IRB00081742

An observation study comparing prospective use of Imipenem/Cilastatin/ Relebactam (IMI/REL) to retrospective data using Meropenem/Vabobactam (MVB)and Ceftazidime/Avibactam CZA) in treatment of Klebsiella Producing Carbapenemase Enterobacteriaceae infection

IRB Approval
13MAR21

NCT04785924

ATRIUM HEALTH
CONSENT TO PARTICIPATE IN A RESEARCH STUDY
AND AUTHORIZATION TO DISCLOSE HEALTH INFORMATION

Sponsor / Study Title:	**Atrium Health Infectious Disease / "An observation study comparing prospective use of Imipenem/Cilastatin/Relebactam (IMI/REL) to retrospective data using Meropenem/Vabobactam (MVB) and Ceftazidime/Avibactam (CZA) in treatment of Klebsiella Producing Carbapenemase Enterobacteriaceae infections at a tertiary care hospital"**
Protocol Number:	**MISP-59805 / Atrium Health Number (03-21-23)**
Principal Investigator: (Study Doctor)	**Christopher Polk, M.D.**
Telephone:	[redacted]
Address:	**Atrium Health** **Infectious Disease Kenilworth** [redacted]

This form is for use in a research study that may involve subjects who may or may not have the capacity to consent to take part in the study. When the subject cannot legally consent to take part, pronouns "you" and "your" should be read as referring to the subject rather than the person (legally authorized representative) who is signing and dating this form for the subject. In cases where the subject's representative gives consent, the subject should be informed about the study to the extent possible given his/her understanding. During the course of the study, if the subject regains the capacity to consent, informed consent will be obtained from the subject and the subject offered the ability to leave the study if desired.

1. KEY INFORMATION

You are being asked to take part in a research study. Before you agree, it is important that you read and understand this informed consent form. Participating in this research study is voluntary. If you decide not to be in the research study, it will not impact your clinical care. If you decide to be in the research study, you may change your mind at any time during the study and you can stop participating. Take all the time you need to make your choice. Ask us any questions that you may have. It is okay to ask more questions after you decide to be in the study.

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This is a research study of an antibiotic treatment, Imipenem/Cilastatin/Relebactam (IMI/REL) for treatment of infections caused by certain types of drug resistant bacteria, Klebsiella Producing Carbapenemase (KPC) Enterobacteriaceae. IMI/REL is approved by the United States Food and Drug Administration (FDA) as an antibiotic for treatment of pneumonia, intra-abdominal, and urinary tract infection which has activity against KPC containing Enterobacteriaceae, drug resistant pathogens also known as Carbapenemase Resistant Enterobacteriaceae (CRE). There are limited treatment options for CRE infections, so this research study is being conducted to gain more information on the use of IMI/REL to treat CRE infections. If you qualify, you may participate in the research study for up to 90 days. The use of IMI/REL on this study is considered investigational. An investigational use is one that is not approved by the FDA.

- The study will include a screening phase to determine if you qualify during your hospitalization.
- The study will include a study treatment phase, during which you will receive study therapy with IMI/REL. This will last as long as your study doctor judges that you need antibiotic study therapy and will be administered while you remain in the hospital. All subjects enrolled in this study who qualify will be treated with the study drug, IMI/REL.
- The study will include a follow-up phase until Day 90, or until you stop your study participation.

During the different phases of the research study, you will be asked to complete different study procedures or answer questions in order to monitor your health and response to the study drug. Most procedures will be done while you are admitted to the hospital, and others may be done when you are not required to stay at the hospital (after discharge).

If you agree to participate in this study, the study drug may have a positive effect on your health, but there is no guarantee because the study drug may need to be used outside of its FDA approved indication. If the study drug does not successfully treat your infection, your study doctor will switch you to another alternative treatment. It is possible that you will not benefit from your participation, but information learned from the study may help other people in the future. The knowledge gained from this study may help doctors determine what treatment to provide other people with CRE infections in the future.

While the research study team will take measures to monitor the safety of the research subjects, there may be serious risks involved with participating in this research study. The risks may be associated with the study drug itself, and/or the study procedures. There may be other risks that are not known. More detail about the risks can be found under the "Safety" section.

You can also choose not to participate in this research study and may have options of getting other treatments for your CRE infection. Your study doctor will discuss these other options with you.

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2. INTRODUCTION AND BACKGROUND INFORMATION

You have been invited to participate in this study because you have been diagnosed with a CRE infection and there are limited available treatment options. The investigational treatment involves the administration of IMI/REL via intravenous (IV, into the vein) infusion. "Investigational" means that the study drug may be used outside of the indications it is approved for by the United States Food and Drug Administration (FDA) in the USA.

2.1. Who is Paying for this Study?

Merck, a pharmaceutical company who manufactures the study drug, is providing the study drug at no cost to you. Merck is paying the study doctor and the study site to perform parts of this study.

2.2. What is the Purpose of this Research Study?

The purpose of this study is to find out how effective the study drug is in treatment of CRE infections. The study drug has been approved by the FDA for use in pneumonia, intra-abdominal, and urinary tract infections but not specifically for infections caused by CRE. The study drug does have activity in laboratory testing to treat CRE infection caused by KPC containing bacteria, and prior studies with the study drug have included treatment of these types of infections in a small number of subjects.

2.3. How Many People Will Participate in this Research Study?

15 subjects at Atrium Health will participate in this study.

2.4. What Kind of Investigational Study Treatment will be Tested in this Main Study?

IMI/REL is a carbapenem class antibiotic which will be used in the study. You will receive this study treatment intravenously every 6 hours while hospitalized for a duration as determined by your treating doctors and the study doctors. Duration of study therapy will be determined based on the severity and type of your CRE infection.

2.5. What are the Chances that I will get the Investigational Drug?

All subjects enrolled in this study will receive study drug IMI/REL.

2.6. What Will I be Responsible for if I Participate?

While you are participating in this study, you will be expected to do the following:

- You will be asked to receive all study-required treatments and complete all study-required procedures.
- If you are discharged from the hospital you may be asked to return to the clinic at specific visit dates and follow the study doctor's directions. While you are in the hospital you must

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participate in all your clinical assessments and follow the study doctor's directions.

- You should not participate in other research studies that include investigational study treatments, procedures, or devices as long as you are on study.
- If you are approached to participate in another study, you should discuss the new study with your study doctor before agreeing to participate.
- You will be asked to share with your study doctor what medications you are taking because some medications should not be used while you are on the study.
- You should also report to your study doctor any changes in your health or new health issues you may experience whether or not you think it is related to your study treatment.
- If you are a woman of childbearing potential you must agree to not become pregnant and use contraception until after your last dose of the study drug. If you do become pregnant you must contact the study doctor. (See section 4.4 below.)

2.7. How Long is the Study?

Your participation in this study will last about 3 months. You will be closely followed for the duration of your hospitalization and for 90 days after receiving study drug. Study procedures / visits will occur every day you are hospitalized and receiving the study drug and then 30 and 90 days after starting study treatment. Following your discharge from the hospital, your study doctor or study nurse will reach out for follow-up information on your condition until 90 days after receiving the study drug to make sure you aren't experiencing any adverse events (side effects). You will be asked to provide several methods of contact information (telephone, cell phone, email address, primary care physician information) to allow the study team to contact you.

3. STUDY PROCEDURES

3.1. What Types of Procedures are Required, and How Frequently do I Visit the Clinic?

3.1.1. Screening

To begin the study, your study doctor will evaluate you during a screening period to determine if you meet the study requirements for participation.

During this time period, the following will be performed while you are in the hospital:

- The study team will explain the study to you. If you wish to take part, you will sign and date the informed consent form
- The study team will do a physical examination, including weight, and will ask questions about your medical history, medications you are taking, current condition, smoking history, and demographics (information like your gender, ethnicity, and age)
- The study team will measure your vital signs including temperature, oxygen saturation (amount of oxygen in your blood), respiratory (breathing) rate, blood pressure, and heart rate
- Collection of blood for laboratory testing
- If you are a woman of childbearing potential, you will also undergo a urine pregnancy test

If you meet the study requirements after the above assessments are completed, you will be able to participate in the study.

3.1.2. Study Treatment Phase

If you qualify for the research study, then you will receive study drug.

On each day of dosing, the following will be performed:

- The study team will do a physical examination and re-review your medical history, medications you are taking, and current condition
- The study team will measure your vital signs including temperature, oxygen saturation, respiratory rate, blood pressure, and heart rate
- Blood may be collected from you for laboratory testing
- You will receive an infusion of the study drug, IMI/REL, every 6 hours or less frequently if dosing needs to be adjusted for your kidney function

3.1.3. Follow-Up Phase (From end of study treatment up to Day 30)

At end of study drug treatment and at day 30 after starting study treatment:

- The study team will ask you about any changes to your health and medications
- The study team will do a symptom-directed physical examination
- The study team will measure your vital signs including temperature, oxygen saturation, respiratory rate, blood pressure, and heart rate
- Blood will be collected from you for laboratory testing
- The study team will assess you for resolution of infection

If you are discharged from the hospital before Day 30, you will be asked to return to the clinic for an outpatient visit or the study team will call you to assess if there have been any changes to your health.

3.1.4 Day 90

This visit will be conducted by phone or in-person to assess your vital signs and ask you about any changes to your health and medications.

SAFETY

3.2. What are the General Risks of Participating in this Study?

While the study team will take measures to monitor the safety of the research subjects, there may be serious risks involved with participating in this research study. The risks may be associated with the study drug itself and / or the study procedures. In addition to the adverse effects noted below, there is a risk that you may experience new or unexpected adverse effects, some of which may have a delayed onset. Your study doctor will closely monitor your health throughout this study. Your study doctor will discuss with you any questions regarding risks, discomforts, and adverse effects.

3.3. What are the Known Side Effects of IMI/REL?

Observed Risks:

As of August 2020, IMI/REL has been administered to over 430 subjects in studies of its efficacy (how well the study drug works) in treating urinary tract and intra-abdominal infection and pneumonia. The FDA has warned to watch for seizures or C diff associated (antibiotic induced) diarrhea in subjects administered IMI/REL, but not all potential side effects (also known as adverse effects) in humans are known.

Common (occurred in fewer than 10% but in more than 2% of study subjects) Adverse Effects
• Diarrhea • Nausea and vomiting • Headache • Abnormal liver tests (possible liver damage and can cause tiredness, jaundice [yellowing of the skin and eyes])
Uncommon and Rare (occurred in less than 2% of study subjects) Adverse Effects
• Infusion Reaction (including dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath, sick to your stomach, or pain at the site of infusion. Although usually reversible with treatment, it can be severe or life threatening) • Anemia (lower number of red blood cells that can cause tiredness and shortness of breath) • Hypertension (high blood pressure) • Central nervous system reactions including agitation, confusion and disorientation • Abnormal pancreas laboratory tests • Abnormal kidney laboratory tests (possible kidney damage)

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3.4. What are the Risks Associated with Procedures Done in this Research Study?

Blood Collection

The risks of collecting blood include pain at the site of the needle entry, a bruise at the point where the blood is taken, redness and swelling of the vein and infection, and a rare risk of fainting.

Intravenous (IV) Infusion

The risks of intravenous infusion include temporary discomfort from the needle stick, bruising, bleeding, and rarely, infection. Temporary discomfort may be experienced while receiving the intravenous infusion.

Allergic Reaction Risks

As with taking any drug, there is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:

- Rash
- Wheezing and difficulty breathing
- Dizziness and fainting
- Swelling around the mouth, throat or eyes
- A fast pulse
- Sweating

Please seek treatment immediately and tell the study doctor and study team if you have any of these symptoms.

Unforeseen Risks

Since the study drug is investigational, there may be other risks that are unknown.

3.5. What do I Need to Know about Reproductive Health/Sexual Activity if I am in this Study?

The effects of IMI/REL on human sperm and eggs have not been studied. The effects on the developing fetus exposed to IMI/REL during pregnancy and the risk of birth defects are also unknown or may be unforeseeable. Therefore, both men and women should not attempt pregnancy, and women should not be pregnant or breastfeeding while taking part in this study.

If sexually active, women should use highly effective methods of birth control prior to study entry and during treatment with the study drug. Examples of highly effective birth control methods include:

- Combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Injectable
  - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system
- Bilateral tubal occlusion (tubes tied)
- Vasectomized partner
- Sexual abstinence (Refraining from all acts of vaginal sex)

If you or your partner become pregnant while on the study, it is important that you tell your study nurse/study doctor immediately.

If you are female and considered to be post-menopausal, you are not required to use contraception while in this study. Rarely, women considered to be post-menopausal become pregnant.

If you are planning to breastfeed during this study, please tell the study doctor immediately. Women who are breastfeeding are not allowed to take part in this study.

4. POTENTIAL BENEFITS

Are there Benefits to Taking Part in this Study?

Your condition may get better, stay the same, or get worse. It is possible that your CRE infection will not respond to study treatment. We are unsure if you will receive any benefits by taking part in this research study; however, the knowledge gained from this study may help doctors determine what treatment to provide other people with CRE infection in the future.

5. ALTERNATIVE TREATMENT OPTIONS

What Other Procedures or Courses of Treatment Might be Available to me?

You do not have to take part in this research study. You may decide to continue with the standard of care alone.

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You also have the right to choose comfort care (also known as palliative care) with the aim to reduce your pain and discomfort but not the cause. Or you may choose to receive no treatment at all. The study doctor will discuss the available options with you, including their risks and benefits.

6. POTENTIAL FINANCIAL CONFLICTS, COSTS, AND COMPENSATION

6.1. Financial Conflict of Interest

This research is being sponsored by Atrium Health. Funding for this study is being provided by Merck. This means that Merck is reimbursing the research team for the some of the costs of doing the study. Your study doctor does not have a financial stake in the results of the study.

6.2. Financial Disclosure

The doctors will receive no financial benefit in any form by asking you to participate in this study.

6.3. Are there any Financial Costs to Being in this Study?

There are no costs associated with the study-specific procedures set forth in the study plan that are not part of the routine care.

Some of the drugs, tests, or procedures used in this study may be a part of standard medical care, which means that the drugs, tests, or procedures would likely be part of the management of your condition even if you did not take part in this study. You or your insurance company are responsible for the cost of standard medical care, which may include your inpatient hospitalization.

You are encouraged to discuss your study participation with your insurance company so you fully understand any costs or expenses, including copays and/or deductibles that you may have to pay for.

6.4. Compensation For Participation

You will not be paid for being in this study.

7. COMPENSATION FOR INJURY

What should I do if I am injured as a result of being in this study?

In the event that you are harmed as a result of your participation in this study, we will provide or arrange for treatment as necessary. This treatment, as well as other medical expenses, will be billed to you or your insurance company in the usual manner. You do not waive any legal rights by signing this consent form.

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If you become ill or are hurt while you are in the study, get the medical care that you need right away.

If your insurance is billed, you may be required to pay deductibles and co-payments that apply. You should check with your insurance company about any such payments.

In no way does signing this consent form waive your legal rights nor does it relieve the investigators or involved institutions from their legal and professional responsibilities.

8. CONFIDENTIALITY

8.1. Will my Confidentiality be Maintained?

The records of this study will be kept private. If any report about this research is published, we will not include any information that will make it possible to identify you. However, there is some risk that de-identified data might be re-identified. Also, your record for this study may be reviewed and/or photocopied by Atrium Health, or by representatives of the Food and Drug Administration or other government agencies.

To ensure that your information collected for this study will be kept private, your name will not be used whenever possible. A code will be used instead of your name. All of your study data will be kept in a secure location.

The confidentially of your medical records will be maintained to the extent permitted by applicable laws. If the results of the trial are published, your identity will remain confidential. Using your subject identification number only, the results and other information for the study may be submitted to regulatory agencies where the investigational product (study drug) may be submitted for approval.

9. SUBJECT RIGHTS

9.1. Whom to Contact About This Study

During the study, if you experience any medical problems, suffer a research-related injury, or have questions, concerns or complaints about the study, please contact the study doctor at the telephone number listed on the first page of this consent document. If you seek emergency care, or hospitalization is required, alert the treating physician that you are participating in this research study.

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An institutional review board (IRB) is an independent committee established to help protect the rights of research subjects. If you have any questions about your rights as a research subject, and/or concerns or complaints regarding this research study, contact:

- By mail:
  Study Subject Adviser
  Advarra IRB
  [redacted]
- or call **toll free**: [redacted]
- or by **email**: [redacted]

Please reference the following number when contacting the Study Subject Adviser: Pro00045929.

9.2. What are my Rights as a Research Subject?

Your participation in this study is completely voluntary. You should feel under no pressure to be in the study. If you decide not to be in the study, that will not in any way harm your relations with your doctors or with Atrium Health. You are free to stop being in the study if you change your mind after entering it. This would not harm your relations with your doctors or Atrium Health.

If you choose to be in this study, you have the right to be treated with respect, including respect for your decision whether you wish to continue or stop being in the study. You are free to choose to stop being in the study at any time.

If the study team thinks at any time participation in the study is a risk to your health or safety or that you are unable to reasonably comply with the terms and conditions of the study, they may withdraw you from the study. Your participation in this study may be stopped by the investigator without your consent if he or she believes it is in your best interest.

Choosing not to be in this study or to stop being in this study will not result in any penalty to you or loss of benefit to which you are entitled. Specifically, your choice not to be in this study will not negatively affect your right to any present or future medical treatment at this institution.

Any new findings developed during the course of this research that may affect your willingness to continue in this study will be shared with you.

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9.3. Can I Stop Participating in the Study?

You are free to partially or completely stop participating in the study at any time. If you decline to continue to receive study-required treatment and /or other study procedures, but allow your study doctor to continue to monitor your health, this is considered partial withdrawal of consent. If you do not want to continue to receive study-required treatment and /or other study procedures and you do not allow your study doctor to continue to monitor your health for the purpose of this study, this is called full withdrawal of consent.

If you stop participating in this study, you will not lose any benefits except those you might have been receiving in connection with the study.

If you decide to stop participating in the study, or are removed from the study, or the study is stopped, the study doctor will ask you to return for a follow-up visit. You should discuss further treatment options with your study doctor when your participation in this study ends.

10. CONSENT SUMMARY

Your participation in this study is optional and voluntary; you are free to withdraw from the study at any time without prejudice to your future care. If you choose not to participate, there are no penalties, loss of any benefits, or medical care that you are entitled to get from this hospital or from your healthcare providers.

If you do participate in the study and then decide to withdraw, you should notify your study doctor so that your part in the study may be stopped in an orderly manner, come back to the clinic for a final assessment, and discuss your future care. Any data or samples that were submitted prior to your withdrawal will be retained by Merck and will be analyzed. Public health records may also be used to confirm if you remain alive after you have withdrawn your participation.

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 includes a summary of the study results. You can search this Web site at any time.

You or your legally authorized representative will be kept informed of any medically important information that may relate to your willingness to continue to participate in this study. You may be asked to sign and date a revised consent document at that time.

You may ask any questions about this study at any time.

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AUTHORIZATION TO USE AND DISCLOSE YOUR PROTECTED HEALTH INFORMATION

If you wish to participate in this research study, you

_____

Printed Name of Research Subject

must sign this Authorization. By signing this Authorization, you give all healthcare providers, including Atrium Health, permission to use or disclose (release) your protected health information, both past and present, for the research study described here:

"**An observation study comparing prospective use of Imipenem/Cilastatin/Relebactam (IMI/REL) to retrospective data using Meropenem/Vabobactam (MVB)and Ceftazidime/Avibactam (CZA) in treatment of Klebsiella Producing Carbapenemase Enterobacteriaceae infections at a tertiary care hospital"**

The protected health information that we may use or disclose (release) for this research may include all information in your medical record, such as results of physical examinations, medical history, lab tests, or certain health information indicating or relating to a particular condition.

The health information listed above may be used by and/or disclosed (released) to:

- Study investigator and study team
- Study sponsor (Atrium Health)
- Regulatory or other governmental authorities of the United States or other countries based on this study
- Merck pharmaceutical company
- Atrium Health employees
- Other persons or agencies as required by law or allowed by federal regulations
- Data coordinating centers that will receive and process PHI; and/or
- Advarra Institutional Review Board (Advarra IRB).

Atrium Health is required by law to protect your protected health information. By signing this Authorization, you authorize Atrium Health to use and/or disclose (release) your protected health information for this research study. Those persons who receive your protected health information may not be required by Federal privacy laws (such as the Privacy Rule) to protect it and may share your protected health information with others without your permission, if permitted by laws governing them. Your protected health information may then no longer be protected by the Privacy Rule.

Please note that you do not have to sign this Authorization, but if you do not, you may not receive research-related treatment through this study. However, Atrium Health may not condition (withhold or refuse) your other Atrium Health providers treating you on whether you sign this Authorization.

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You may change your mind and withdraw (take back) this Authorization at any time, except to the extent that Atrium Health or Merck has already used or disclosed your protected health information based on this Authorization. To withdraw this Authorization, you must write to the Study Doctor at the address listed on the first page of this form.

No publication or public presentation about the research described above will reveal your identity without another Authorization from you. If all protected health information that does or can identify you is removed, the remaining information will no longer be subject to this Authorization or federal rules (such as the Privacy Rule) and may be used or disclosed for other purposes.

When the research for which the use or disclosure is made involves treatment and is conducted by Atrium Health: To maintain the integrity of this research study, you generally will not have access to your personal health information related to this research until the study is complete.

At the conclusion of the research study and at your request, you generally will have access to your protected health information. Access to your protected health information in a medical record is described in the Notice of Privacy Practices provided to you by Atrium Health.

When conducting research, the data and results may be used or disclosed for further treatment outcomes research or to research a secondary result. This Authorization will remain in effect after the end of the current study, and any future related secondary study unless it is revoked by you in writing as described above.

_____

Signature of Research Subject or Research Subject's Legally Authorized Representative

_____

Printed name of Research Subject or Research Subject's Legally Authorized Representative

_____

Date

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11. STATEMENT OF CONSENT

I have read this form and its contents were explained to me. I agree to be in this research study for the purposes listed above. All of my questions were answered to my satisfaction. I will receive a signed and dated copy of this form for my records. I am not giving up any of my legal rights by signing this form.

_____ ____/____/____ _____
Signature of Research Subject Date Time

_____
Printed Name of Research Subject

_____ ____/____/____ _____
Signature of Legally Authorized Representative (if applicable) Date Time

_____
Printed Name of Legally Authorized Representative (if applicable)

STATEMENT OF PERSON EXPLAINING CONSENT

I have carefully explained to the subject or the subject's legally authorized representative the nature and purpose of the above study. There has been an opportunity for the subject or the subject's legally authorized representative to ask questions about this research study. I have been available to answer any questions that the subject or the subject's legally authorized representative has about this study.

_____ ____/____/____ _____
Signature of Person Explaining Consent Date Time

_____
Printed Name of Person Explaining Consent

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