

Revefenacin in Acute Respiratory Insufficiency in COPD (RARICO)

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**UNIVERSITY OF CALIFORNIA LOS ANGELES
CONSENT TO PARTICIPATE IN RESEARCH**

**Revefenacin in Acute Respiratory Insufficiency in COPD
(RARICO)**

INTRODUCTION

Igor Barjaktarevic MD, PhD, Nida Qadir MD, Joanne Bando MD, and associates from the Division of Pulmonary & Critical Care Medicine at the University of California, Los Angeles are conducting a research study. This study is being funded by Theravance and Mylan Pharmaceuticals.

KEY INFORMATION:

The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form.

Revefenacin in Acute Respiratory Insufficiency in COPD (RARICO) is a randomized, controlled, double-blinded, multi-center trial evaluating the use of nebulized Revefenacin in comparison to nebulized Ipratropium in patients with COPD and acute respiratory failure requiring invasive mechanical ventilation.

WHY AM I BEING INVITED TO TAKE PART IN A RESEARCH STUDY?

We invite you to take part in a research study because you have a history of chronic obstructive pulmonary disease (COPD) and currently have acute respiratory failure requiring mechanical ventilation. COPD is the collective term for a number of lung diseases that prevent proper breathing, and include emphysema and chronic bronchitis. Patients with COPD sometimes develop acute respiratory insufficiency, a condition in which their breathing declines and they require support from a ventilator, or breathing machine. As a person with COPD who is currently suffering from acute respiratory insufficiency, you qualify to participate in the study evaluating the safety and feasibility of an inhalational medication use in these settings.

WHAT SHOULD I KNOW ABOUT A RESEARCH STUDY?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.

- You can discuss this study with friends and family.
- You can also discuss it with your health care doctor or request a second opinion.

WHY IS THIS RESEARCH BEING DONE?

Patients with COPD are often hospitalized with acute respiratory insufficiency, which can be life-threatening. Supportive care for these patients typically includes the use of steroids, inhalers that dilate the bronchi and bronchioles to increase airflow to the lungs, and airway clearance therapy (ACT) to clear mucus from the lungs.

Bronchodilators are inhaled medications that represent a key medical therapy in daily management of COPD and consist of beta-agonists and muscarinic antagonists. Revefenacin (trade name YUPELRI®) is a new bronchodilator long-acting muscarinic antagonist (LAMA) which has been approved by the Food and Drug Administration (FDA) for the maintenance management in individuals suffering from COPD. The ability to administer LAMAs through the ventilator has previously been hindered due to their limited availability in a nebulized form that can be readily administered through the ventilator circuit. A short-acting version of these medications (short-acting muscarinic antagonists, or SAMAs), has been readily available in nebulized form that can be administered through the ventilator circuit and is typically given to patients with COPD and acute respiratory failure. The most commonly used SAMA in this setting is ipratropium.

Revefenacin is the first FDA-approved nebulized once-daily LAMA. Given its function as a long-acting bronchodilator that is practical to administer through a ventilator circuit, Revefenacin may have the potential to improve lung mechanics and decrease the duration of mechanical ventilation in COPD patients with acute respiratory failure. Given its long-acting nature, Revefenacin may also have the potential to reduce the need for additional treatments, such as rescue inhalers.

The research is being done to find out whether patients with COPD and acute respiratory failure receiving Revefenacin have similar outcomes to patients receiving ipratropium, a short-acting muscarinic agent (SAMA) that has been used as a standard of care.

HOW LONG WILL THE RESEARCH LAST AND WHAT WILL I NEED TO DO?

We expect that you will be in this research study for the duration of your hospitalization. You will be randomly assigned to receive either Revefenacin or ipratropium for up to 7 days, or for the duration of the time that you are on mechanical ventilation, whichever is shorter. During the time that you are on mechanical ventilation, your respiratory mechanics on the ventilator will be assessed up to 9 times, which may in some cases require giving you additional, short-acting medications for sedation. The study team will follow you for the duration of your hospitalization and collect clinical data. More detailed information about the study procedures can be found under **“WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?”**

WHAT KINDS OF RISKS OR DISCOMFORTS COULD I EXPECT?

Revefenacin has not been tested in the population of patients on mechanical ventilation. It has been approved for the maintenance therapy of COPD and has been recommended to be used with standard jet nebulizers, a type of delivery device for inhalational drugs. In this study, we are testing Revefenacin use in COPD patients who are not in their steady health state but rather suffer from an additional acute disorder that has led to acute respiratory insufficiency and we are delivering the drug via more novel mesh nebulizers (Aerogen). Taken together, the study procedures may lead to increased risk of side effects of LAMAs: urinary retention, constipation, hypersensitivity reactions, paradoxical bronchospasm (worsened obstruction of the airflow), cardiac arrhythmias, worsening of glaucoma. In addition cough, nasopharyngitis, upper respiratory infection, headache and back pain are possible side effects. Given long duration of study drug metabolites, higher-efficiency nebulizer use may lead to increased concentrations of drug in your body, increasing chance for above listed side-effects. During the study, you will be subjected to daily short guided ventilator adjustment which may require additional sedation and exposure to ventilator settings that may be less comfortable settings. Additional study-related procedures and lab testing will be required including at least three analysis of arterial blood. In case you are randomized to the control arm of the study, you will receive Ipratropium 4 times every day during the first 7 days of the study or for the duration of mechanical ventilation, whichever is shorter. This dosing will be pre-fixed and will not be gauged on the subjective assessment of your needs. The dose of other rescue inhalers (Albuterol, a short-acting beta agonist bronchodilator) will be guided by the primary medical team as per your needs.

Unknown risks and discomforts:

The experimental treatments may have side effects that no one knows about yet. The researchers will let you know if they learn anything that might make you change your mind about participating in the study.

In order to minimize the risks related to the study participation, we:

1. Will apply enrollment criteria to eliminate subjects at increased risks of complications
2. Will discuss the risks of study participation and clarify all study procedures prior to consenting.
3. Will perform lab testing to ensure no significant liver dysfunction is present. Also will perform pregnancy testing on all female subjects within reproductive age.
4. Will avoid enrolling patients who are moribund, or whose survival may be affected by the goals of care
5. Will strictly plan to document all respiratory interventions in the RT logbook and CRF.
6. Will plan on discontinuation of the study interventions in case of significant adverse effects as defined in Chapter 10.

ARE THERE ANY BENEFITS IF I PARTICIPATE?

Revefenacin was developed to produce long-acting bronchodilation and a high degree of lung selectivity with a once-daily dose. Bronchoprotective effects of the drug could be observed as early as 5-minutes after administration of a dose. The effects were sustained for an extended period of time and lasted up to 24 hours. Revefenacin was well-tolerated by patients and did not produce typical systemic adverse effects associated with anti-cholinergic therapies in published literature. Its specificity may lead to improved bronchodilatory effect (airways opening) in comparison to Ipratropium. The results of the study will contribute to medical knowledge and may help future patients with COPD and acute respiratory failure.

WHAT OTHER CHOICES DO I HAVE IF I DON'T WANT TO PARTICIPATE?

Standard medical care for COPD in acute respiratory failure does not include Revefenacin. Participation in research is completely voluntary. You can decide to participate or not to participate. If you decide not to join this study, you will continue to receive current standard medical care for COPD and acute respiratory failure. If you decide to participate in the study, you may discontinue your participation at any time and without anybody's permission.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

21 people will take part in this study at UCLA, with enrollment occurring at both the Ronald Reagan UCLA Medical Center and UCLA-Santa Monica.

WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

Before you begin the study:

- Before you begin the study, we will look at your medical record and talk to your treatment team to confirm that you meet the criteria required to participate in the study.
- If you do meet all eligibility criteria, we will discuss the study participation details with you if your level of consciousness allows for it. In case you are not in the position to provide written consent, we will attempt to identify a health care proxy who is willing to make decision about the participation in the study on your behalf.
- Once the eligibility to consent is established and full consent is obtained, you will be randomly assigned to receive Revefenacin or Ipratropium in a 2-to-1 manner. In other words, two-thirds of the participants will receive Revefenacin, and one-third will receive Ipratropium.
- You, the study investigators, and your clinical team (doctors, nurses and respiratory therapists involved in your care) will not know which drug you are receiving

- There will be a “washout period” for participants who were previously receiving LAMAs or SAMAs. If you were previously receiving LAMAs, these will be held for 24 hours prior to starting the study drug. If you were previously receiving SAMAs, these will be held for 6 hours prior to starting the study drug.

During the study:

- Everyone in the study will continue to receive all other standard care for COPD and acute respiratory failure.
- **If you are assigned to receive Revafenacin**, you will receive nebulized Revafenacin 175 mcg once daily as your first daily dose of study drug. Since Revafenacin is dosed once a day and Ipratropium is dosed 4 times daily, your subsequent doses on a given day will consist of the equivalent amount of nebulized physiological solution (normal sterile) which have been made to look like the study drugs, but have no activity and represent placebo.
- **If you are assigned to receive Ipratropium**, you will receive nebulized Ipratropium every 6 hours.
- The study drug will be continued for 7 days, or until mechanical ventilation is discontinued, whichever occurs first
- Respiratory variables will be collected while you are on the ventilator prior to starting the study drug, and then at multiple time points during the study, up to 9 times in total. In order to adequately capture your respiratory variables, you may require additional short-acting sedative agents to ensure your comfort on the ventilator. Most patients will already be receiving sedation while on mechanical ventilation, so you may not require additional sedation.
- If not done by your clinical team, we will collect a blood sample on day 3 and day 7 of the study to ensure that the study drugs have not had any adverse effects. In most cases, the blood tests we review will be part of routine medical care and will not require an additional blood draw, but in the event that it is not collected by your clinical team, we will collect up to 1 tablespoon of blood.
- While you are in the hospital, we will review your medical records to see how you are doing. We will record information like your temperature, blood pressure, the medications you are receiving, your laboratory values, your use of devices to help you breathe.

CAN THE RESEARCHERS REMOVE ME FROM THIS STUDY?

The researchers may end your participation in this study for a number of reasons, such as if your safety and welfare are at risk. The researchers or the study sponsor might also decide to stop the study at any time. You can also agree to be in the study now and change your mind later. If you wish to stop, please tell us right away. Leaving this study early will not stop you from getting usual regular medical care. If you leave the study early, we will keep information already collected for the study, but no new information will be collected.

HOW WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT CONFIDENTIAL?

The researchers will do their best to make sure that your private information is kept confidential. Information about you will be handled as confidentially as possible, but participating in research may involve a loss of privacy and the potential for a breach in confidentiality. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security.

Use of personal information that can identify you:

All identifiable information about you will be replaced with a code. A list linking the code and your identifiable information will be kept separate from the research data.

How information about you will be stored:

All data (clinical data, recordings, laboratory specimens, and other records) kept at the site will be physically and electronically secured to maintain subject confidentiality. Paper records with subject data will be stored in locked office or cabinet. Computer records will be password protected, and encrypted when possible. The study database is maintained behind a secure firewall, access is password protected and uses encryption for all data entry and access.

People and agencies that will have access to your information:

The research team, authorized UCLA personnel, the study sponsor (, and regulatory agencies such as the Food and Drug Administration (FDA), may have access to study data and records to monitor the study. Research records provided to authorized, non-UCLA personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

Employees of the University may have access to identifiable information as part of routine processing of your information, such as lab work or processing payment. However, University employees are bound by strict rules of confidentiality.

Because this study involves the treatment of a medical condition and/or medical procedures, a copy of this consent form will be placed in your medical record. This will allow the doctors that are caring for you to obtain information about what medications and/or procedures you are receiving in the study and treat you appropriately.

How long information from the study will be kept:

The researchers intend to keep the research data and records indefinitely for future research, and data collected for this study may be shared with other researchers for other studies that are unknown at this time. Any data shared with other researchers, will not include your name or other personal identifying information.

USE OF DATA AND SPECIMENS FOR FUTURE RESEARCH

In the future, data collected for this study may be shared with other researchers for other studies that are unknown at this time. Any data shared with other researchers, will not include your name or other personal identifying information.

ARE THERE ANY COSTS FOR TAKING PART IN THIS STUDY?

The study will pay for research-related items and/or services that are provided only because you are participating in the study. These research-related items and/or services are explained in other areas of this consent form.

You or your health plan may be responsible to pay for all the types of items listed below:

- Items and services that would have been provided to you even if you were not in the study
- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items and/or services

WILL I BE PAID FOR MY PARTICIPATION?

You will not be paid for your participation in this research study.

WHO CAN I CONTACT IF I HAVE QUESTIONS ABOUT THIS STUDY?

The Research Team:

You may contact Igor Barjaktarevic at 310 825-2616 or 310 825-8599 with any questions or concerns about the research or your participation in this study. You can also call the UCLA Page Operator at (310) 825-6301 to reach pulmonary fellow on call 24 hours a day, 7 days week.

UCLA Office of the Human Research Protection Program (OHRPP):

If you have questions about your rights while taking part in this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, you may contact the UCLA OHRPP by phone: (310) 206-2040; by email: participants@research.ucla.edu or U.S. mail: UCLA OHRPP, Box 951406, Los Angeles, CA 90095-1406.

Public Information about this Study:

ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This website will not include

information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT HAPPENS IF I BELIEVE I AM INJURED BECAUSE I TOOK PART IN THIS STUDY?

It is important that you promptly tell the researchers if you believe that you have been injured because of taking part in this study. You can tell the researcher in person or call him/her at the numbers listed above.

If you are injured as a result of being in this study, UCLA will provide necessary medical treatment. The costs of the treatment may be covered by the University of California or the study sponsor Theravance and [Mylan Pharmaceuticals](#), or billed to you or your insurer just like other medical costs, depending on a number of factors. The University and the study sponsor do not normally provide any other form of compensation for injury. For more information about this, you may call the UCLA Office of the Human Research Protection Program at (310) 206-2040 or send an email to participants@research.ucla.edu.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You can choose whether or not you want to participate. Whatever decision you make, there will be no penalty to you, and you will not lose any of your regular benefits.

- You have a right to have all of your questions answered before deciding whether to take part.
- Your decision will not affect the medical care you receive from UCLA.
- If you decide to take part, you can leave the study at any time.
- If you decide to stop being in this study, you should notify the research team right away. The researchers may ask you to complete some procedures in order to protect your safety.
- If you decide not to take part, you can still get medical care from UCLA.

HOW DO I INDICATE MY AGREEMENT TO PARTICIPATE?

If you want to participate in this study you should sign and date below. You have been given a copy of this consent form and the Research Participant's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

SIGNATURE OF THE PARTICIPANT

Name of Participant

Signature of Participant

Date**SIGNATURE OF THE PARTICIPANT'S LEGAL REPRESENTATIVE**

Name of the Participant's Legal Representative

Signature of Participant's Legal Representative

Date**SIGNATURE OF PERSON OBTAINING CONSENT**

Name of Person Obtaining Consent

Contact Number

Signature of Person Obtaining Consent

Date