IRB Protocol# 2000028712
NCT04649229

COMPOUND AUTHORIZATION AND CONSENT FOR PARTICIPATION IN A RESEARCH STUDY

YALE UNIVERSITY
YALE UNIVERSITY SCHOOL OF MEDICINE
YALE-NEW HAVEN HOSPITAL
YALE-NEW HAVEN HOSPITAL: SAINT RAPHAEL CAMPUS

Study Title: Mechanism(s) Underlying Hypotensive Response to ARB/NEP Inhibition – Aim 3
Principal Investigator (the person who is responsible for this research):
Nancy J. Brown, MD
Phone Number: **203-785-4672**
24-Hour Phone Number: **Christopher Maulion, MD: 203-583-1874**

Research Study Summary:

- We are asking you to join a research study.
- The purpose of this research study is to find out if substance P, a chemical that occurs naturally in our bodies and helps control blood pressure, affects how a heart failure medication called Entresto (sacubitril/valsartan) works on blood pressure, urine production, and the excretion of salt in the urine.
- Study procedures will include:
    - Measuring the effect of Entresto on blood pressure, urine production, and the excretion of salt while you are receiving a drug that blocks the effects of substance P, called aprepitant, versus while you are receiving a placebo (no medicine).
    - Using a drug called PAH to measure the blood flow to your kidney, and a drug called iohexol to measure kidney function.
- 7 total visits: 1 screening visit (30 minutes), 4 study day visits (6 hours), 2 dose escalation visits (30 minutes) over about 7 weeks are required.
- There are some risks from participating in this study including: risks of placing intravenous catheter and side effects of the study medications
- The study may have no benefits to you; however, we may learn more about how to treat heart failure.
- Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You can also change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.
- If you are interested in learning more about the study, please continue reading, or have someone read to you, the rest of this document. Take as much time as you need before you make your decision. Ask the study staff questions about anything you do not understand. Once you understand the study, we will ask you if you wish to participate; if so, you will have to sign this form.

Why is this study being offered to me?
You are being asked to take part in this research study because you have heart failure. We are looking for about 80 people to take part in this study.

Who is paying for the study?
The study is investigator-initiated and is funded by an endowment under Dr. Brown as well as a grant from the National Institutes of Health.

What is the study about?

APPROVED BY THE YALE UNIVERSITY IRB 5/27/2022

The purpose of this study is to find out if substance P, a chemical that occurs naturally in our bodies and helps control blood pressure, affects how a heart failure medication called Entresto (sacubitril/valsartan) works on blood pressure, urine production, and the excretion of salt in the urine.

What are you asking me to do and how long will it take?
If you agree to take part in this study, you will complete seven total study visits described below.

Procedures to be followed: Screening Visit (30 minutes)
If you decide to take part in the study, you will come to the Yale Church Street Research Unit (CSRU).

- We will ask you about your medical history.
- You will have a complete physical.
- We will take your blood (about 4 teaspoons) to check that you are healthy enough to participate.
- If you had not had an echocardiogram in the last 6 months leading to participation in this study, a limited echocardiogram will be performed. This may require another appointment.

If your physical and bloodwork show that you are eligible to continue with the study, your primary care physician or cardiologist will be notified of your enrollment into the study. We will ask you to stop taking your ACE inhibitor or angiotensin receptor blocker (ARB) 48 hours prior to the first study day. You will come in for the first two study days four-days apart. On each study day you will be given the heart failure drug Entresto. You will also receive aprepitant or matching blank (placebo) pill in a randomized order, decided by chance, much like the toss of a coin.

Study Day 1 (6 hours)

On the day before this study visit, you will be asked to collect your urine for 24 hours in a jug that we will give you when you sign consent.

- You will come to the CSRU on the morning assigned (based on when we asked you to stop your medications).
- You will have nothing to eat or drink after midnight the night before.
- You will take your usual medications that morning except as advised by the study nurse. We will have you wait to take your fluid pill until the end of the study day.
- We will collect urine for a pregnancy test if you are able to have children.
- We will ask you to empty your bladder, and we will weigh you.
- You will be asked to lie down and will remain lying down except to use the bathroom until the end of the study day.

We will put a small tube in the vein (intravenous or IV) of each arm – one to give you medicine and one to take blood.

A cuff will be placed on your arm to measure your blood pressure and heart rate every 5 minutes for the rest of the study day. After this, you will rest for at least 30 minutes.

We will begin to give you the drugs para-aminohippurate (PAH) and iohexol through the tube in your arm. The use of PAH in this study is investigational, which means it is not approved by the FDA for the use described in this study.

- Ninety minutes later, we will take a blood sample (two teaspoons).
- We will then give you a pill of Entresto to take by mouth with a small amount of water. Entresto is a drug approved by the Food and Drug Administration to treat heart failure.
- At the same time, we will begin giving you either a medication called Aprepitant, a drug that is FDA-approved to treat nausea, or a matching placebo (blank) pill. Neither you nor the study doctors will know which you are getting, but we can find out if there is a need.

We will continue to measure your heart rate and blood pressure for 6 hours after we start the medication. We will collect urine and blood (1 tablespoon) at 1, 2, 4, and 6 hours from the start of the study medication. Before the blood draw at hour 4 we will have you stand so we can check your blood pressure and heart rate while you are standing. We will take a total of 6 tablespoons of blood during each study day.

You will then be finished with the study day.

Home Care for 2 Weeks

- We will give you Entresto to take twice daily for the next 2 weeks.
- We will give you a blood pressure cuff and tell you how to monitor your blood pressure at home.
- We will have you take your blood pressure every day. If the top number is below 85 or you have symptoms of low blood pressure such as light-headedness, we will stop the Entresto.

Dose Escalation Visit (30-60 minutes)

At the end of the 2 weeks, we will have you come to the CSRU for a dose escalation visit

- We will measure your blood pressure and blood hematocrit, potassium, and creatinine.
- If these are within range, we will give you a higher dose of Entresto to take twice daily for the next 3 weeks.
- If it looks like increasing the dose will reduce your blood pressure too much or increase your potassium and creatinine too much, we will instead continue the original dose.

Study Day 2 (6 hours)

On the day before this study visit, you will be asked to collect your urine for 24 hours in a jug that we will give you when you sign consent.

- You will come to the CSRU on the morning assigned, four days after the first study day.
- Nothing to eat or drink after midnight
- We will collect urine for a pregnancy test if you are able to have children.
- We will ask you to empty your bladder, and we will weigh you.
- You will be asked to lie down and will remain lying down except to use the bathroom until the end of the study day.

We will put a small tube in the vein (intravenous or IV) of each arm – one to give you medicine and one to take blood.

A cuff will be placed on your arm to measure your blood pressure and heart rate every 5 minutes for the rest of the study day. After this, you will rest for at least 30 minutes.

We will begin to give you the drugs para-aminohippurate (PAH) and iohexol through the tube in your arm.

- Ninety minutes later, we will take a blood sample (two teaspoons).
- We will then give you a pill of Entresto to take by mouth with a small amount of water. Entresto is a drug approved by the Food and Drug Administration to treat heart failure.
- At this visit, we will begin giving you either Aprepitant, a drug that is FDA-approved to treat nausea, or a matching blank (placebo) pill. This will be the opposite of what you received on the first visit. Neither you nor the study doctors will know which you are getting, but we can find out if there is a need.

We will continue to measure your heart rate and blood pressure for 6 hours after we start the medication. We will collect urine and blood (1 tablespoon) at 1, 2, 4, and 6 hours from the start of the study medications. Before the blood draw at hour 4, we will have you stand so we can check your blood pressure and heart rate while you are standing. We will take a total of 6 tablespoons of blood during each study day.

You will then be finished with the study day.

Home Care for 3 Weeks

- We will give you Entresto to take twice daily at either a new dose or continuing the original dose as instructed for the next 3 weeks.
- We will have you take your blood pressure every day. If the top number is below 85 or you have symptoms of low blood pressure such as light-headedness, we will stop the Entresto. We will again have you check your blood pressure during these three weeks to make sure it does not get too low.

Dose Escalation Visit (30-60 minutes)

At the end of the 3 weeks, we will have you come to the CSRU for a second dose escalation visit.

- We will measure your blood pressure and blood hematocrit, potassium, and creatinine.
- If these are within range, we will give you a third dose of Entresto to take for the next 10 days. Alternatively, we will continue the dose you were already taking.

Study Day 3 (6 hours)

On the day before this study visit, you will be asked to collect your urine for 24 hours in a jug that we will give you when you sign consent.

- You will come to the CSRU on the morning assigned, approximately 10 days after your last dose escalation visit.
- Nothing to eat or drink after midnight
- We will collect urine for a pregnancy test if you are able to have children.
- We will ask you to empty your bladder, and we will weigh you.You will be asked to lie down and will remain lying down except to use the bathroom until the end of the study day.

We will put a small tube in the vein (intravenous or IV) of each arm – one to give you medicine and one to take blood.

A cuff will be placed on your arm to measure your blood pressure and heart rate every 5 minutes for the rest of the study day. After this, you will rest for at least 30 minutes.

We will begin to give you the drugs para-aminohippurate (PAH) and iohexol through the tube in your arm.

- Ninety minutes later, we will take a blood sample (two teaspoons).
- We will then give you a pill of Entresto to take by mouth with a small amount of water. Entresto is a drug approved by the Food and Drug Administration to treat heart failure.
- At this visit, we will begin giving you either Aprepitant, a drug that is FDA-approved to treat nausea, or a matching blank (placebo) pill. This will be the opposite of what you received on the first visit. Neither you nor the study doctors will know which you are getting, but we can find out if there is a need.

We will continue to measure your heart rate and blood pressure for 6 hours after we start the medication. We will collect urine and blood (1 tablespoon) at 1, 2, 4, and 6 hours from the start of the study medication. Before the blood draw at hour 4, we will have you stand so we can check your blood pressure and heart rate while you are standing. We will take a total of 6 tablespoons of blood during each study day.

You will then be finished with the study day.

Study Day 4 (6 Hours)

On the day before this study visit, you will be asked to collect your urine for 24 hours in a jug that we will give you when you sign consent.

- You will come to the CSRU on the morning assigned, approximately 3 days after your last study day.
- Nothing to eat or drink after midnight
- We will collect urine for a pregnancy test if you are able to have children.
- We will ask you to empty your bladder, and we will weigh you.You will be asked to lie down and will remain lying down except to use the bathroom until the end of the study day.

We will put a small tube in the vein (intravenous or IV) of each arm – one to give you medicine and one to take blood.

A cuff will be placed on your arm to measure your blood pressure and heart rate every 5 minutes for the rest of the study day. After this, you will rest for at least 30 minutes.

We will begin to give you the drugs para-aminohippurate (PAH) and iohexol through the tube in your arm.

- Ninety minutes later, we will take a blood sample (two teaspoons).
- We will then give you a pill of Entresto to take by mouth with a small amount of water. Entresto is a drug approved by the Food and Drug Administration to treat heart failure.

- At this visit, we will begin giving you either Aprepitant, a drug that is FDA-approved to treat nausea, or a matching placebo (blank) pill. This will be the opposite of what you received on the third visit. Neither you nor the study doctors will know which you are getting, but we can find out if there is a need.

We will continue to measure your heart rate and blood pressure for 6 hours after we start the medication. We will collect urine and blood (1 tablespoon) at 1, 2, 4, and 6 hours from the start of the study medication. Before the blood draw at hour 4, we will have you stand so we can check your blood pressure and heart rate while you are standing. We will take a total of 6 tablespoons of blood during each study day.

You will then be finished with the study day.

End of Study and Follow up

Following completion of the last study day, you will be provided a prescription for the final dose of Entresto. We will send a letter to your primary care physician and cardiologist documenting the final dose and any side effects that you may have had at higher doses.

What are the risks and discomforts of participating?

Inconveniences

- Not eating or drinking after midnight on the night before each study
- Collecting all your urine in a jug for 24 hours for 4 days
- Traveling to the CSRU and picking up your medications
- Spending study days in the CSRU

Risks of the IV Catheters

Having an intravenous (IV) line placed is a very safe procedure. Catheters are put into blood vessels with needles. Needles may cause pain, bruising, and bleeding; they can cause light-headedness or fainting. You might feel a small amount of pain when the IV is placed but it does not last very long. There is a slight chance that multiple needle-sticks will be needed to make sure the IV is placed correctly. A bruise or a minor infection might develop where the IV catheter is placed. A bruise will go away by itself and it might help if you wrap a warm towel around your arm. Infections can also be treated if necessary.

Risks of frequent blood draws

Frequent blood draws can lead to anemia.

Risks of holding ACE inhibitors or ARBs

You will be asked to stop your ACE inhibitor or ARB 48 hours prior to the initial study day. There is a small theoretical risk of feeling worse from your heart failure. This may include worsening heart failure symptoms and changes in your blood pressure.

Unknown risks

There may be unforeseen risks or risks that are not yet known as a result of participating in this study.

Risks of Entresto

Rare

- Swelling of your face, lips, tongue, and throat (angioedema). If severe and not treated could cause trouble breathing and death

Uncommon

- Low blood pressure and dizziness
- Decrease in renal function
- "High potassium" (hyperkalemia)

Risks of Aprepitant

Uncommon

- Weakness, fatigue, nausea, diarrhea, dehydration, constipation, indigestion, and hiccups
- Low blood pressure
- Decreased white blood cell count
- Abnormal liver functions tests

Risks of Iohexol

Rare

- Hypersensitivity (allergic reaction) to iohexol. It can range from rashes to difficulty breathing, shock, and sudden death. To minimize this risk, emergency equipment and trained personnel will be available during the administration of the drug
- Cardiovascular reactions: Hemodynamic disturbances including shock and cardiac arrest may occur during or after administration

Uncommon

- Contrast induced acute kidney injury: Acute injury including renal failure can occur

Risks of Para-aminohippurate (PAH)

Rare

- Flushing, nausea, vomiting and abdominal pain
- Hypersensitivity reactions including anaphylaxis, angioedema, hives, and rapid changes in blood pressure

Uncommon

- Tingling
- Warmth or the desire to move your bowels or urinate shortly following initiation of infusion

Reproductive Risks

We do not know whether this drug could damage genes or have negative effects on development of the fetus. There are no research studies on animals on this topic.

If you are a woman able to have children, you are encouraged to use birth control while you are participating in this study. The study doctor will discuss acceptable methods of birth control with you.

How will risks be managed and minimized?

When you receive your first dose of Entresto/ aprepitant at the CSRU, we will closely monitor your blood pressure, kidney function, potassium level, and any potential allergic reactions (hypersensitivity) or angioedema that may occur. In the case of an allergic reaction, you will be treated immediately with glucocorticoids and anti-histamines, as appropriate. You will be asked to carry a wallet card stating your participation in this study and risk for developing angioedema.

In the setting of angioedema, the offending medication(s) will be discontinued immediately. Treatment of angioedema may include glucocorticoids and anti-histamines with escalation to additional treatment (i.e., icatibant) as deemed necessary and you will be withdrawn from the study. A study doctor will be present during infusion of PAH and iohexol.

How will I know about new risks, new diagnoses, or important information about the study?

We will tell you if we learn any new information that could change your mind about taking part in this study. You will be informed of any discovered diseases and will be instructed to contact your doctor.

How can the study possibly benefit me and other people?

Entresto has been shown to be effective in the treatment of congestive heart failure in certain patients. There may or not be a benefit to you from being on this drug.

We are investigating how Entresto works to lower blood pressure and change salt excretion. Even if this study does not benefit you directly, what we learn from this study may possibly help other patients with heart failure in the future. You will be provided the medication Entresto during the duration of the study. The benefits to science and other people may include a better understanding of treatment of heart failure.

Are there any costs to participation?

If you take part in this study, you will not have to pay for any services, supplies, study procedures, or care that are provided for this research only (they are NOT part of your routine medical care). However, there may be additional costs to you. These can include costs of transportation and your time to come to the study visits. You or your health insurance must pay for services, supplies, procedures, and care that are part of your routine medical care. You will be responsible for any co-payments required by your insurance. You will not have to pay for taking part in this study. The only costs include transportation and your time coming to the study visits.

Will I be paid for participation?

You will be paid for taking part in this study. If you complete the entire study, you will be paid a total of $1,200 for your time. If you do not complete the study, you will be paid $300 for each 6-hour study day that you complete. There is no planned reimbursement for the screening and dose escalation visits.

Study payment will be mailed to you in the form of a Bank of America Visa card. In order to issue you this card, we will need to provide Bank of America with your name, address, and phone number. The Bank of America Visa card will be good for three years. Please read the disclosure document that is included with the card.

According to the rules of the Internal Revenue Service (IRS), payments that are made to you as a result of your participation in a study may be considered taxable income. You are responsible for paying state, federal or other taxes for the payments you receive for being in this study. Taxes are not withheld from your payments.

The costs of study-required tests and procedures previously described in this document will be paid for by the Investigator. You will not be billed for any tests done as a part of this study.

What are my choices if I decide not to take part in this study?

Instead of participating in this study, you have some other choices.
You could:

- Get treatment without being in a study. The medical treatment of heart failure is similar and readily available without participation in the study.

How will you keep my data safe and private?

Confidentiality

All efforts, within reason, will be made to keep your personal information in your research record confidential, but total confidentiality cannot be guaranteed. Information that could identify you will be kept in a locked cabinet or a password-protected computer and your samples and data will be coded. Only members of Dr. Brown's study team will have access to this information for study analysis.

The investigator may share your information, without identifiers, to others or use it for other research projects not listed in this form. Yale University, Dr. Brown and her staff will comply with any and all laws regarding the privacy of such information. There are no plans to pay you for the use or transfer of this de-identified information. This information may be shared with other/future researchers without additional consent.

This research is covered by a Certificate of Confidentiality from the National Institutes of Health. The researchers with this Certificate may not disclose or use information, documents, or biospecimens that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other action, suit, or proceeding, or be used as evidence, for example, if there is a court subpoena, unless you have consented for this use. Information, documents, or biospecimens protected by this Certificate cannot be disclosed to anyone else who is not connected with the research except, if there is a federal, state, or local law that requires disclosure (such as to report child abuse or communicable diseases but not for federal, state, or local civil, criminal, administrative, legislative, or other proceedings, see below); if you have consented to the disclosure, including for your medical treatment; or if it is used for other scientific research, as allowed by federal regulations protecting research subjects. You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement 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.

We will put information from this study into your Electronic Medical Record (EMR). This will include research test results. Your health care providers will be able to see these test results. Other people or groups such as a health insurance company who have access to your EMR may see this information.

Privacy

Any samples and information about you may be made available to others to use for research. To protect your privacy, we will not release your name. You will not receive any benefit as a result of the tests done on your samples. These tests may help us or other researchers learn more about the causes, risks, treatments, or how to prevent this and other health problems.

Your samples may be used to make new products or tests. These may have value and may be developed and owned by the study staff, Yale University, and/or others. If this happens, there are no plans to provide money to you.

Study Results
At the end of the study, we will publish a paper in a medical journal, summarizing the final results. If you would like, we will send you a copy of the paper that is published.

What Information Will You Collect About Me in this Study?
The information we are asking to use and share is called "Protected Health Information." It is protected by a federal law called the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA). In general, we cannot use or share your health information for research without your permission. If you want, we can give you more information about the Privacy Rule. Also, if you have any questions about the Privacy Rule and your rights, you can speak to Yale Privacy Officer at 203-432-5919.

The specific information about you and your health that we will collect, use, and share includes:

- Research study records that will be kept in a secure web-based data collection system
- Medical and laboratory records of only those services provided in connection with this study.
- Records about phone calls made as part of this research
- Records about your study visits
- Information obtained during this research regarding
    - Physical exams
    - Medical History
    - Laboratory, x-ray, and other test results
    - Diaries and questionnaires
    - Records about any study drug you received

- The entire research record and any medical records held by Yale New Haven Hospital created from study start date will be kept until 7 years after publication date. After that time, records may be archived for an additional 5 years and then shredded.

How will you use and share my information?
We will use your information to conduct the study described in this consent form.
We may share your information with:

- The principal investigator, Nancy J. Brown, MD
- Co-Investigators and research staff
- Co-Investigators at Vanderbilt
- Study Coordinator and Members of the Research Team
- The U.S. Department of Health and Human Services (DHHS) agencies
- Representatives from Yale University, the Yale Human Research Protection Program, and the Institutional Review Board (the committee that reviews, approves, and monitors research on human participants), who are responsible for ensuring research compliance. These individuals are required to keep all information confidential.
- The U.S. Food and Drug Administration (FDA) This is done so that the FDA can review information about any drugs used in this study. The information may also be used to meet the reporting requirements of drug regulatory agencies.
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, according to the study plan.
- Data and Safety Monitoring Boards, and Institutional Review Board and others authorized to monitor the conduct of the Study

We will do our best to make sure your information stays private. But, if we share information with people who do not have to follow the Privacy Rule, your information will no longer be protected by the Privacy Rule. Let us know if you have questions about this. However, to better protect your health information, agreements are in place with these individuals and/or companies that require that they keep your information confidential.

Why must I sign this document?

By signing this form, you will allow researchers to use and disclose your information described above for this research study. This is to ensure that the information related to this research is available to all parties who may need it for research purposes. You always have the right to review and copy your health information in your medical record.

However, this is a double blinded treatment study and if you sign this permission form, you will not be allowed to look at or copy your study related information until after the research is completed.

What if I change my mind?

The authorization to use and disclose your health information collected during your participation in this study will never expire. However, you may withdraw or take away your permission at any time. You may withdraw your permission by telling the study staff or by writing to Nancy J. Brown, MD at the Yale University, New Haven, CT 06520.

If you withdraw your permission, you will not be able to stay in this study but the care you get from your doctor outside this study will not change. No new health information identifying you will be gathered after the date you withdraw. Information that has already been collected may still be used and given to others until the end of the research study to ensure the integrity of the study and/or study oversight.

Who will pay for treatment if I am injured or become ill due to participation in the study?

If you are injured while on study, seek treatment and contact the study doctor as soon as you are able.

Yale School of Medicine, CSRU, and Yale-New Haven Hospital do not provide funds for the treatment of research-related injury. If you are injured as a result of your participation in this study, treatment will be provided. You or your insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. You do not give up any of your legal rights by signing this form.

What if I want to refuse or end participation before the study is over?

Taking part in this study is your choice. You can choose to take part, or you can choose not to take part in this study. You also can change your mind at any time. Whatever choice you make, you will not lose access to your medical care or give up any legal rights or benefits.

We would still treat you with standard therapy or, at your request, refer you to a clinic or doctor who can offer this treatment. Not participating or withdrawing later will not harm your relationship with your own doctors or with this institution.

If you do choose to exit the study early, we will need to see you again to assist you in transitioning to your primary cardiologist and your medication needs.
To withdraw from the study, you can call a member of the research team at any time and tell them that you no longer want to take part.

The researchers may withdraw you from participating in the research if necessary. You may be removed from this study without your consent if:

- Staying in the study would be harmful to you
- You no longer meet the requirements of the study
- The study is stopped

If you decide to stop being part of the study, you should tell your study doctor. Deciding to not be part of the study will not change your regular medical care in any way.

What will happen with my data if I stop participating?

Your cancellation will not affect information already collected in the study, or information that has already been shared with others before you cancelled your authorization.

You have the right to see and copy the PHI we gather on you for as long as the study doctor or research site holds this data. To ensure the scientific quality of the research study, you will not be able to review some of your research data until after the research study is finished.

Who should I contact if I have questions?

Please feel free to ask about anything you don't understand.

If you have questions later or if you have a research-related problem, you can call the Principal Investigator at **203-785-4672.**

If you have questions about your rights as a research participant, or you have complaints about this research, you call the Yale Institutional Review Boards at (203) 785-4688 or email.

A description of this clinical trial will be available on *http://www.ClinicalTrials.gov*, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Authorization and Permission

Your signature below indicates that you have read this consent document and that you agree to be in this study.

We will give you a copy of this form.

Participant Printed Name	Participant Signature	Date

Person Obtaining Consent Printed Name	Person Obtaining Consent Signature	Date