

HPS2-THRIVE

Treatment of HDL to Reduce the Incidence of Vascular Events

INVITATION TO JOIN A LARGE MEDICAL RESEARCH PROJECT

A randomised study of ER niacin/laropiprant for the prevention of cardiovascular events in patients with vascular disease

You are being invited to take part in a research study. Please take time to read the following information carefully and discuss it with friends or relatives if you wish. You are entirely free to decide whether or not to take part in this trial. If you choose not to take part, the standard of care given by your own doctors will not be affected.

- Part 1 tells you the purpose of the study and what will happen to you if you wish to take part.
- Part 2 gives you more detailed information about the conduct of the study.

If there is anything that is not clear, or if you would like more information, please call Freephone (0800 585323) or speak to the local HPS2-THRIVE research nurse.

Please see reverse for a summary of the main information contained in this booklet.

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Part 1

Cholesterol, heart disease and strokes

People who have already had a circulatory problem such as a heart attack or stroke are at increased risk of developing further circulatory problems. One of the causes of this circulatory disease is having too much LDL (bad) cholesterol in the blood. We know that lowering this bad cholesterol in the blood with drugs such as statins reduces the risk of a heart attack or stroke. Everybody in this study will therefore be given tablets to lower their bad LDL cholesterol. However, despite effective LDL-lowering treatments, some people still suffer recurrent heart or circulatory problems. This study hopes to find a way of reducing these risks even further.

Does raising good cholesterol with niacin prevent heart attacks and strokes?

As well as LDL (bad) cholesterol there is also HDL (good) cholesterol in the blood. In general, people with higher levels of good HDL cholesterol have fewer heart attacks, strokes or circulatory problems than people with lower levels. Niacin is a medication that increases the amount of good cholesterol in the blood. However, although niacin has been in use for more than 50 years, it is still not clear whether it prevents heart attacks and strokes. Part of the difficulty has been that patients treated with niacin frequently develop flushing (reddening) of the skin, and sometimes other side-effects, making it difficult for people to take their tablets regularly. Extended release (ER) preparations of niacin reduce these side-effects but do not completely avoid them.

A new treatment, laropiprant (formerly MK-0524), has been developed which reduces the flushing caused by niacin. It works by blocking the dilatation of the blood vessels in the skin responsible for the flushing. Therefore laropiprant has been combined in a single tablet with extended release (ER) niacin to make it easier for people to take these treatments regularly. This combination is known as ER niacin/laropiprant (formerly MK-0524A).

What HPS2-THRIVE hopes to answer and how

The aim of HPS2-THRIVE (Treatment of HDL to Reduce the Incidence of Vascular Events) is to find out whether long-term treatment with ER niacin/laropiprant in people who have survived a heart attack, stroke or some other circulatory problem produces benefits by raising HDL (good) cholesterol. It is hoped that this will prevent heart attacks, strokes or the need for arterial bypass procedures (known as revascularisation) but this is as yet unknown.

In order to find out if ER niacin/laropiprant is beneficial, people taking part in the study will be put into 2 groups. This will be done randomly and one group will receive active ER niacin/laropiprant tablets and the other will receive a dummy version which looks and tastes identical. Neither you, nor your nurse or doctor will know whether you are taking the active or the dummy version. At the end of the study the outcome in the 2 groups will be compared. This type of research is called a randomised double-blind study.

Providing effective LDL-cholesterol lowering for all participants

In HPS2-THRIVE everyone will also be asked to take one tablet daily to lower their LDL cholesterol.

This will be either simvastatin alone or a single tablet containing the combination of simvastatin and a drug that also lowers cholesterol called ezetimibe. Which type you are provided with will depend on your previous statin treatment (if any), and your level of LDL (bad) cholesterol. If simvastatin 40 mg alone does not lower your LDL cholesterol enough, you will be given the combination tablet containing ezetimibe 10 mg plus simvastatin 40 mg (known as ezetimibe/simvastatin 10/40 mg).

All participants will therefore have effective LDL cholesterol-lowering treatment which aims, if possible, to get LDL cholesterol levels to below about 2.0 mmol/L (the currently recommended target). Both simvastatin and ezetimibe have previously been shown in large trials to be safe and effective treatments for lowering LDL cholesterol levels in people with circulatory problems.

Why have I been chosen?

HPS2-THRIVE will involve a total of 20,000 men and women. About 7,500 will be from the UK, plus a further 12,500 from Scandinavia and China. Like you, they are being invited to take part because they have already had some circulatory problem. This invitation has been sent either because you have participated successfully in previous trials (such as the Heart Protection Study) or, with the permission of your own doctor, because your medical records suggest you might be suitable for the study.

Do I have to take part?

If you are suitable, it is up to you whether you take part. If you do decide to take part in this study, you would, of course, be free to withdraw from the study treatment at any time without necessarily giving any reason (and without adversely affecting the medical care you can expect from your own doctors). In particular, at the end of the first few months, you will have the chance to withdraw if you have any second thoughts about being in the study or have any problems with study treatments.

What will happen to me if I take part

Everyone taking part will have agreed to do so voluntarily, knowing that it may involve them in taking study treatments for at least 4 years. If you agree to take part, the study nurse will need to see you in the clinic 3 or 4 times in the first 6 months and then 6-monthly. You will be asked some questions about your medical history, have a blood sample taken and measures of your height, weight and blood pressure. If you are eligible and wish to enter the study, you will be asked to sign a Consent Form and be given a copy to keep.

If you are not on a statin for your cholesterol you will be given study simvastatin 40 mg daily to take regularly. Alternatively, if you already take a cholesterol-lowering statin tablet, you will be asked to stop this and take study simvastatin 40 mg daily instead (with or without ezetimibe depending on the dose of statin you have been taking previously). If you are initially given simvastatin 40 mg alone and this is found not to lower your cholesterol enough, it will be changed to the combination of simvastatin and ezetimibe at the second visit.

For your early visits it will be helpful if you could fast. This means avoiding any food or drink (other than water) for at least 4 hours before the clinic. This helps with the reliability of the blood tests and these visits would be scheduled at a time of day to make it easy for you. At these visits the nurse will measure your cholesterol and give you these results.

Early in the study, you will be given a treatment-pack containing active ER niacin/laropiprant tablets. You will be asked to take one tablet a day for the first 4 weeks increasing to two tablets a day for the following four weeks. The study tablets are to be taken with food in the evening or at bedtime. After 8 weeks of taking laropiprant tablets plus the LDL-lowering tablet you would visit the clinic again. You would then decide if you are willing to continue taking study tablets for at least 4 years. The purpose of this part of the study is to make sure that the ER niacin/laropiprant agrees with you. If you do get side-effects at this stage, it may not be appropriate for you to continue in the study.

If you decide to continue, you will be given a further supply of study tablets and an appointment for 3 months time. Throughout the rest of the study, there will be three tablets to be taken each day, the LDL-lowering tablet (simvastatin or ezetimibe/simvastatin) and two tablets which contain either active ER niacin/laropiprant or a similar looking inactive dummy substance called a "placebo". Whether or not a participant receives active or dummy tablets (placebo) will be determined randomly (like tossing a coin). Each participant will have a 50% chance of receiving active ER niacin/laropiprant combination tablets and a 50% chance of receiving placebo ("dummy") tablets. The type of study treatment being taken will not generally be known by you or your doctor. This information will be known only by certain staff at the coordinating centre in Oxford, but it would be made available to your doctor if this were ever medically necessary. This design helps ensure that reliable information will be obtained about the effects of these potentially important treatments.

After the first 6 months you would need to attend for an appointment every 6 months. It will not be necessary to fast for these clinic visits. At every visit (each lasting 20-30 minutes), the study nurse will ask how your health has been since the last appointment, take a blood sample and provide you with more study treatment as required. In the unlikely event of a problem, we may need to ask you to return for an extra visit.

Expenses

You will be offered travel expenses for attending the study clinics.

What do I have to do?

If you agree to enter the study you will be asked to take study tablets daily for at least the next 4 years. The number of extra tablets will increase to 3 in the early stages (but you will no longer need to take your prescribed 'statin' if you were taking one). One tablet will be to control the LDL (bad) cholesterol and the other 2 will be to increase the HDL (good) cholesterol. Only half the participants will get active HDL raising tablets, but everyone will receive active tablets to control their LDL cholesterol.

For the study to get reliable results it is important that as many people as possible continue taking the study tablets during the whole study. If you think you may find that difficult it may be best if you do not join the study.

Similarly, if you think that you may have difficulty attending the study clinic appointments then it is probably best that you do not enter this trial. If you do decide to enter, your GP will be informed.

If you do join the study, we would like you to attend the specially set up study clinics 3-4 times in the first 6 months and then every 6 months. These visits will be extra to any visits to the doctor you may need. Occasionally people may be asked to attend for extra visits if you have a problem with the study tablets. If you are unable to attend on any occasion, or if you have any other queries or

questions about the study you can telephone (Freefone 0800 585323) and either rearrange your appointment or talk to one of the study doctors or nurses.

What is the drug that is being tested?

The drug being tested is a combination of niacin and laropiprant, the combination is called ER niacin/laropiprant. Laropiprant is a new drug which has been well tolerated in previous smaller clinical studies. Laropiprant is being used in this study to reduce any flushing that may occur with niacin. Prior to starting this study about 3000 people have received doses of either laropiprant or ER niacin/laropiprant. As it is a new combination drug, you will be asked to report any adverse effects you think may be due to the treatment.

What are the side-effects and risks of taking part?

Laropiprant is not known to have any particular side-effects, but it is possible there may be some, as yet unknown, side-effects.

Niacin is a drug that has been used to treat cholesterol for over 50 years. However, its use has been limited by skin flushing (defined as a feeling of warmth, redness, itching and/or tingling) as well as other side effects it can produce. Even though laropiprant should reduce any flushing due to the niacin, some people (20-30% in the first week) taking ER niacin/laropiprant may still experience flushing episodes. These episodes are more likely to occur within the first few days of starting treatment and then usually disappear by the end of the first week. They may then recur if you miss the tablets for a few days and then restart. Although occasionally unpleasant, these flushing episodes are not dangerous.

Some people may also experience other side-effects due to niacin, including: gastrointestinal symptoms (tummy upset, nausea or diarrhoea); headaches; skin rashes and rarely allergic reactions. Occasionally niacin can also cause liver problems (fewer than 1 in 100 patients) and this will be monitored by a regular blood test every time you come to the clinic. These liver problems usually resolve when treatment with niacin is stopped but rarely can make people unwell. Niacin can also increase blood sugar levels particularly in people with diabetes. The significance of such changes is unclear, but will be monitored during the study.

The simvastatin and ezetimibe are generally well tolerated although occasional side-effects have been reported. Very occasionally they can cause a muscle problem called 'myopathy' which causes muscle pain and/or weakness with abnormal blood tests, but this is rare (typically less than 1 in 10,000 affected per year among people of European origin but, information from the study so far shows rates of about 1 or 2 per 1000 per year in Chinese people). The risk may be increased slightly by taking additional niacin. **If, after joining the study, you were to develop some unexpected symptoms – in particular soreness or weakness of your muscles which is not the result of exercise or some other activity – you should to contact your study nurse, or one of the doctors at the coordinating centre (24 hour Freefone 0800 585323) in order to obtain advice.**

Effects of other treatments on taking part?

Certain medications when taken with simvastatin can increase the risk of the muscle side-effects. The most common of these are the antibiotics erythromycin and clarithromycin, but certain other drugs should also be avoided with study treatment including: fibrate cholesterol-lowering tablets,

verapamil, amiodarone, ketoconazole and itraconazole (your GP should be aware of this). People already taking these tablets will not be suitable to join the study. Also, if you have a history of cancer, other than skin cancer, in the last 5 years you would not be eligible for the study. People taking warfarin tablets are able to join the study but may need some extra anticoagulant (INR) checks when starting or stopping study treatments. Other tablets which people with a history of heart or circulatory problems commonly take are not known to interact with study treatments.

What are the possible benefits of taking part?

We hope that both the study treatments may help you by reducing the risk of a heart attack or stroke, however, this cannot be guaranteed. The information we get from this study may help us to treat future patients with heart disease better, and, if successful, may help to prevent many thousands of heart attacks, strokes and bypass procedures around the world.

What happens at the end of the study?

When the research study finishes we will inform you and your GP of the study results. Based on these, you will then be able to decide whether or not you should take ER niacin/laropiprant regularly. After the study finishes we will no longer continue to provide study medication for you. But, if the study results suggest you would benefit, your GP should be able to prescribe the treatments. We will also publish the study results in a professional medical journal as soon as possible after the study finishes. You would not be identified individually in any published report.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2. The contact number for complaints is Freefone 0800 585323.

Will my taking part in this study be kept confidential?

Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

Contact Details

**Any questions about the study should be directed to the coordinating centre in Oxford
either by telephone
(24-hour Freefone service: 0800 585323)**

**or by post to:
HPS2-THRIVE, CTSU, Richard Doll Building, Old Road Campus, Roosevelt Drive, Oxford,
OX3 7LF.**

**Alternatively you can e-mail us on thrive@ctsu.ox.ac.uk
This completes Part 1 of the Information Sheet.**

**If the information in Part 1 has interested you and you are considering participation,
please continue to read the additional information in Part 2 before making any decision.**

Part 2

What if new information becomes available?

Sometimes during the course of a research project relevant new information becomes available about the treatment that is being studied. If this happens we will tell you and your own doctor about it, and you can discuss whether you want to continue in the study. A study doctor is available through the 24-hour Freefone service (0800 585323) if either you or your GP need to discuss any new information.

What will happen if I don't want to carry on with the study?

You are free to withdraw from study treatment or from follow-up at any time. However, in order to obtain results that are as reliable as possible we would like to keep in contact with you at least by telephone to find out your progress. If you decide to stop the study treatment, we shall ask you to continue attending the study clinic if at all possible.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (**24-hour Freefone service: 0800 585323**). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

In the unlikely event of you being harmed as a result of taking part in HPS2-THRIVE, insurance cover is provided by Merck & Co., Inc. who provide the study medication. Compensation for any injury caused by taking part in the study will be provided in accordance with the guidelines of the Association of the British Pharmaceutical Industry (ABPI). Compensation would be paid where the injury probably resulted from your taking the study drugs (or from any test or procedure) in line with the protocol. Any payment would be without legal commitment. We would not be bound by these guidelines where the injury resulted from a drug or procedure outside the trial protocol or if the protocol was not followed. In addition, you would retain the same rights of care as any other patient treated in the National Health Service.

Will my taking part in this study be kept confidential?

Information collected about you for the study will be entered directly onto a computer where it is stored securely, using encryption. This information will then be transferred to the central coordinating office at Oxford University where it will be stored long-term on computers protected by firewalls and in a secure building. In the central databases, personal information is stored separately from study information to which it is linked by a unique number. Access to study information is restricted to authorised study personnel on a need to know basis, and is controlled by usernames and passwords.

The coordinating centre would seek information from participants' own doctors and from NHS and other central registries about any serious illnesses (such as heart attacks, strokes, cancers etc) that occur (this requires patient identifiable information to be sent to these bodies). All information received would be used, in confidence, only for medical research purposes and for routine

regulatory and audit purposes. Nurse monitoring staff from the coordinating centre in Oxford may occasionally ask your permission to be present during your clinic visit to ensure procedures are being properly followed. Authorised people from regulatory agencies, the drug company and NHS bodies may look at the study information to ensure that the study is being carried out correctly but will be bound by rules of confidentiality.

Involvement of the General Practitioner/Family doctor (GP)

Your GP will be notified of your participation in the trial. Other medical practitioners not involved in the research who may be treating you should be made aware of your participation in this trial. You will be provided with a small card to carry giving details of the study. Your GP may be asked for additional medical details or given feedback on study findings.

What will happen to any samples I give?

Blood samples taken in the clinic will be used to check cholesterol levels, for safety checks and for central storage for trial related measures. A liver blood test will be done at every visit and if there are possible muscle problems a muscle blood test will also be done. Samples sent to the central laboratory are identified by a unique number linked in the computer to other study information.

You would also be asked if you are willing to allow us to store samples of your blood and urine for future analyses (including of your genes). This would be entirely optional and you would receive more information and a separate leaflet about this if you decide to take part in the trial.

Will any genetic tests be done?

This would be an entirely optional part of the trial and you would receive more details about this and asked to sign an additional consent form if you decide to take part.

What will happen to the results of the research study?

It is intended to publish the results of the research study in the appropriate scientific journal. No individual participant would be identified in any report or publication.

Who is organising and funding the research?

HPS2-THRIVE has been designed, and is coordinated, by Oxford University's Clinical Trial Service Unit. It involves the collaboration of many doctors and nurses around the country as well as in Scandinavia and China. The study design has been reviewed and agreed by independent Research Ethics Committees, which include people from outside the medical profession. An independent Data Monitoring Committee will review various outcomes among participants during the study, and will inform the organisers if any important new information has emerged that needs to be provided to participants and their doctors.

Packaged study treatment has been provided free by Merck & Co., Inc. who also provide a grant to Oxford University to run the study. The study is, however, conducted independently of the pharmaceutical company who have no say in its day-to-day running.

Who has reviewed the study?

This study was given a favourable ethical opinion for conduct in the NHS (or private sector) by the Thames Valley Multicentre Research Ethics Committee.

Please keep this information leaflet for your own records.

THANK YOU FOR TAKING THE TIME TO READ THIS SHEET

Summary of invitation to take part in HPS2-THRIVE

- Having circulatory problems increases the risk of subsequent heart attacks and strokes
- Statins and ezetimibe lower LDL (bad) cholesterol, and this benefits people who have survived a heart attack or stroke. Everyone in this study will be given LDL-lowering treatment
- Niacin raises HDL (good) cholesterol but side-effects include flushing of the skin
- ER niacin/laropiprant contains extended release niacin combined with laropiprant to reduce the flushing, and make the niacin easier to take.
- Half of those taking part in the study will be given active ER niacin/laropiprant and half will be given a dummy (placebo) version. Neither you nor your doctors will know which, and this will be decided randomly (like tossing a coin)
- The purpose of HPS2-THRIVE is to find out whether raising HDL cholesterol with ER niacin/laropiprant prevents heart attacks and strokes in people with circulatory problems who are already on treatment to lower LDL-cholesterol
- If ER niacin/laropiprant is shown to be safe and effective for people with circulatory disease, then its widespread use could lead to the prevention of many thousands of heart attacks and strokes and the saving of many lives
- With your help we can answer this question reliably with HPS2-THRIVE

**If you have any questions about the study then please contact the coordinating centre on:
Freephone 0800 585323**

THANK YOU FOR YOUR HELP