TRUST LOGO

Optimising Primary Therapy in Primary Biliary Cholangitis (OPERA) Trial

Participant Information Sheet

INVITATION

We are inviting you to take part in a research trial called OPERA. This information sheet tells you more about why it is being done and what it might mean for you. Please read the following information carefully to help you decide if you want to take part. You don't have to decide straight away and you may want to talk to your friends and family before making a decision. Ask us if you have any questions or you want to know more.

SUMMARY

People diagnosed with primary biliary cholangitis (PBC) are initially given a drug called ursodeoxycholic acid (UDCA or "urso") for a year. If this drug isn't improving their blood tests sufficiently, other drugs such as obeticholic acid (brand name OCALIVA) may then also be prescribed.

- Urso is less likely to work for some people than others. For these people, waiting a year to change therapy delays the use of other therapies and may reduce their chances of their working.
- This study will look at giving obeticholic acid straight away to people who are less likely to respond to urso, rather than waiting a year.
- We are hoping to recruit 106 patients in total from across the UK.
- If you meet the criteria and decide to take part you will be given either the treatment drug obeticholic acid or a placebo (a 'dummy' drug). You will have an equal chance of being in each group. Everyone will also take urso (the current treatment).
- You, your doctor and the research team will not know which drug you are taking until the end of the trial.
- During the trial, you will have regular visits to clinic (5 over a year) and calls so that we can check how you are doing and review your medication. We will take small amounts of blood to check you are well enough to continue participating and to understand your response to trial medication.
- You will also be asked to complete questionnaires and some assessments.
- We also want to look at your liver using a Fibroscan, which is like an ultrasound, to measure how elastic (or how stiff) your liver is.

Please read the following information for further details about the trial if you are interested in taking part and see page 14 for contact details

Why is OPERA needed?

Despite recent progress in the treatment of PBC, a number of patients still go on to develop cirrhosis and need liver transplants. One possibility is that current treatments are not as effective as they could be because of the way in which we use them. The current treatment approach is to start with gentle treatment with urso and only move on to more powerful treatments in people who don't respond to urso. Response to urso is at present only assessed after it has been used for a year and this approach, by its nature, introduces delay in the addition of other therapies alongside urso. At present we do not know if this delay in adding additional therapy to urso is a contributor to the ongoing risk seen in PBC. OPERA will explore whether using one of the existing additional PBC drugs (Obeticholic Acid, brand name OCALIVA) at the beginning of the disease in patients who are most at risk of not responding to urso makes a difference to treatment success in PBC.

Why am I being invited to take part?

You have been invited to take part because you have recently been diagnosed with PBC and your blood tests suggest that you might be at an increased risk of not responding to urso in the future. You are aged 18 or over and your clinical team think that you could meet the criteria to take part. If you have any questions about your diagnosis, please speak to your clinical team.

Do I have to take part?

No, it is entirely up to you to decide if you want to take part. If you choose not to, you will continue to get the normal (standard) treatment arranged by your doctor.

If you agree to take part, you can change your mind and withdraw from the trial **at any time** without having to give a reason. Your future care will not be affected in any way.

What will taking part in OPERA involve?

Taking part in this trial involves attending 5 hospital appointments over a year. This is around 2 more appointments than you would usually have in this time. There will also be one planned phone call to check on how things are going.

You will be prescribed obeticholic acid or placebo "dummy" tablets for 26 weeks (around 6 months) and we will then continue to follow you up as part of the trial for another 26 weeks. This is to see if any benefits that arise from taking the trial medicine continue after you stop taking the medicine. Your total time on the trial will be around 52 weeks (1 year). You will give blood samples and complete questionnaires during your involvement in the trial. We will also monitor you throughout the trial to check how you are doing when you are on trial medication. You will also be asked to have a scan (called a Fibroscan; a normal part of the assessment of people with PBC).

There will also be an opportunity to take part in a further sub-study of OPERA. The details of this additional study are provided on page 13. It is absolutely fine if you just want to take part in the OPERA trial itself and not the sub-study.

What medication would I take during the trial?

If you take part in this trial you will be prescribed either obeticholic acid or a placebo. A placebo is a dummy medicine that looks the same as the real one but is a harmless substance that has no effects. Both obeticholic acid and the placebo "dummy" medicine are tablets taken orally (by mouth) once per day. To keep the trial fair, which of these you are given is decided randomly by a computer, a bit like flipping a coin. Your doctor can't influence or decide which you will receive. You will have an equal chance of receiving obeticholic acid or the placebo. OPERA is a "double-blinded" trial which means that neither you nor the doctors looking after you will know during the trial whether you have received obeticholic acid or the placebo. The medication you are taking will remain unknown unless there is a clinical reason or emergency which means this information is needed for your safety. You will be able to ask at the end of the trial which medication you received.

You will also be prescribed urso therapy, which is part of the normal treatment for PBC (this is the medicine that you would be starting on if you weren't taking part in the trial meaning that being in the trial doesn't take away any of the normal treatments you would take).

Placebo and urso
(50% of patients)

Half of patients taking part in the trial will receive placebo tablets. This is a 'dummy' drug. It looks the same as the real drug but it is made with non-active ingredients. Everyone will also take urso.

Obeticholic Acid and urso
(50% of patients)

Half of patients taking part in the trial will receive Obeticholic Acid tablets. Everyone will also take urso.

To enable your body to adjust to the trial medication, you will be prescribed a low dose of medication for the first 12 weeks of the trial followed by a higher dose for the next 14 weeks, unless you have had any problems taking the medication. If you have too many side effects with the higher dose of the trial medication, your trial doctor will be able to adjust your dose. The lower and then the full dose used are the same doses as are used in NHS practice for the treatment of PBC when it is used in people who have not responded to urso therapy alone. In other words they are the standard doses for PBC. You will spend the last 26 weeks on the trial taking no trial medication, just urso.

If you take bile acid binding resin medication e.g. Colesevelam (Cholestagel), Cholestyramine (Questran, Questran Light, Prevalite, Cholestyramine Light) or Colestipol (Colestid), trial medication should be taken at least 4-6 hours before or 4-6 hours after taking bile acid binding resin, or at as great an interval as possible.

If you feel unwell while taking the medication, you can contact the trial team to discuss this at any point during the trial. A participant trial card will be provided giving details of who to contact if there are any problems or issues.

How do I take part?

If you want to take part in the trial, you will be invited to a trial visit where someone from the research team will go through this information sheet and answer any questions you may have. If you are happy to take part in the trial, you will be asked to complete a consent form.

If you decide to take part, at this visit your doctor will carry out some assessments to check your health and find out if you can take part in the trial. This will include:

- Going through your medical history and any medication you take.
- A clinical exam, including recording your weight, heart rate, blood pressure and temperature.
- Providing a small blood sample to check your kidneys, liver, cholesterol, clotting and full blood count.
- A fibroscan, which is a type of ultrasound that looks at the liver. It is a simple, quick and painless test that gives immediate results. It does not have any potential complications or risks and is non-invasive, which means that it does not break the skin or enter your body. It may be that you will already have had a fibroscan carried out as part of your clinical care. If this has been within the last 3 months you won't need to have it done again at the beginning of the OPERA trial.
- If you have the potential to become pregnant you will also need to provide a urine or blood sample for pregnancy testing (see page 8 for further information on pregnancy).

Once they have got the results of these tests, the doctor will let you know whether or not you can take part in the trial.

If you are not able to take part at this stage, you will continue to receive the usual NHS medical care you would receive outside of the study. If you are suitable for the study and still wish to take part, your next visit will be arranged where you will be prescribed trial medication.

What assessments and questionnaires would I complete?

Fibroscan

A fibroscan is a type of ultrasound that can measure the degree of fibrosis or scarring in your liver. It is a simple, quick and painless test that uses high frequency sound waves, and gives immediate results. It does not have any potential complications or risks and is non-invasive, which means that it does not break the skin or enter your body.

A fibroscan will be taken at the start of the trial, before you are prescribed any trial medication (unless you have had it done in the previous 3 months). The scan will be repeated after you have stopped taking the trial drug so that we can compare and observe if there are any differences between both scans. The scan is used to measure how elastic (or how stiff) your liver is.

The scan should take between 10 and 20 minutes to perform. It is part of the normal assessment of PBC in NHS clinics.

Blood samples

Most of the blood samples for this study will be analysed in the hospital laboratories, just like they are in routine care. These are to check how you are reacting to the trial medication – someone from either the research team or your care team will contact you if there are ever any concerns from these results.

As part of the trial, some of your blood samples will also be analysed by researchers at Newcastle University. These will be used to measure chemicals in your blood which are released by the immune system when it is activated (chemokines and cytokines). We are looking at whether these might be a useful new way for us to how understand how active your PBC is and how well it might be responding to treatment. The hope is that this may form a useful new test to use in the clinic in the future.

These samples will be stored at Newcastle Biobank until they are analysed. Researchers at Newcastle University who store and analyse these samples will not know your identity. They will use your unique trial identification ("code") number and date of birth instead of your name being written on trial documents. Only the research team at your hospital will be able to link this number back to you using your name and NHS Number.

Optional Blood and Urine Samples for Future PBC Research

It is very helpful for researchers to have access to blood and urine samples in order to develop new potential treatments and tests for PBC. As part of the OPERA trial, you will have the option to provide extra samples to be stored in Newcastle Biobank and used in future PBC research.

These samples and the information associated with the samples (e.g. time of collection) that are stored at Newcastle Biobank will use your unique trial identification "code" number instead of your name, so that you can't be identified from these samples. This means you will not receive any feedback on the research performed on your samples. PBC researchers can apply to Newcastle Biobank to use these samples in their research. They can be used in future PBC research, which may include research which takes place outside of the UK.

If you agree to for your samples to be used for future PBC research, you will have the following options:

- Storage and use of any leftover blood following the tests at Newcastle University described above (otherwise any leftover samples will be destroyed after analysis)
- Providing an extra blood sample (around 1 teaspoon each) at 3 visits (visits 2, 4 and 5), as well as the time you last ate, and last took trial medication
- Providing a urine sample at visits 2 and 5

You can choose to consent to all, some or none of these options as part of the OPERA trial – they are optional and will not affect your participation in the trial in anyway.

Questionnaires (PBC-40, EQ-5D-5L and Patient Health Questionnaire)

These are questionnaires that ask you questions about the symptoms of PBC and the ways in which it is impacting on your quality of life. Each assesses different aspects of PBC and each will take around 5 minutes for you to complete. There are no right or wrong answers as they are designed simply to find out how you are feeling. They are widely used in PBC clinics in normal care and you may well have filled these in before. If so, we will still ask you to complete them again as we need to find out exactly how you are feeling at the beginning of the trial so we can compare it to how you feel at the end of the trial. We will also ask you to answer a question about how you feel your general health is. We may send some of your trial questionnaires to you to be completed at home rather than in person at your trial visits. This is to limit the time you need to spend at the clinic visits. Your trial team will discuss this with you and confirm you are happy for this to happen.

Patient Diary

You will be given a diary to record the dose of trial medication you have taken, any other medications you may be taking and any missed doses. We will also ask you to record any symptoms or medical events you may have had (anything from headaches to breaking a bone). The trial team will then go through this with you when you attend your visits.

Medication and Empty Bottles

As part of the research, we need to be able to track and account for all of the trial medication, and therefore need to count the number of tablets that are left in your bottles of trial medication. We will therefore ask you to bring your trial medication bottles with you to each visit (even if they are empty).

Trial Visit Summary

Appointment to find out more and check if you can take part

Visit 1 (around 1 hour)

- Opportunity for you to discuss the trial with a member of the research team and complete the consent form
- Discussion of any medications you are already taking and any illnesses
- Blood tests (approx. 4 tbsp.)
- Physical exam, heart rate, blood pressure and temperature
- Fibroscan (if not already done in the last 3 months)
- Urine pregnancy test (for patients with potential to become pregnant)

6 months of trial medication + urso

Week 0: Visit 2 (around 30 minutes)

- Discussion of any new medications you are taking and any illnesses
- Blood tests (approx. 4 tbsp.)
- Optional – blood and urine samples for future research
- Optional Sub-study - Biopsy scheduled
- Completion of questionnaires (these take about 15 minutes)
- Be given your trial medication, patient safety card and a patient diary

Week 4: "Visit" 3 (telephone call)

The trial team will give you a call to check how you are getting on and go through your patient diary with you to check any medications you are taking, and any illnesses or side-effects.

Week 12: Visit 4 (around 15 minutes)

- Patient Diary review – medication, side effects, illness
- Blood tests (approx. 4 tbsp.)
- Optional – blood sample for future research
- Return your trial medication including used packaging
- Be given more trial medication

Week 26: Visit 5 (around 30 minutes)

- Patient Diary review – medication, side effects, illness.
- Return your trial medication including used packaging
- Physical exam, heart rate, blood pressure and temperature
- Blood tests (approx. 4 tbsp.)
- Fibroscan
- Optional – blood and urine samples for future research
- Optional Sub-study - Biopsy scheduled
- Completion of questionnaires (these take about 15 minutes)

You will stop trial taking medication after this visit but continue to take urso

6 months of urso

Week 52: Visit 6 (around 30 minutes)

- Blood tests (approx. 4 tbsp.)
- Completion of questionnaires (these take about 15 minutes)

This is your last trial visit and you will then return to normal NHS care

End of trial participation

Pregnancy, Contraception and Breastfeeding

To take part in the trial, you must not be pregnant, breastfeeding or be planning a pregnancy during the time of the trial. This is because we do not know the effect of the trial medication during pregnancy. If you could potentially become pregnant, during this time you must use what is called an 'acceptable' method of contraception.

These methods include:

- combined hormonal contraception (oral, intravaginal, transdermal)
- progestogen only hormonal contraception (oral, injectable, implantable)
- intrauterine device (IUD)
- intrauterine hormone-releasing system (IUS)
- vasectomised partner
- bilateral tubal occlusion
- sexual abstinence*
- progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- male or female condom with or without spermicide
- cap, diaphragm or sponge with spermicide

*Defined as refraining from heterosexual intercourse for the entire duration. Please note periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

If you could potentially become pregnant you will be asked to take a pregnancy test at your first trial visit. This is to ensure that you are eligible to participate in the trial.

If you become pregnant during the trial, you should stop taking the trial drugs and tell your trial doctor or research team **immediately**. If this happens, your pregnancy will be followed to its outcome (for example, until you have your baby). We will ask you as part of the consent process to confirm you are happy for the research team to follow any pregnancies to completion and up to a year after birth.

If your partner becomes pregnant during the trial, you will need to notify your trial doctor or research team. If this happens, we will ask your partner to give permission to follow up on their pregnancy to its outcome and up to a year after birth.

FURTHER INFORMATION

a) Expenses: We will reimburse any reasonable travel costs for you attending your trial visits. Please make sure you keep receipts to give to the trial team to arrange payment.

b) What are the possible benefits of taking part? We cannot promise the trial will help you directly. We hope the information we get from this trial will help to improve the treatment for PBC patients in the future who are at high risk of progression of their disease to cirrhosis.

By being part of this trial you will also be more closely monitored and have follow up visits and calls which would not happen as part of your normal care.

c) What are the possible risks of taking part? We want you to be safe in the trial at all times, but all medical treatments carry some risk. Obeticholic acid is currently licenced and used by the NHS in some patients diagnosed with PBC. It is therefore a drug which is already used in PBC and one where the doctors who manage PBC have a lot of experience.

Some of the more common side effects-you might experience could include things like:

- Pruritus (itchy skin)
- Abdominal pain and discomfort

To closely monitor how you are doing during your participation in the trial, we will need to do the following:

- We will check you at each trial visit to see if you have experienced any side effects, and it is very important that you tell the trial doctor or nurse about any side effects or other medical concerns that you have. Many reactions go away soon after you stop your medication. In some cases, reactions can become serious, long lasting, or may never go away. Our experience of using Obeticholic Acid in normal clinical practice suggests that this is very rare indeed.
- We will need to take blood samples from you. Taking blood samples may cause some discomfort and minor pain, and some patients occasionally feel faint during or after the procedure. Sometimes patients will have some bruising where the blood has been taken. Trained members of staff will perform these procedures and every effort will be made to prevent these problems.
- If you have the potential to become pregnant, we will ask you questions about contraceptive use and ask you to take a pregnancy test. If you do become pregnant during the trial, there may be a risk as explained above.

d) What happens at the end of the trial?: At around 26 weeks into the trial, you will stop taking the trial medication. After this you will not be given any more medication as part of the trial, but will continue to take urso as prescribed by your doctor. You will have one more visit at 52 weeks and then after this you will return to normal NHS care. We are also happy to tell you and your doctor which trial group you were in (i.e. did you take obeticholic acid or dummy tablet) after the completion of the trial (when all patients have finished).

e) What if new information becomes available? Sometimes during the course of a trial, new information becomes available about the drug being tested. If this happens, your trial doctor will tell you about it and discuss with you whether you want to continue in the trial. If you decide to withdraw, the trial doctor will make arrangements for your usual routine care to continue. On receiving new information, the trial doctor might consider it to be in your best interests to withdraw you from the trial. He/she will explain the reasons and arrange for your usual routine care to continue.

f) What will happen if I do not want to carry on with the trial? You can decide to stop taking trial medication at any time and still continue to be followed up as part of the trial and complete the trial assessments.

You can also choose to fully withdraw from the trial at any time. You do not have to give a reason, though it is helpful to the research team if you do. A decision not to take part at any

stage will not affect the care you receive from your doctors and nurses. If you withdraw from the trial, we will keep the information about you that we have already obtained. On the initial consent form that you sign, we will also ask for your consent to continue collecting information from your NHS hospital notes (e.g. blood test results) for the time you would have taken part in the study. You can ask us not to do this if you prefer.

If you withdraw and with your consent, the trial team will contact you around 4 weeks after you have stopped your trial medication to check if you have experienced any problems.

g) What if there is a problem? If you have a concern about any aspect of your participation in this trial, you can speak to the trial doctor or a member of the trial research team who will do their best to answer your questions. Further contact details are included at the end of this information sheet.

If you prefer to raise your concerns with someone not involved in your care, you can contact the Patient Advise and Liaison Service (PALS). This service is confidential and can be contacted through any of the details below:

Telephone SITE TO LOCALISE
Email SITE TO LOCALISE
Address SITE TO LOCALISE

Alternatively, if you wish to make a formal complaint you can contact the Patient Relations Department through any of the details below:

Telephone SITE TO LOCALISE
Email SITE TO LOCALISE
Address SITE TO LOCALISE

h) What if something goes wrong? In the unlikely event something goes wrong and you are harmed during this research due to someone's negligence, then you may have grounds for a legal action for compensation, but you may have to pay your legal costs. NHS Indemnity does not offer no-fault compensation (i.e. for harm that is not anyone's fault). Newcastle University also has insurance arrangements in place to cover Newcastle University staff involved in designing and managing the study.

i) Who is organising and funding the trial? This trial is funded by the National Institute for Health Research, the national research funder linked to the NHS and the Dept of Health and Social Care. They will play no role in the delivery of the trial and will have no access to any of your data. The trial drug is being provided by a company called Intercept Pharmaceuticals, Inc. Intercept Pharmaceuticals, Inc. are based outside of the UK in the United States.

The doctor in charge of the study (also known as the 'Chief Investigator') is Professor Dave Jones, who is a consultant physician who specialises in liver disease and research. He is based in Newcastle upon Tyne.

This trial is sponsored by The Newcastle upon Tyne Hospitals NHS Foundation Trust. The study sponsor has overall responsibility for the study. The study is managed by the Newcastle Clinical Trials Unit, Newcastle University, on behalf of the Sponsor.

j) How will my information be used? We will need to use information from you and your medical records for this research project. This information will include your name, contact details, date of birth and NHS number. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead. We will keep all information about you safe and secure.

Some of your anonymised information will be sent to the United States. They must follow our rules about keeping your information safe.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

We must archive all trial information for at least 5 years after the trial ends. Your name and contact details will be stored by your hospital. Any trial data held by the trial team at Newcastle University will have a code number instead of your name.

k) Will my taking part be kept confidential? Your participation in the trial will be confidential, however we will let your GP know that you are taking part so that they are aware in case you contact them about any medical problem, as well as the doctor/care team who referred you for the trial. They will not know which treatment you are taking. They will also be given a copy of this information sheet.

The information you provide during the course of this trial will be securely stored using a database called “Sealed Envelope”. Your name and contact details will not be saved on this database, and you will only be identified on this database through a unique study number and date of birth, sex and ethnicity.

The trial team at your hospital will have access to your medical records during the trial to organise planned visits as well as for ongoing safety. Some parts of your medical records and the data collected for the study may also be looked at by authorised persons from the government medicines agency (MHRA), the Newcastle upon Tyne Hospitals NHS Foundation Trust and/or the Newcastle Clinical Trials Unit to check that the study is being conducted to the correct standards. All will have a duty of confidentiality to you as a research participant.

A copy of the trial consent form you complete will be sent by secure email to Newcastle Clinical Trials Unit for checking. It will then be deleted and no documents containing your name will be sorted at Newcastle Clinical Trials Unit.

If there are any serious side effects to the study medicine, we would send details of them to the government medicines agency (MHRA). There is a specific form to do this, and only your code number would be sent to them.

If you experience any serious reactions or become pregnant while on the trial, we will send this information to the company supplying the trial drug as they require this information as part of their record keeping on the trial drug, we have specific forms to send this information, and only your code number will be used.

l) What are my choices about how my information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have, as well as any stored samples.
- If you choose to stop taking part in the study, we would like to continue collecting information about your health from your hospital. If you do not want this to happen, tell us and we will stop.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.

m) Where can I find out more about how my information is used?

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- our leaflet available from www.hra.nhs.uk/patientdataandresearch
- by asking one of the research team
- by sending an email to the Sponsor Data Protection Officer at nuth.dpo@nhs.net

n) What will happen to the results of the research trial? The results will be published in medical journals and presented in meetings to other doctors, nurses, researchers and patients. All trial data that is published will be anonymous. Your identity will always be protected. Fully anonymised data may be made available to other researchers to help inform other research. If you would like to see the results of this trial, we will make them available once they are published.

o) Who has reviewed the trial? The funder reviewed the trial plan as part of the application for funding. All research in the NHS is also looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This trial has been reviewed and approved by xxxxxx, as well as the Health Research Authority (HRA) and the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA is responsible for approving all studies involving medicines. The Newcastle Upon Tyne Hospitals NHS Foundation Trust has reviewed all the study documentation and assessed the risks of this study as part of our responsibility as study Sponsor.

OPTIONAL – OPERA LIVER BIOPSY STUDY

If you decide to take part in OPERA, you will also have the option to take part in a sub-study which will look at liver tissue in the form of two liver biopsies: one before and one after the trial treatment period.

Why am I being invited to take part in the sub-study?

We are inviting everyone who is taking part in the OPERA study to also take part in the biopsy sub-study. You can't take part in the biopsy study unless you are also taking part in the main OPERA study.

What is a liver biopsy and what does it involve?

A liver biopsy is a standard clinical test which can be very helpful in helping to diagnose and treat liver disease. It adds information that is over and above that which can be derived from blood tests and scans. This relates to, in particular, the actual mechanisms by which the liver is being injured in a disease. In the UK around 20% of PBC patients will have one or more liver biopsies at some point as part of their clinical care. A biopsy is usually carried out as a day case procedure, with a stay of a few hours in hospital. Sometimes, if people live a long way away or there is no one living or staying with them, it is better for people to stay the night in hospital after a biopsy. The biopsy is normally taken in the x-ray department, with an ultrasound scan to guide the procedure. The skin is frozen using a local anaesthetic and a small needle inserted into the liver and then removed very quickly. The whole procedure normally takes around 30 minutes. After the procedure people are asked to lie flat for a couple of hours. Around 1 in 300 people can have some bleeding after the biopsy and 1 in a 1000 other types of complication.

Why include liver biopsy in OPERA?

A key question that we are attempting to answer in OPERA is why some people have more aggressive forms of the disease (and, of course, how we can better treat them). One suggestion is that in people with more aggressive disease the cells that line the bile duct undergo a process called "senescence" where they cease to function normally and remain alive (they have been called "zombie cells"). In the OPERA study we will explore this in more detail and look at whether the use of Obeticholic Acid in early disease can prevent or reverse this process. At present there is no way to look at senescent cells in the liver other than with a liver biopsy. This means that the information we get from the liver biopsy part of the study will give us important clues as to PBC and its best treatment. What would be ideal, of course, would be a blood test that allows us to study senescent cells without a liver biopsy. The UK-PBC study which led to OPERA has identified a possible blood test that may allow us to do just this. As part of the OPERA biopsy study we would look at the results with this test in the context of known liver biopsy change to decide whether the test may be useful in the future in avoiding the need for biopsy.

What will happen with the liver biopsy samples?

The biopsy samples will first be analysed at your local hospital as per usual clinical practice. In the unlikely event that the biopsies identify any abnormalities, you will be informed of these by your doctor. The samples will then be sent for trial analysis at NovoPath (part of Newcastle

Hospitals). Researchers at NovoPath who analyse these samples will not know your identity. They will use your unique trial identification ("code") number and date of birth instead of your name being written on trial documents. Only the research team at your hospital will be able to link this number back to you using your name and NHS Number. Once the samples have been analysed for the trial, any remaining tissue will be returned to your local hospital.

If I don't want to do the liver biopsy study can I still take part in OPERA?

Yes!! The biopsy part of the study is entirely voluntary and wouldn't impact at all on your taking part in the trial itself.

LOCAL CONTACT DETAILS

If you are interested in the trial or would like any further information about the study or the rights of participants, please feel free to contact the people below.

They are also who you or your doctor should contact in case of any concerns between study visits.

[LOCAL CONTACT DETAILS]

Notes

Please use this page to make any notes you would like to ask the trial team/trial doctor.