days

Cohort 6: AVYCAZ 2.5 g IV as a 2-hour infusion every 8 hours for 7 days combined with ATM 2 g IV as a 2-hour infusion every 6 hours for 7 days

Day 1 (Study Drug)
On Day 1, you will be administered your first dose of the study antibiotic(s). The antibiotic(s) you will receive will be based on which cohort you are enrolled. The following will be performed:

- Symptom-directed physical exam
- Vital signs (pre-am dose and 1-hour after starting first am dose administration)
- Review of any adverse events (side effects) and any new medications or supplements you may be taking
- Study drug administration
- Blood collection to determine the amount of the study drug(s) in your body (Plasma PK sample) as follows:
  - All cohorts: Pre-dose (10 minutes prior to the start of giving you the study drug(s) (infusion)) and the following times after the start of study antibiotic(s) infusion(s):, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, hours (approximately 5 tablespoons/72 mL)
- Urine collection to determine the amount of the study drug(s) in your body (Urine PK sample) >0 to 4, >4 to 8, >8 to 12, and >12 to 24 hours after the morning dose of antibiotic(s) administration

Day 2 (Study Drug)
The following will be performed:

- Symptom-directed physical exam
- Vital signs (morning)
- Review of adverse events and any new medications or supplements you may be taking
- Study drug(s) administration
- Safety labs (approximately 1 tablespoon/15mL)

Days 3 (Study Drug)
The following will be performed:
- Symptom-directed physical exam
- Vital signs (morning)
- Review of adverse events and any new medications or supplements you may be taking
- Study drug(s) administration
- Plasma PK sample (approximately 1 teaspoon/6ml each day)

Day 4 (Study Drug)
The following will be performed:
- Symptom-directed physical exam
- Vital signs (morning)
- Review of adverse events and any new medications or supplements you may be taking
- Study drug(s) administration
- Safety labs (approximately 1 tablespoon/15mL)
- Urine collection for routine lab tests

Day 5(Study Drug)
The following will be performed:
- Symptom-directed physical exam
- Vital signs (morning)
- Review of adverse events and any new medications or supplements you may be taking
- Study drug(s) administration
- Safety labs(approximately 1 teaspoon/ 5mL)
- Plasma PK sample (approximately 1 teaspoon/ 6ml each day)

Day 6 (Study Drug)
The following will be performed:
- Symptom-directed physical exam
- Vital signs (morning)
- Review of adverse events and any new medications or supplements you may be taking
- Study drug(s) administration
- Safety labs (approximately 1 tablespoon/15mL)
- Urine collection to determine the amount of the study drug(s) in your body (Urine PK sample):
  - >0 to 4, >4 to 8, >8 to 12, and >12 to 24 hours after the start of the morning dose administration

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Day 7 (Study Drug)
The following will be performed:

- Symptom-directed physical exam
- Vital signs (morning)
- Review of adverse events and any new medications or supplements you may be taking
- Study drug(s) administration – the study drug(s) will be stopped after the morning dose is administered on Day 7.
- Safety labs (approximately 1 teaspoon/6ml each day)
- Blood collection to determine the amount of the study drug(s) in your body (Plasma PK sample) as follows:
  - All cohorts: Pre-dose and the following times after the start of study antibiotic(s) infusion(s): 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 18 and 24 hours (approximately 6 tablespoons/96 mL)

Day 8 (Day of Discharge)
The following will be performed:

- Complete physical exam, review of medications or supplements you are taking and review of changes in medical history
- Vital signs (morning)
- Review of adverse events
- Single 12-lead ECG
- Blood collection for routine lab tests and plasma PK (approximately 1 tablespoons/15 mL)
- Urine collection for routine lab tests

Visit 3: Final Study Visit Day 11 +3 days (Outpatient)
The following will be performed:

- Complete physical exam
- Vital signs
- Review of adverse events and concomitant medications and supplements
- Single 12-lead ECG
- Blood collection for routine lab tests (approximately 1 tablespoon/15mL)
- Urine collection for routine lab tests

Early Termination Visit (if needed)
The following will be performed:

- Complete physical exam, review of medications or supplements you are taking and review of changes in medical history
- Vital signs
- Single 12-lead ECG

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- Review of adverse events
- Blood collection for routine lab tests and plasma PK (approximately 1 tablespoons/15 mL)
- Urine collection for routine lab tests

Unscheduled Visit (if needed)
The following will be performed:

- Complete physical exam
- Vital signs
- Review of adverse events and concomitant medications and supplements
- Single 12-lead ECG
- Blood collection for routine lab tests and plasma PK (approximately 1 tablespoons/15 mL)
- Urine collection for routine lab tests

HOW LONG WILL I BE IN THIS STUDY?
If you qualify for this study, your participation will last approximately 2 months and will include about 11 study visits. The screening period will last up to 30 days and there will be 7 days of study drug administration and about 7 days of follow-up. The follow-up period will be longer than 7 days if you continue to have side effects from the drug. You will be followed until your side effects resolve or stabilize.

You can choose to stop participating at any time without penalty or loss of any benefits to which you are entitled, and you will continue to receive care, but not as a part of this study. However, if you decide to stop participating in the study, we encourage you to talk to your doctor or the study doctor Jeffrey Guptill first.

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. In addition, there may be uncommon or previously unknown problems that might occur. You should discuss these with the study doctor and your regular health care provider if you choose.

Ceftazidime-avibactam (AVYCAZ) may cause some, all or none of the side-effects listed below.

- Hypersensitivity reactions: Serious and occasionally fatal allergic (anaphylactic) reactions and serious skin reactions have been reported in patients receiving beta-lactam antibacterial drugs. **Please notify study staff if you are allergic to antibiotics (cephalosporins, penicillins, or carbapenems).**
- *Clostridium difficile*-associated diarrhea has been reported for nearly all antibiotics, including AVYCAZ, and may range in severity from mild diarrhea to deadly inflammation of the colon. The diarrhea may start during or after the AVYCAZ is administered. *C. difficile* occurs naturally in the

colon. Treatment with antibiotics alters the normal flora (microorganisms that live in the colon) and may permit overgrowth of *C. difficile*.

- Central Nervous System Reactions: Seizures, non-convulsive status epilepticus (NCSE) (a seizure that causes primarily altered mental status), encephalopathy (altered mental state that is sometimes accompanied by physical changes), coma, asterixis (tremor of the hand when the wrist is extended), neuromuscular excitability (tingling in muscles), and myoclonia (twitching of muscles) have been reported in patients treated with ceftazidime, particularly in the setting of kidney impairment.
- Nervous system: headache, dizziness
- Gastrointestinal: abdominal pain, nausea, vomiting, and diarrhea

The following selected adverse reactions were reported in ceftazidime-avibactam treated patients at a rate of less than 1% in the Phase 3 trials.

- Decrease in level of platelets in the blood (the part of your blood that is involved with clotting)
- Irritation at drug administration site
- Yeast infection (candidiasis)
- Decreased potassium levels in the blood and changes in enzymes that diagnose liver function
- Altered sense of taste
- Acute renal failure, renal impairment, nephrolithiasis (or kidney stone)
- Rashes (including red raised or hives), itching
- Anxiety

Additionally, adverse reactions reported with ceftazidime alone that were not reported in AVYCAZ treated patients in the Phase 3 trials are listed below:

- Blood and lymphatic disorders –
  - Agranulocytosis - Lack of one major class of infection fighting white blood cells
    - hemolytic anemia – type of decreased red blood cells caused by improper breakdown of red blood cells.
    - leukopenia – low level of white blood cells in the blood
    - lymphocytosis – increase in the number of lymphocytes in the blood. Lymphocytes are a part of the blood involved with fighting infection
    - neutropenia – Decrease in the number of neutrophils in the blood. Neutrophils help the body fight infection.
    - thrombocytosis – High platelet count in the blood. Platelets are involved with blood clotting.
    - eosinophilia – a high level of white blood cells in the blood. Eosinophils help fight diseases
- General disorders and administration site conditions –
  - Inflammation at the infusion site.
  - blood collecting at the site of the injection
  - bruise at the site of infection

- Jaundice (yellow discoloring of the skin)
- Increased blood lactate dehydrogenase (an enzyme that frequently indicates tissue damage)
- Prolonged prothrombin time (time required to clot blood)
- Paresthesia (prickly or tingling sensation usually in the hands, arms, legs or feet)
- Tubulointerstitial nephritis (injury to the renal tubules or interstitium of the kidney) which can lead to decreased kidney function
- Vaginal Inflammation
- Skin and subcutaneous tissue disorders
  - Angioedema –swelling under the skin
  - Erythema multiforme – skin lesions that look like bulls eyes
  - Stevens-Johnson syndrome – rare disorder of skin leading to painful red or purplish rash that spreads and blisters
  - Toxic epidermal necrolysis – widespread swelling, redness and necrosis of the skin.

Laboratory Changes
Coombs test – a test to determine if your body has antibodies. Antibodies help your body protect itself. However, the body can develop antibodies against itself. The Coombs test measures if you have antibodies to your own body's red blood cells. Rarely, people who have taken this drug have changed from not having these antibodies to having these antibodies.

Aztreonam (ATM) may cause some, all or none of the side-effects listed below.

- Local reactions (e.g., inflammation, bruising, discomfort/swelling) following intravenous administration. Systemic reactions (considered to be related to therapy or of uncertain cause), occurring in up to 1.3% of people on this medication, include diarrhea, nausea and/or vomiting, and rash.
- Reactions occurring at an incidence of less than 1% are listed within each body system in order of decreasing severity:
  - Hypersensitivity – severe allergic reaction
  - Changes in kidney function.
  - Hematologic – changes in levels of various components of your blood.
  - Gastrointestinal – abdominal cramps and *Clostridium difficile*-associated diarrhea. *Clostridium difficile*-associated diarrhea has been reported for nearly all antibiotics, including ATM, and may range in severity from mild diarrhea to deadly inflammation of the colon. The diarrhea may start during or after the ATM is administered. *C. difficile* occurs naturally in the colon. Treatment with antibiotics alters the normal flora (microorganisms that live in the colon) and may permit overgrowth of *C. difficile*.
  - Onset of diarrhea, bloating, nausea, pus in stool, cramps, etc. may occur during or after antibiotic treatment.

- Dermatologic – toxic epidermal necrolysis (widespread swelling, redness and necrosis of the skin), purpura (patches of purplish discoloration on the skin), erythema multiforme (skin lesions that look like bulls eyes), exfoliative dermatitis (intense and usually widespread reddening of the skin), urticaria (hives), petechiae (Pinpoint flat round red spots under the skin), pruritus (localized or generalized itching), diaphoresis (sweating)
- Cardiovascular – low blood pressure, changes in the ECG that are not permanent ECG changes, flushing
- Respiratory – wheezing, shortness of breath, chest pain
- Hepatobiliary – inflammation of the liver and yellow discoloration of the skin.
- Nervous System – seizure, confusion, balance issues, tingling or numbness, changes in sleep pattern, dizziness
- Musculoskeletal – muscle aches
- Special Senses – ringing in the ears, double vision, mouth ulcer, altered taste, numb tongue, sneezing, nasal congestion, bad breath
- Other – vaginal cyst infection, inflammation of the vagina, breast tenderness
- Body as a Whole – weakness, headache, fever, general fatigue

Studies indicate that increase in liver enzymes in the blood due to mild inflammation of the liver can occur in 10 to 38% of individuals who receive aztreonam. The enzyme abnormalities typically occur after several days of therapy. Among patients who experience liver enzyme increase while receiving aztreonam, the increases in liver enzymes are mild-to-moderate in nature and nearly all patients have no symptoms. For patients who have increase in liver enzymes, liver enzymes typically go back to normal once aztreonam is stopped. No individual cases of major liver injury or failure due to aztreonam therapy have been reported in studies.

Laboratory Changes: Adverse laboratory changes without regard to drug relationship that were reported during clinical trials were:

- Liver- Increases in liver enzymes; signs or symptoms of liver dysfunction occurred in less than 1% of recipients
- Blood-increases in prothrombin and partial thromboplastin times, positive Coombs' test (see laboratory changes for AVYCAZ®.
- Renal-increases in serum creatinine.

The side effects of AVYCAZ combined with ATM are expected to be similar to the side effects of AVYCAZ alone and ATM alone. However, there is a possible chance for more side effects with AVYCAZ combined with ATM because of taking the two drugs together.

Female
The effects of the study drug on a developing pregnancy or breastfeeding infant are not known. Women who are pregnant, planning a pregnancy or breastfeeding are not allowed to participate in studies of the drug.

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If you are a woman who could possibly become pregnant (you have not completed menopause, or you have not had a hysterectomy and/or both tubes and/or both ovaries removed) and you have a partner who is able to father children, a blood pregnancy test will be done, and it must be negative to continue in the study. In women 40 years old and older, blood pregnancy tests can sometimes give a false positive or indeterminate result, and additional testing may be required.

You and your partner must agree to either abstain completely from vaginal intercourse for 30 days to taking the study drug, the duration of the study, and for 30 days afterwards, or use one of the following methods of contraception for the same length of time: (a) partner vasectomy, (b) bilateral tubal ligation, (c) intrauterine device (IUD), (d) hormonal methods (birth control pills, implants, injections, patches, vaginal rings),. If you are not currently using one of these methods, your study doctor will discuss options with you, given your personal preferences and the level of protection required for this study. Because no method of birth control is 100% effective, you should notify your study doctor immediately if you think there is any chance you could be pregnant during the 30 days after the study. Females who become pregnant during the study will be taken off the study drug and will be followed until the outcome of the pregnancy is known.

Male
The effects of the study drug on a pregnancy which began while the father was taking the drug are not known. If you have a partner who could possibly become pregnant (she has not completed menopause, or she has not had a hysterectomy and/or both tubes and/or both ovaries removed), you must agree to either abstain completely from vaginal intercourse for the duration of the study and for 30 days afterwards, or, if you have not had a vasectomy, use a condom with spermicide every time you have vaginal intercourse for the same length of time. You should inform your partner about your participation in this study; if she becomes pregnant within 30 days after completion of the study, you should inform your study doctor immediately.

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

Risks of placement of IV catheter and study product administration through the IV:
The study drug is administered through an IV catheter which is a small, flexible hollow tube inserted into a vein in your arm. Inserting an IV requires a needle and can cause localized discomfort. During IV infusion you are unlikely to feel discomfort. The vein the catheter is inserted in may become inflamed with signs of redness and warmth at or near the IV insertion site. Inflammation in a vein due to a blood clot is also a potential risk. This would be a hard area the study doctor could feel near the IV insertion site. In some instances the vein may develop a small rupture causing the Study Drug to leak out of the

vein. This is generally not dangerous, but can cause discomfort and bruising. There is a risk of infection; however, this is a small risk as aseptic technique will be used.

Risks of Electrocardiogram (ECG):
Possible side effects of the ECG are skin irritation, itching and redness from the ECG electrode pads.

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.

ARE THERE BENEFITS TO TAKING PART IN THE STUDY?
While there are no direct benefits to you by participating in this study, we hope that in the future the information learned from this study will benefit other people with bacteria or other infection related illnesses.

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 (private), 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 working with the DEPRU, 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, and procedures may be reported to the National Institutes of Health (NIH) and its representatives. In addition, your records may be reviewed in order to meet federal or state regulations. Reviewers may include representatives from the FDA, representatives and representatives of NIH, the Duke University Health System Institutional Review Board, and others as appropriate. If any of these groups review your research record, they may also need to review your entire medical record.

As part of this study, you will be asked to have certain tests and procedures performed. Some of these test results will be recorded in your medical record and will be reported to the representatives and representatives of NIH. Some of the tests will be performed solely for research purposes and could not be used for diagnosis or treatment. These test results will not be available in your medical record.

Consent to Participate in a Research Study

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 share 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 shared with 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.

Sharing the information from this study 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 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 participation 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.

Some information collected in research studies is maintained in your medical record. All of the blood and urine collected to determine the amount of the drugs in the body are being done only because you are in this study. The study results will not be provided to you OR sent to your physician, but may be available in your DUHS medical record.

The study results will be retained in your research record for at least two years after the study is completed and the FDA is notified. 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. Your permission to access your medical records expires at the end of the study, however your permission to use research information collected about you does not expire.

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

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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?
There are no costs for you to participate in the study. The study drug(s) will be provided to you free of charge. You will not be charged for any procedure performed for the purpose of this study. 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.

Your study doctor or staff will go over the reimbursement process and other patient travel management services available to you.

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.

WHAT ABOUT COMPENSATION?
You will be reimbursed up to $2,600.00 for your expenses related to your participation (parking, gas, and time).

Day	Compensation
Screening	$100
Inpatient visit	$300/night
Outpatient visit	$100

You will be reimbursed based upon the completion of the visits listed. If the study team requests that you come in for an unscheduled visit, you will be reimbursed $50 for the completion of each of the unscheduled visits.
Payment received as compensation for participation in research is considered taxable income to the research subject. If payment to an individual exceeds $600 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 $600 during any calendar year will result in a 1099 (Miscellaneous Income) form being issued to the individual and a copy sent to the IRS.

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 obligation by Duke University, Duke University Health System, Inc., your Duke physician's or NIH to provide monetary payment or free medical care to you in the event of a study-related injury. In general, no long-term medical or financial payment for research-related injuries will be provided by the NIH or the Federal Government.

For questions about a research-related injury, contact Dr. Jeffrey Guptill at (919) 684-1672 during regular business hours and 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 or blood and urine samples will be collected for study purposes unless the data concerns 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, including blood and urine samples to determine the concentration (amount) of the drugs in your body, 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. Guptill in writing and let him know that you are withdrawing from the study. His mailing address is: Box 3854, Duke University Medical Center, Durham NC 27710. The study doctor 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 normally 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 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 you no longer meet eligibility criteria or noncompliance to study procedures or safety concerns. If this occurs, you will be notified and your study doctor will discuss this with you. If the doctor determines

you must not continue in the study, no new data about you or blood and urine samples will be collected for study purposes unless the data concerns 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, including the results of the analysis of your blood and urine, and any new information about an adverse event related to the study, will be sent to the study sponsor. Your blood and urine samples collected during the study will not be stored for future research and will not result in any commercial profit. You will not be compensated for the use of your samples other than what is described in this consent form.

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, medical emergencies or a research-related injury, or if you have problems, concerns, questions or suggestions about the research, contact Dr. Jeffrey Guptill at **(919) 684-1672** during regular business hours and 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.

DUKE UNIVERSITY HEALTH SYSTEM

A Phase I, Open Label Study in Healthy Adults to Evaluate the Safety and Pharmacokinetics of AVYCAZ® in Combination with Aztreonam (COMBINE)
DEPRU# NJ07

Consent to Participate in a Research Study

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