Welcome to the PARABLE clinical trial page of the Heartbeat Trust website. This page contains information about the PARABLE clinical trial that is currently recruiting patients in the STOP-HF Service of St Michaels Hospital, Dun Laoghaire, Co Dublin. We hope you find this information useful. If you have any questions, please do not hesitate to contact us using the 'Contact us' tab of the website, or alternatively please call 01 2713071.

Official title

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

Who is conducting this research?

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 are the Principal Investigators (lead researchers) of this clinical trial.

The study is being funded (sponsored) by the Heartbeat Trust.

Novartis Ireland Ltd (a pharmaceutical Company) is providing the study drug (Entresto® (valsartan and sacubitril) and Diovan® (valsartan)).

The study has been reviewed and approved by the Irish Medicines Regulator, the Health Products Regulatory Agency and the St. Vincent's Healthcare Group, Ethics and Medical Research Committee

What is the purpose of this clinical trial?

The purpose of the PARABLE clinical trial is to find out if the drug Entresto is safe and has beneficial effects on the heart and blood vessels in 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).

What are the study drugs?

You may receive either Entresto (the study drug made up of valsartan and sacubitril) or valsartan (a comparator drug). You will also receive a placebo tablet (an inactive form of the drug similar to a sugar tablet). In this way, neither the clinical trial personnel nor the participant will know whether you are taking Entresto or valsartan. The study medication you receive will be determined by chance (similar to tossing a coin).

Entresto is a new drug that was approved for use in heart failure by the authorities in the United States (the Food and Drug Administration (FDA)) and Europe (the European Medicines Agency (EMA)) in 2015.

Entresto blocks the angiotensin II receptor and neutral endopeptidase, two important systems involved in the development and progression of heart failure.

Valsartan is included in the study as a comparator drug. Valsartan was chosen as the comparator for this study because some of the conditions that you may have (such as high

blood pressure, diabetes, coronary heart disease, and others) are commonly treated with valsartan or other similar drugs called renin angiotensin aldosterone system blockade (RAAS) medications. This study will evaluate whether Entresto, when compared to valsartan, is safe and well tolerated, and helps to improve your heart conditions, including the development of heart failure.

Where is the PARABLE clinical trial taking place?
The PARABLE clinical trial is being conducted in the STOP-HF Service of St Michaels Hospital in Dun Laoghaire, Co Dublin. This is where you will be reviewed by the study doctor or nurse at each study visit. You will also be required to attend the Radiology Department of St Vincents Private Hospital following the initial study visit, at 9 months and following the 18 month (final) study visit for a scan of the heart (cardiac MRI (magnetic resonance imaging)).

Who will participate in this study?
Approximately 250 men and women aged 40 years and older, will be asked to participate in the study.

What is the criteria for being eligible to participate in this study?
In order to be eligible to participate in this clinical trial you must be older than 40 years of age and have risk factors for developing heart failure which must include high blood pressure and/or diabetes. You must also have increased levels of the hormone natriuretic peptide in your blood.

How long will the study last?
18 months

What tests and procedures are involved?
You will be asked to come to the STOP-HF Service of St Michaels Hospital on 11 occasions over an 18 month period (approximately every 3 months though more often for the first six weeks). The following tests and procedures will be carried out at each visit:

<u>Screening visit (Visit 1).</u>
The study doctor will discuss the study with you and will ask you to sign this consent form giving your permission for all study-related tests to be carried out. The doctor will perform a physical examination, measure your heart rate and blood pressure, verify details of your medical history, and will ask you about any medications that you are taking. An echocardiogram (a non-invasive, ultrasonic picture of your heart) will be performed to see how well your heart is functioning. Blood samples will be taken. 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. If appropriate, a pregnancy test will be performed to exclude pregnancy.

<u>Baseline visit (Visit 2)</u>
(Screening and baseline (Visit 1 & Visit 2) may be performed on the same day if all information/results are available. If not, visit 2 will take place approx. 2 weeks after visit 1).

The doctor will perform a physical examination, measure your heart rate and blood pressure, measure your height, weight and waist and hip circumference. Blood samples will be taken for safety tests and biomarkers (chemicals in your blood which can indicate your disease status) and you will be asked to give a urine sample.

A blood pressure monitor, know as an ambulatory blood pressure monitor (ABPM) will measure your blood pressure over a 24 hour period 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 on a Saturday morning at St Vincent's Private Hospital to further evaluate heart structure and function. MRI is a test that produces very clear pictures, or images, of the human body without the use of x-rays. MRI uses a large magnet, radio waves and a computer to produce these images. Please allow two hours for your MRI examination. In most cases, the procedure takes 40 to 80 minutes. After the examination, generally, you can resume your usual activities and normal diet immediately. This will be carried out at the beginning of the study, at nine months and at the end of the 18 month study period.

You will be asked to complete three questionnaires. One will assess your Quality of Life (general well-being) and the other two 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 questionnaires will take approximately 20 minutes of your time. If any illnesses (e.g anxiety, depression) are identified on completing these questionnaires, appropriate referral pathways will be put in place to manage such illnesses. At the end of this visit, the study doctor will give you your study medications.

<u>Follow-up visits (Visit 2 to Visit 11)</u>
All visits will take place in the STOP-HF Service of St Michael's Hospital. At every follow-up visit, the following procedures will be performed:

- You will be asked how you are feeling and 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
- Your study doctor will give you study medications
- You must bring back all of the containers of study medication at each visit. You will be asked about your use of the study medication at these visits.
- Pregnancy test (if appropriate)

<u>Follow-up visits 8 (at 9 months) and 11 (last visit at 18 months)</u>
In addition to the procedures outlined in the paragraph above, the following procedures will be performed at visit 8 and visit 11:

- An echocardiogram
- A cardiac MRI (performed on a Saturday morning at St Vincent's Private Hospital)

- 24 hour blood pressure monitoring (ABPM)
- An electrocardiogram (ECG)
- Questionnaires
- You will be asked to provide a urine sample (at visit 6 also)
- Pregnancy test (if appropriate)

Can participants withdraw from the study?
If you initially decide to take part in this clinical trial, you can subsequently change their mind without difficultly. This will not affect you 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.

What happens if a healthcare professional needs to know what medication I am taking?
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 were taking in case of an emergency by calling this number: XXXXXXX

What medications are not allowed when taking the study medication?
You must not take certain kinds of medicines during the study because taking them with your study drug may increase the likelihood of harm to you.

To ensure your safety, it is important that at each visit you tell your doctor about all medications that you are presently taking. This includes prescription drugs, medications that do not require prescription ("over the counter" products like pain relievers 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, like drugs that block the renin-angiotensin system, also referred to as RAAS blockers. Please also inform your doctor if the dose of any of the drug(s) you are taking changes during your participation in the study.

When possible, please inform your study doctor or study nurse before changing any medication or changing the dose of medication.

How do I take my study medicine?
The study medication will be provided in 2 bottles at each visit. One bottle will contain the study medication (either Entresto or valsartan) and the other bottle will contain a placebo tablet. You will take 2 tablets (one from each bottle) with a liquid, with or without food, in the morning and another 2 tablets with a liquid, with or without food, in the evening.

The doses of Entresto that will be administered in this study are 50 mg, 100 mg and 200 mg twice daily. The doses of valsartan that will be administered are 40 mg, 80 mg and 160 mg twice daily. During the first two to four weeks of the study, the dose will be increased gradually from the lower to the higher dose of each medicine.

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 drug.

What happens if I forget to take my study medicine?
If you forget to take a dose of study medication, do not take a double dose to make up for a forgotten dose. If you forget to take a dose 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.

Are there any risks involved in participating in this clinical trial?
As with any other medication, Entresto and valsartan may result in some side effects.

The most common side-effects of Entresto are postural orthostatic tachycardia (increased heart rate when you stand up), dizziness, headache, and orthostatic hypotension (low blood pressure when you stand up).

The most common side-effects of valsartan are viral infection, fatigue, and abdominal pain. Rare cases of angioedema (swelling of the face, extremities, eyes, lips, tongue, and difficulty breathing) have been reported with valsartan.

Other potential risks of treatment with valsartan and Entresto may include low blood pressure and changes in potassium levels in the blood. Low blood pressure could produce dizziness or fainting. Changes in potassium levels can make your heart beat abnormally.

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.

Blood tests will be taken at each study visit. 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.

Do my personal details remain confidential?
Your identity will remain confidential. A study number will identity you. Your name will not be published or disclosed to anyone.

Would you like any further information?
The study doctor or nurse will answer any questions you have about this research study or your participation in the study. Please call if you have any questions about the study (Phone: 01 2713071). Please call or come to the STOP-HF Service if you have any injury, illness or side effect.