THE STOP-HF SERVICE

St Michael's Hospital

Dun Laoghaire

Co Dublin.

PARTICIPANT INFORMATION AND CONSENT FORM

STUDY TITLE

Prospective comparison of ARni with ArB in patients with natriuretic peptide eLEvation (PARABLE)

NAME OF PRINCIPAL INVESTIGATORS

Professor Kenneth McDonald, Consultant Cardiologist, St Vincent's University Hospital and Dr Mark Ledwidge (PhD), Research Director of the Heart Failure Unit, St Vincent's University Hospital.

WHAT IS THE PURPOSE OF THIS STUDY?

You are being invited to join in a research study (the PARABLE study). The purpose of this study is to find out if the medicine, Entresto® (previously known as LCZ696) can help patients with high blood pressure and/or diabetes or other risk factors for developing heart failure (a condition where the heart muscle is weakened and cannot pump enough blood to meet the body's needs for blood and oxygen). Thank you for taking time to read this.

If you agree to join this study, you may receive either:

- Entresto (the study medicine made up of valsartan and sacubitril), **or**
- Valsartan (the comparator medicine)

Entresto is a new medicine that was approved for use in heart failure by the authorities in the United States and Europe in 2015. Valsartan is commonly used to help control high blood pressure.

This study will evaluate if Entresto, when compared to valsartan, is safe and well tolerated, and helps to improve your conditions, including the development of heart failure.

WHY HAVE I BEEN CHOSEN?

You have been invited to take part in this study because you have either high blood pressure and/or diabetes.

WHAT WILL HAPPEN IF I VOLUNTEER TO TAKE PART?

We are going to ask 250 men and women aged 40 years and older, to take part in the study. If you agree to take part, you will be asked to come to the STOP-HF Service of St Michaels Hospital in Dun Laoghaire, 11 times over 18 months (about every 3 months though more often for the first six weeks).

Your participation is entirely voluntary. If you initially decide to take part, you can later change your mind without difficultly. This will not affect your future treatment in any way. Furthermore, your doctor may decide to withdraw you from this study if he feels it is in your best interest.

Let's look at what will happen at each visit in turn.

Screening visit (Visit 1).

The study doctor will discuss the study with you. He/she will ask you to sign this consent form giving your permission for all study-related tests to be carried out.

The doctor will carry out a physical examination and measure your heart rate and blood pressure. You will be asked questions about your medical history and medications that you are taking.

An echocardiogram (an ultrasonic picture of your heart) will be performed to see how well your heart is functioning, (unless one was done in the last 6 months).

Approximately 20ml of blood (4 teaspoonfuls) will be taken at this visit These will be used for routine safety tests, which include your blood cell count, and tests to ensure that your kidneys and liver are functioning properly. This amount of blood loss should not affect your ability to perform any activities and should be replaced by your normal body processes. If appropriate, a pregnancy test will be performed to exclude pregnancy.

Baseline visit (Visit 2)

The doctor will perform a physical examination, measure your heart rate and blood pressure, measure your height, weight and waist and hip size. Blood samples will be taken for safety tests and biomarkers (chemicals in your blood which can help to monitor the function of your heart). You will be asked to give a urine sample.

We will give you a blood pressure monitor, know as an ambulatory blood pressure monitor (ABPM) to wear for 24 hours. This will measure your blood pressure even when you are sleeping. An echocardiogram may be performed if you did not have one at Visit 1. An electrocardiogram (ECG) will be performed by placing sensors/electrodes on the skin of your chest in order to trace the electrical impulses occurring in the heart.

A cardiac MRI (magnetic scan of the heart) will be organized and performed at St Vincent's Private Hospital or St Vincent's University Hospital, Dublin 4 to further look at the heart structure and function. MRI is a test that produces very clear pictures of the human body without the use of x-rays. Please allow one hour for your MRI examination. In most cases, the procedure takes 45 minutes. After the examination, generally, you can resume your usual activities and normal diet immediately. The MRI examination is safe and poses no risk to the average patient if appropriate guidelines are followed.

You will be asked to complete three questionnaires; Questionnaire 1 will assess your Quality of Life (general well-being). The other two questionnaires will assess your cognitive function (aspects of perception, thinking, reasoning and remembering).

We will also ask you to complete the cognitive function questionnaires five years after you have completed the study (we will contact you to arrange this). Answering these three questionnaires will take about 30 minutes of your time in total. If we identify any illnesses (e.g. anxiety, depression) when you complete these questionnaires, we will arrange for follow-up to manage such illnesses.

At the end of this visit, the study doctor will give you your study medications. Screening and baseline visits may be combined to reduce the number of visits you have to make to the STOP-HF Service.

Follow-up visits (Visit 3 to Visit 11)

At every follow-up visit, the following procedures will be performed:

- You will be asked how you are feeling
- You will be asked about other medications you have taken
- You will have a physical examination
- Your blood pressure and heart rate will be measured
- Blood samples will be collected from you for laboratory tests, biomarker measurement, and biobanking
- Pregnancy test (if appropriate)
- Your study doctor will give you study medications
- You will be asked about your use of the study medication

Follow-up visits 8 (at 9 months) and 11 (last visit at 18 months)

In addition to the procedures outlined in the paragraph above, the following procedures will be performed:

- An echocardiogram
- A cardiac MRI (performed at St Vincent's Private Hospital or St Vincent's University Hospital) (at the 18-month visit only)
- 24-hour blood pressure monitoring (ABPM)

- An electrocardiogram (ECG)
- Questionnaires
- You will be asked to provide a urine sample (also at visit 5 and 6)
- Pregnancy test (if appropriate)
- ECG heart monitor (optional at month 18)

At the 18-month study visit, you may be asked to wear an ECG monitor. This is a small portable device that measures the hearts activity. It has wires with electrodes that attach to your skin. It helps to identify people with an irregular heart rhythm (e.g. paroxysmal atrial fibrillation. If you agree, we will place the monitor on you for five to seven days. We will ask you to keep a diary of any heart symptoms that you might experience during this time. We will also ask you to answer some questions on how easy or difficult and comfortable the device was to wear. Table 1 (on the next page) outlines all the study visits that will be required throughout the 18 month study period. All efforts will be made to minimize the number of visits during this study.

STUDY MEDICINE

You may receive the study medicine (Entresto) or the comparator medicine (Valsartan). The study medication you receive will be determined by chance (similar to tossing a coin). You and your study doctor will not know which medicine you are taking until after the study is finished. However, your doctor can find out which medicine you are taking in case of an emergency.

There are three doses of each medicine:

- Entresto: 50 mg, 100 mg and 200 mg
- Valsartan: 40 mg, 80 mg and 160 mg

During the first four weeks of the study, the dose will be increased gradually from the lower to the higher dose.

It is very important that you continue to take the study medication as instructed throughout the study. If at any time you experience any problems or decide that you no longer wish to continue in the study, you should contact your study doctor before stopping the study medicine.

It is very important that you bring back all the unused study medication at every visit. The study medication must be taken only by the person the study doctor gave it to, and it must be kept out of the reach of children.

HOW TO TAKE YOUR MEDICINE?

The study medication will be provided in 2 bottles at each visit. One bottle will contain the study medication and the other bottle will contain a placebo tablet (an inactive form of the medicine similar to a sugar tablet).

You will take a total of 4 tablets per day. You will take 2 tablets (one from each bottle) in the morning and another 2 tablets in the evening. Swallow the tablets with a glass of water. You can take the study medication with or without food.

If you forget to take a dose of study medication, do not take a double dose to make up for a forgotten dose. Instead, take it as soon as you remember it and then take the next dose at the right time. You can make a note of the missed dose and tell the study doctor at your next clinic visit.

MEDICATIONS THAT ARE NOT ALLOWED

You must not take certain kinds of medicines during the study. Therefore, it is very important that you tell your study doctor about any new medications you are taking. This includes prescription medicines, medications that do not require prescription ("over the counter" products like pain medicines or cough/cold medicine), natural/homeopathic medicines, herbal remedies, and vitamins. The study doctor will tell you which medicines not to take during the study. Medicines that are similar to the study medicines (Entresto and valsartan) are also not allowed. These are called RAAS blockers. Please also inform your doctor if the dose of any of the medicines you are taking changes during your participation in the study.

Table 1. The tests and procedures that will be carried out at each visit

Visit number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Timepoint	**Screening**	**Day 0 Baseline**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 13 / Mth 3**	**Wk 26 / Mth 6**	**Wk 39 / Mth 9**	**Wk 52 / Mth 12**	**Wk 65 / Mth 15**	**Wk 78 / Mth 18**
Length of time it takes for each visit	**90 mins[%]**	**2 hours[%]**	**45mins**	**45mins**	**45mins**	**45mins**	**45mins**	**2 hours**	**45mins**	**45mins**	**2 hours**
Determine if you are suitable for the study	x										
Sign consent form if willing to participate	x										
Medical history	x										
Ask about other medicines you are taking	x	x	x	x	x	x	x	x	x	x	x
Pregnancy test*	x	x	x	x	x	x	x	x	x	x	x
Physical exam	x	x	x	x	x	x	x	x	x	x	x
Blood pressure and pulse	x	x	x	x	x	x	x	x	x	x	x
Blood test	x	x	x	x	x	x	x	x	x	x	x
Urine sample		x			x	x		x			x
Height (H) and weight (W)		H/W						W			W
Waist/hip size		x						x			x
24-hour blood pressure monitor		x						x			x
Electrocardiography (ECG)		x						x			x
Echocardiography	X[¥]	x[†]						x			x
MRI (St Vincent's Private Hospital, or St Vincent's University Hospital)		x									x
Questionnaires**		x						x			x
Assess for side-effects of medicines			x	x	x	x	x	x	x	x	x
Dispense medication		x	x	x	x	x	x	x	x	x	
5-7-day ECG monitor (optional)											x

[¥] Echo may be needed at Visit 1 if one hasn't been performed in the previous six months.

[†] If an Echo is performed at Visit 1, it does not have to be repeated at Visit 2 unless the doctor decides otherwise

*Pregnancy test will be carried out in women of childbearing potential

**Two questionnaires will also completed five years after you have completed the study.

[%] Screening and baseline visits are often combined in which case the total duration of the visit is approximately 3 hours

ARE THERE ANY BENEFITS FROM MY PARTICIPATION?

You will not benefit directly from taking part in this study. You will receive more frequent and careful medical attention during the study. You may benefit from the extra medical care and the tests performed during the study. The findings made during the study may help in the treatment of others with high blood pressure and/or diabetes in the future.

ARE THERE ANY RISKS INVOLVED IN PARTICIPATING?

As with all medicines, Entresto and valsartan may cause side effects, although not everyone gets them. Patients taking Entresto and valsartan can develop low blood pressure (dizziness, light-headedness), a high level of potassium in the blood and decreased kidney function. However, the amount of potassium in your blood and the effect of the medicine on your kidneys will be checked at every visit.

Stop taking the study medicines and seek immediate medical attention if you notice any swelling of the face, lips, tongue and/or throat, which may cause difficulties in breathing or swallowing. These may be signs of angioedema (an uncommon side effect which may affect up to 1 in 100 people).

Your doctor is aware of the potential side effects, as well as the best methods for treating them, and will discuss the risks with you before you begin taking study medication. Problems or side effects that are not now known could also occur during the study. Should you experience any problems, you should report these to the study doctor.

Most of the tests done at each visit are standard medical tests. The most unpleasant is having blood samples taken at every visit. Between 15mls and 50mls of blood (3 to 10 teaspoonfuls) will be taken at each visit. The total amount of blood taken over the 18-month study period will be approximately 400mls. The risks of taking blood may include fainting, pain, and/or bruising. Rarely, these may be a small blood clot or infection at the site of the needle puncture.

WHAT HAPPENS IF I DO NOT AGREE TO PARTICIPATE?

If you decide not to participate in this study, your treatment will not be affected in any way.

COMPENSATION

Insurance is in place for people participating in this study. This insurance covers any harm that may be caused to you by participating in the study. You will not be paid for taking part in this study.

WHO IS ORGANISING AND FUNDING THIS RESEARCH?

This study is organised by the Heartbeat Trust Charity. It is part-funded by a pharmaceutical company named Novartis.

HAS THIS STUDY BEEN REVIEWED BY AN ETHICS COMMITTEE?

Yes, the St. Vincent's Healthcare Group, Ethics and Medical Research Committee have reviewed and approved this study.

CONFIDENTIALITY & DATA PROTECTION

This Participant Information and Consent Form provides guidance and information to PARABLE research participants regarding the processing of their personal data. The Heartbeat Trust is committed to protecting and respecting your privacy. This Participant Information and Consent Form sets out the basis on which any personal data we collect from you or that you provide to us will be processed by us an independent data controller. Please read this section of the Participant Information and Consent Form carefully to understand our treatment and use of your personal data.

The processing of your personal data will be in compliance with the Data Protection Acts 1988 to 2018 (as amended) and the General Data Protection Regulation (the "Data Protection Legislation").

Identity of the controller of personal information

For the purposes of the Data Protection Legislation, the Heartbeat Trust is an independent data controller.

Company Name: The Heartbeat Trust
Company Type: Charity
Company Registration number: 375112
Registered office: 3 Crofton Terrace, Dun Laoghaire, Co Dublin, A96 K2R5

Contact details of the Data Protection Officer

The data protection officer for the Heartbeat Trust is Olive Cummins. Her contact details are as follows: Phone 01-2845735 (Option 4) or email olive.cummins@heartbeat-trust.org.

Processing your personal data

The Heartbeat Trust will process your personal data for the following purposes on the basis of your consent:

Personal data	**Purpose of processing**[1]
1. Identification e.g. name, address, date of birth (please note this information will be anonymised/coded before leaving the Heartbeat Trust)	(a)Originally captured as part of medical care (b) used for purpose of carrying out research
2. Clinical History	Subject medical and medication history is relevant to study outcomes
3. Test results	Clinical care, safety measures, research outcomes
4. Questionnaires	Subject reported outcomes required to measure response to treatment

Where does the Heartbeat Trust obtain my personal data from?

Most of the personal data we process is obtained from you directly, but we also obtain personal data about you from your:

- medical notes,
- laboratory test results,
- test/procedure results (e.g. ECG, echocardiograph, MRI, blood results),
- study provided home monitoring devices,
- GP, during the study.

Sharing of your personal data

Your personal data will be shared with:

Person/Company/institute	Requirement for sharing
The Conway Institute, University College Dublin	A portion of your blood samples may be sent to research partners*.
Queens University Belfast	A portion of your blood samples may be sent to research partners*.
Maastricht University, the Netherlands	A portion of your blood samples may be sent to research partners*.
Datascan Document Services, Dublin	A duplicate copy of your case report form may be made by Datascan for back-up purposes.
Almac Group	This company provides the dispensing platform for the PARABLE study. Initials, gender and date of birth are provided for subject identification purposes*.
O'Connell Data Consulting Limited	All subject data will be shared with this company for data analysis purposes*.

*Please note this information will be anonymised/coded before leaving the Heartbeat Trust

Disclosures to Third Parties

In certain circumstances, we share and/or are obliged to share your personal data with third parties outside the Heartbeat Trust, for the purposes described above and in accordance with Data Protection Legislation.

These third parties include but are not limited to:

- St Vincent's Hospital Group (including St Michaels Hospital);

- the Health Products Regulatory Authority;
- the European Medicines Agency;
- St. Vincent's Healthcare Group Ethics Committee;
- relevant industry bodies;
- your GP and community pharmacist;
- external professional advisors; and
- others, where it is permitted by law, or where we have your consent.

Transfers outside the European Economic Area

Your personal information may be transferred, stored and processed in one or more countries outside the European Economic Area ("EEA"), for example, when one of our service providers use employees or equipment based outside the EEA. For transfers of your personal data to third parties outside of the EEA, we take additional steps in line with Data Protection Legislation. We have put in place adequate safeguards with respect to the protection of your privacy, fundamental rights and freedoms, and the exercise of your rights, e.g. we establish an adequate level of data protection through EU Standard Contractual Clauses based on the EU commission's model clauses.

How is my personal data secured?

The Heartbeat Trust operates and uses appropriate technical and physical security measures to protect your personal data. We have taken appropriate security measures to protect your personal data from accidental or unlawful destruction, loss, alteration, unauthorised disclosure of, or access, in connection with this research study. Access is only granted on a need-to-know basis to those people whose roles require them to process your personal data. In addition, our service providers are also selected carefully and required to use appropriate protective measures.

Storage of personal data

We will keep your personal data for up to 10 years.

Your rights

You may have various rights under Data Protection Legislation. However, in certain circumstances, these rights may be restricted. In particular, your rights may be restricted where this is necessary: (i) for the prevention, detection, investigation and prosecution of criminal offences; (ii) in contemplation of or for the establishment, exercise or defence of a legal claim or legal proceedings (whether before a court, tribunal, statutory body or an administrative or out-of-court procedure); and/or (iii) for the performance of a task carried out in the public interest or in the exercise of official authority vested in the Heartbeat Trust.

These rights may include (as relevant):

(i) **The right of access** enables you to check what type of personal data we hold about you and what we do with that personal data and to receive a copy of this personal data;

(ii) **The right to object** to processing of your personal data where that processing is carried out on the basis of our legitimate interests. We will stop using your personal data unless we can demonstrate an overriding legitimate ground for the continued processing of this personal data;

(iii) **The right to rectification** enables you to correct any inaccurate or incomplete personal data that we hold about you;

(iv) **The right to erasure** enables you to request that we erase personal data held about you in certain circumstances;

(v) **The right to restrict processing** of your personal data by us in certain cases, including if you believe that the personal data held about you is inaccurate or our use of the personal data is unlawful; and

(vi) **The right to data portability** enables you to receive your personal data in a structured, commonly used and machine-readable format and to have that personal data transmitted to another data controller

Your right to lodge a complaint with a supervisory authority

Without prejudice to any other administrative or judicial remedy you might have, you have the right under data protection legislation to lodge a complaint with the Office of the Data Protection Commissioner in Ireland if you consider that we have infringed applicable data protection legislation when processing your personal data.

Changes to this information

We may decide to make changes to this Participant Information and Consent Form. If a change is made, we will notify you in person of such changes. An updated Participant Information and Consent Form will be provided to you in advance of any change taking effect.

QUESTIONS

The study doctor will answer any questions you have about this research study. You can ask questions any time during the study. Please call if you have any questions about the study. Please call or come to the STOP-HF Service if you have any injury, illness or side effect.

CONTACT DETAILS

If you or your relatives have any questions regarding this study, please do not hesitate to contact Professor Kenneth McDonald on 01 2713071. (The STOP-HF Service, St Michael's Hospital, Dun Laoghaire). Further information can also be found on the Heartbeat Trust website: http://heartbeat-trust.ie/research/current-projects/

INFORMED CONSENT FOR <u>PARTICIPATION IN THE CLINICAL TRIAL.</u>

PLEASE WRITE YOUR INITIALS IN THE APPROPRIATE BOX

- I have read and understood the Participant Information and Consent Form
  YES □ NO □
- I have had the opportunity to ask questions and discuss the study
  YES □ NO □
- I have received satisfactory answers to all my questions YES □ NO □
- I have received enough information about this study YES □ NO □
- I understand that I am free to withdraw from the study at any time without giving a reason and without this affecting my future medical care
  YES □ NO □
- I consent to take part in this research study having been fully informed of the risks, benefits and alternatives. YES □ NO □
- I consent to wear the 5-7 day ECG monitor YES □ NO □
- I give informed consent to have my data processed as part of this research study. YES □ NO □

Participant's Signature: _____Date: _____

Participant's Name in print: _____

Investigator's Signature: _____Date: _____

Investigator's Name in print: _____

STORAGE & FUTURE USE OF INFORMATION:

PLEASE WRITE YOUR INITIALS IN THE APPROPRIATE BOX

- I give permission for material/data to be stored for possible future research related to the current study only if consent is obtained at the time of the future research but only if the research is approved by a Research Ethics Committee. YES ☐ NO ☐

- I give permission for material/data to be stored for possible future research related to the current study without further consent being required but only if the research is approved by a Research Ethics Committee. YES ☐ NO ☐

- I give permission for material/data to be stored for possible future research unrelated to the current study only if consent is obtained at the time of the future research but only if the research is approved by a Research Ethics Committee. YES ☐ NO ☐

- I give permission for material/data to be stored for possible future research unrelated to the current study without further consent being required but only if the research is approved by a Research Ethics Committee. YES ☐ NO ☐

- I agree that some future research projects may be carried out by researchers working for commercial/pharmaceutical companies. YES ☐ NO ☐

- I understand I will not be entitled to a share of any profits that may arise from the future use of my material/data or products derived from it. YES ☐ NO ☐

Participant's Signature: _____Date: _____

Participant's Name in print: _____

Investigator's Signature: _____Date: _____

Investigator's Name in print: _____