The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

RITPBC

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PARTICIPANT INFORMATION SHEET

Title of Project: Rituximab for the Treatment of Fatigue in Primary Biliary Cirrhosis (RITPBC Study)
Chief Investigator: Professor David Jones

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. One of our team will go through the information sheet with you and answer any questions you have. Please ask the study doctor or nurse if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this leaflet.

Please start by reading the study summary. If you think you might be interested in taking part, then please go on to read the remainder of this information sheet.

STUDY SUMMARY

Primary Biliary Cirrhosis (PBC) is a liver disease that predominantly affects females, can present for the first time at any age and which develops over many years. It is caused by the immune system attacking the body's own tissues. People with PBC frequently experience profound fatigue or tiredness which they liken to their "batteries running down" and although people still want to undertake normal activities they often lack the energy to be able to do them. This reduces quality of life, makes it difficult for people to work and can end up with them becoming isolated in the community. At present we have no treatment for fatigue in PBC. Finding a treatment for fatigue in PBC is one of the highest research priorities identified by patient groups.

The aim of this study is to undertake a clinical trial to examine the effects of a treatment ("Rituximab") on severe fatigue in PBC to help us understand whether this will be a potentially useful treatment. The information that this will give us about how energy generation changes in patients with PBC with and without the treatment will also help us to develop new treatments for fatigue in other diseases. The study has the potential to improve the quality of life of many patients with PBC, for whom there is currently no hope of improvement.

We will perform a randomised controlled study of Rituximab therapy in PBC compared to placebo.

A randomised controlled trial (RCT) is an experimental design used for testing the effectiveness of a new medication. Individuals are assigned randomly to a treatment group (experimental therapy) and a control group (placebo or standard therapy) and the outcomes are compared. This trial is strengthened by being a double-blind study.

Randomisation increases the likelihood that the two groups being treated will be similar. Each participant will be allocated a unique randomisation number, which will be concealed until after each eligible patient has been accepted for the trial. These precautions mean that people who decide whether a patient is eligible to participate in the trial cannot influence which treatment a patient is allocated to receive. This protects the study from conscious or unconscious bias, which would make the test unreliable.

Many trials are set up so that no one knows who has been allocated to receive which treatment. This is known as blinding and helps reduce the effects of bias when comparing the outcomes of the treatments. As this study is a double-blind trial, both the medical staff organising the treatment and those taking part in the trial do not know who is receiving which treatment.

For this study there is a 50% chance that you will receive the study drug Rituximab and a 50% chance that you will receive the placebo.

You can find more information on randomisation and blinding on the following website:
http://www.nhs.uk/Conditions/Clinical-trials/Pages/Fairtests.aspx

The study will be performed in a specialised clinical research environment at Clinical Research Facility Royal Victoria Infirmary. We have, for many years, worked closely with PBC patient groups to focus on the problems that are important to our patients. This study is fully supported by Liver North, a liver disease charity and patient support group.

The study will take place over approximately one year and involve between 9 and 20 visits depending on the planning of some investigations. We will ask you to provide some extra blood (up to 6 teaspoonfuls) at the start of the study and after three, six, nine and twelve months. In addition to this we will ask you to complete some quality of life questionnaires, you will have your activity levels monitored for a week using a small device (the size of a wrist watch), exercising twice on an exercise bike to measure your oxygen used, and have two MRI scans.

You are invited to participate in the study as your doctor feels you are eligible to take part.

Any information collected about you during this study will be kept strictly confidential.

Taking part in this study is entirely voluntary. If you do agree to participate, you are free to withdraw at any time and without having to provide a reason. You will be asked to sign a consent form to confirm that you are willing to take part.

If you are interested in taking part in the study please continue to read the rest of this information sheet. Part 1 tells you the purpose of this study and what will happen to you if you take part. Part 2 gives you more detailed information about how the study will be carried out.

INFORMATION SHEET PART 1

What is the purpose of this study?

You have been invited to participate in this study because you have Primary Biliary Cirrhosis (PBC) and have fatigue. Rituximab is a relatively new drug that has been used in patients with Rheumatoid Arthritis and found to improve fatigue in this patient group. Rituximab treatment results in depletion of B lymphocytes; these are immune cells that are thought to play an important role in PBC. Rituximab is administered via intravenous infusion over several hours. One treatment course comprises two infusions two weeks apart. The main purpose of this study is to investigate whether Rituximab improves fatigue in PBC and if it does, how this happens. To this end we will measure markers of muscle function, activity and quality of life before and up to one year after the first infusion of Rituximab. We hope to find whether Rituximab affects fatigue and how this happens. Participation in the study will last approximately one year.

Who can take part?

To take part in this study you must:

- have moderate or severe fatigue assessed as having a fatigue domain score of >33
- be aged 18 years or older
- willing and able to provide written informed consent
- available for the duration of the study
- willing and able to comply with the procedures required as described in this information leaflet and as directed by the study doctor or nurse

You cannot take part in this study if:

- the above does not apply to you
- you are currently taking part in another clinical study
- you have any condition which, in the opinion of the investigator, might interfere with evaluating the study objectives
- there is any reason you might not be able to have an MRI scan
- you have had major surgery within 4 weeks of study entry
- you have had vaccination within 4 weeks of study entry (patients requiring seasonal Flu or travel vaccines will be required to wait 4 weeks post vaccination to enrol in the study)
- you are pregnant or planning to become pregnant for the duration of study

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

Which treatments are being used in the study?

If you agree to take part in the study you may receive an infusion through a drip that either contains Rituximab or a salt solution (placebo). Neither the medical staff organising the treatment, nor you, will know which treatment you will receive.

Rituximab/placebo therapy

B-cells are involved in fighting infection and causing inflammation. We also believe that they play an important role in causing fatigue in PBC. The number of B-cells in the blood can be greatly reduced by using Rituximab. Rituximab/placebo is given by drip and involves being in the Clinical Research Facility for several hours on the day of your treatment. A course of Rituximab/placebo consists of two drips given a fortnight apart. Before each Rituximab/placebo treatment all participants will receive Paracetamol and an antihistamine orally and a steroid by a drip. These help to minimise side effects that sometimes occur when Rituximab/placebo is given. The paracetamol and steroid may temporarily improve the symptoms of your PBC but the purpose of the study is to look at the effects of the treatment over a year. All participants will remain double-blinded throughout the study.

What will happen to me if I take part?

If you decide to participate in this study, you will be allocated at random to receive either Rituximab treatment or a salt solution (placebo). The study will take place over approximately one year and involve between 9 and 20 visits depending on the planning of some investigations. All patients will be asked to provide some extra blood (up to 6 teaspoonfuls) at the start of the study and after three, six, nine and twelve months for analysis of the cells and proteins in your blood and will collect normal clinical information about the severity of your liver disease. In addition you will have your activity levels monitored for a week using two different activity monitors. They are small devices,, one worn on the wrist and one worn on the upper arm. You will also have an exercise test on an exercise bike t and a MRI scan before and after the treatment. Full details of what will happen to you are in Part 2 of this information sheet.

Reimbursement

You will be reimbursed travel expenses for study related visits.

What do I have to do?

To take part in the study you must make yourself available for all study visits and comply with the instructions given to you. You also need to report any possible side effects and new health problems. It is advised patients are vaccinated against Flu and receive Pneumovax before treatment.

What are the side-effects of any treatment received when taking part?

Infusion of Rituximab leads to infusion reactions in about 30% of patients during the first infusion, but the chance is lower with subsequent infusions. Usually these are mild and self-limited and include local skin irritation, light-headedness, dizziness and nausea. Severe allergic reactions requiring emergency

treatment are very rare. Rituximab leads to a modest increase of infections, notably upper respiratory and urinary tract infections.

What are the possible disadvantages and risks of taking part?
Blood sampling can sometimes cause bruising and soreness of the arms, or very rarely a blockage of the vein or a small nerve injury which can cause numbness and pain. Normally these problems resolve with time. Some people may faint while blood is being drawn.

Measurement of physical activity is a routine clinical investigation which involves wearing two small devices, one is like an armband to be worn on the back of the upper right arm and the other is worn on the wrist for a week.

Two MR scans of your muscles will take place whilst you perform gentle exercises by repeated flexion of the foot against a weight and the MRI scanner measures acid accumulation. MR scanning can be very noisy, and sometimes people tell us they feel more tired than normal after they have exercised in the scanner.

Detection of unsuspected abnormalities on subjects undergoing research MR scans at the Newcastle MR Centre
Research MR scans undertaken at the Newcastle MR Centre are for research, not clinical purposes. As such they will not be routinely examined or reported by a radiologist. However, if a previously unsuspected abnormality is detected by one of the MR Centre radiographers or other staff, then the scan will be referred to a qualified radiologist for a radiological opinion. The study doctor will then be informed by the radiographer and may then discuss the case with the radiologist and/or other specialists as appropriate. The decision as to what further action is needed, including how to communicate such findings to you and your GP, will be the responsibility of the study doctor.

Should I take contraception during the study?
If appropriate we will advise you about contraception before you decide whether to take part in the study. Male patients should continue to use a reliable method of contraception for 12 months after the last Rituximab/placebo treatment.

Can I become pregnant or breast feed during the study?
You must not take part if you are breastfeeding, pregnant, planning to become pregnant or are not using a reliable method of contraception. A pregnancy test will be performed in women of child-bearing potential before starting treatment. If you are treated with Rituximab/placebo then you should not fall pregnant or breastfeed for 12 months after your last Rituximab/placebo treatment course.

What are the possible benefits of taking part?
You may not gain any direct medical benefit from participating in this study, but we hope to find that Rituximab has a positive effect on fatigue in PBC. If, during the course of the study, we find that you have a medical condition of which you are unaware, we will inform you of our findings and refer you to your GP or an appropriate doctor.

What happens when the research study stops?
At the end of the study, information will be held securely for a maximum of 15 years. You will be provided with contact details of the research team in case you want to discuss any aspect of taking part in the study at a later date.

The study drug (Rituximab) will not be provided after the study has finished.

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.

Will my taking part in this study be kept confidential?
Yes. We will follow ethical and legal practices and all information about you will be handled in confidence. The details are included in Part 2.

This completes Part 1 of the information sheet. If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

INFORMATION SHEET PART 2

What will happen to me if I take part?
If you decide to participate in this study, you will be allocated at random (by chance, like the toss of a coin) to receive either Rituximab treatment or a salt solution (placebo). You are free to decline any drug treatment that is offered to you. All of your other drug therapy will remain unchanged, unless your doctor tells you otherwise.

The study will take place over approximately one year and involve between 9-20 visits depending on the planning of some investigations. If you take part you will be asked to complete quality of life questionnaires and have your activity levels monitored for a week using two small devices to be worn on the wrist and on the upper arm. During two of the visits you will exercise on an exercise bike and at two separate visits your muscle function will be assessed during an MR scan. All study visits will take place at the Newcastle Clinical Research Facility (NCRF) at the Royal Victoria Infirmary (RVI) apart from the MR scans which will take place at the Newcastle Magnetic Resonance Centre (NMRC) which is based at the Campus for Ageing and Vitality. Please see the Table of Events Flow Diagram at the end of this information sheet.

We will ask you to provide some extra blood (up to 6 tea spoon-full) at the start of the study and after three, six, nine and twelve months for analysis of the cells and proteins in your blood. In the future, we hope that these samples will help us predict which patients will respond best to treatment.

Visit 0 (screening)

Your first visit is to take place up to 2 weeks before visit 1. At this screening visit you will have the opportunity to ask any questions and discuss the study in full. If you decide you want to take part in the study you will then:

- sign the Informed Consent Form
- be asked questions about your general health
- be asked permission for us to inform your GP that you are taking part in a clinical research study
- be given a full physical examination
- have blood samples taken for a number of routine laboratory tests to check it is safe for you to start Rituximab (unless this has been done in the past month)

If any of the tests or examinations detects an infection or another problem, there may be a need to stop your participation in the study. This is in order to ensure your safety. If we detect any problems we will discuss these with you and refer you to the appropriate clinician for treatment or care. It may be possible to be screened again for entry into the study after treatment of some infections or problems. This will depend on the nature of the condition and will be at the discretion of the study doctor.

We will be able to discuss most results with you on the day of your visit but some test results can take up to 10 working days to be processed. Once we have received your results we will contact you to talk about the next step.

Visit 1 (baseline investigations and randomisation)

This visit will take place prior to your first Rituximab/placebo infusion and will involve:

- completion of quality of life questionnaires (PBC-40, PROMIS HAQ, COGFAIL, OGS, ESS and HADS)
- blood samples (approximately 30 ml equivalent to 6 teaspoons)
- an assessment of muscle function using MR (a scan of your muscles whilst you take gentle exercise)
- an assessment of your exercise capacity (measuring how much oxygen you use whilst cycling on an exercise bike)
- assessment of physical activity using two monitors that you wear over a week (the monitors are the size of an armband to be worn on the back of the upper right arm and on the wrist, touching the skin.)
- pregnancy test (for female patients with childbearing potential)
- issuing you with a fatigue diary. You will be asked to complete it for a period of one week during the first week of each month for visits at baseline, 1, 3,6,9 and 12 months
- randomisation to receive either Rituximab or placebo infusion

Visit 2 (1st Infusion)

This visit will take place within 4 weeks of the baseline investigations. At this visit you will receive your infusion of Rituximab or placebo. You will receive information about the procedures involved as part of

your baseline visit. The infusion will last about 5 hours and you will be asked to stay for another hour after the infusion for observation. Lunch and refreshments will be provided during this visit. You will be asked to:

- undergo a physical examination (including vital signs, height and weight)
- repeat blood samples
- you will be asked if you have had any adverse events or if there have been any changes to other medication you were taking since your last visit (visit 1)

Visit 3 (safety visit)

At this visit you will be asked to:

- undergo a physical examination (including vital signs, height and weight)
- repeat blood samples
- you will be asked if you have had any adverse events or if there have been any changes to other medication you were taking since your last visit (visit 2).

Visit 4 (treatment 2)

This visit will take place two weeks after visit 2. At this visit you will receive your second infusion of Rituximab or placebo. The infusion will last about 4 hours and you will be asked to stay for another hour after infusion for observation. Lunch and refreshments will be provided during this visit. You will be asked to:

- undergo a physical examination (including vital signs, height and weight)
- repeat blood samples
- you will be asked if you have had any adverse events or if there have been any changes to other medication you were taking since your last visit (visit 3)

Visits 5-15 (follow-up visits)

These visits will take place weekly for 12 weeks following your 2nd infusion with telephone calls by a Research Nurse. At these visits you will be asked by the Research Nurse if you have had any adverse events or if there have been any changes to other medication you were taking at baseline.

Visit 16 (follow up)

This study visit takes place in the Clinical Research Facility at the Royal Victoria Infirmary 12 weeks after your second infusion. At this visit you will involve:

- an assessment of muscle function using MR (a scan of your muscles whilst you take gentle exercise)
- an assessment of your exercise capacity (measuring how much oxygen you use whilst cycling on an exercise bike)
- undergoing a physical examination (including vital signs, height and weight)
- repeat blood samples as per baseline visit
- completing quality of life questionnaires (PBC-40, PROMIS HAQ, COGFAIL, OGS, ESS and HADS)

- assessment of physical activity using two monitors that you wear over a week (you will be reminded by the Research Nurse to return the monitor either by post in a self addressed envelope or prearranged taxi at the end of the assessment period.)
- you will be reminded to complete your fatigue diary for one week at the beginning of the month for this 3 month visit
- you will be asked if you have had any adverse events or if there have been any changes to other medication you were taking since your last visit (visit 15).

Visits 17-18 (follow up)

These visits will take place at 6 and 9 months respectively after your second infusion. At these visits you will be asked to:

- undergo a physical examination (including viral signs, height and weight)
- complete quality of life questionnaire (PBC-40, PROMIS HAQ, COGFAIL, OGS, ESS and HADS)
- repeat blood samples as per baseline visit
- you will be reminded to complete your fatigue diary for one week at the beginning of the month for the 6, 9 and 12 month visits
- you will be asked if you have had any adverse events or if there have been any changes to other medication you were taking since your last visit

Visit 19 (final assessments)

This final study visit takes place at 12 months after your second infusion. At this visit you will be asked to:

- undergo a physical examination (including vital signs, height and weight)
- complete quality of life questionnaires (PBC-40, PROMIS HAQ, COGFAIL, OGS, ESS and HADS)
- repeat blood samples as per baseline visit
- return your completed fatigue diary
- you will be asked if you have had any adverse events or if there have been any changes to other medication you were taking since your last visit (visit 18)

Travel expenses

You can claim back any travel expenses associated with attending the hospital for the research.

Can I find out the results of the research?

If you would like to know the final results of the study then a copy of the journal article will be sent to you on request. We will also present the findings of the study at LiverNorth meetings which are open to the public and which will be publicised widely.

Who can I speak to if I want further information?

If you would like to speak to someone in the Research team or have any problems or queries, contact Kathryn Houghton on [redacted] or email [redacted], Dr Laura Jopson on [redacted] or email [redacted]. If you would like to speak to another health professional who is not directly involved in the study, Dr Jopson can arrange this for you.

What if new information becomes available?

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

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

You are free to withdraw from the study at any time, without giving a reason, and without your medical care or legal rights being affected. If you choose to stop treatment, you will be asked to continue to attend for follow up visits until the end of the study, but you may choose not to do so. If you withdraw from the study completely the blood samples taken as part of the study so far will be stored and analysed, and the data you have provided in the study will be kept and stored.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak to the Chief Investigator, Professor David Jones, who will do his best to answer your questions. Contact details are: Professor David Jones, telephone: [redacted], email: [redacted]. If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure by speaking to a member of the PALS (Patient Advice and Liaison Service) team directly during Monday to Friday from 9:00am until 5:00pm. Outside of these hours you can leave a message on an answer-machine and you will be contacted the next working day. The service can be contacted on:

Freephone: [redacted]
Text: [redacted]
Email: [redacted]

or by writing to them at their Freepost address.

[redacted]

Alternatively, you can find more information on taking part in clinical trials on the following websites:
http://www.nhs.uk/Conditions/Clinical-trials/Pages/Introduction.aspx
http://www.mrc.ac.uk/Achievementsimpact/Clinicaltrials/TakingPartInATrial/index.htm

In the event that 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 against Newcastle upon Tyne Hospitals NHS Foundation Trust, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate). NHS Indemnity does not offer no-fault compensation (i.e. for harm that is not anyone's fault). Neither the sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust) who has undertaken to manage the study, nor

the management of the hospital/research centre you are attending for your routine treatment, is able to agree in advance to pay compensation for non-negligent harm.

Private medical insurance
Anyone who has private medical insurance is advised to contact their provider to ensure that participating in this study does not affect their cover.

Will my taking part in this study be kept confidential?
Yes. Any personal information pertaining to your participation in the study will remain confidential. Access to this information is strictly controlled by authorised staff. All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital or clinic will have your name and address removed so that you cannot be recognised. You will be assigned a unique study number which will be used to identify your information and biological samples that leave the hospital. We will also enter your information onto a computer database. We will only use your unique study number, your initials and date of birth in this database (your name and address will not be included).

The information we collect from you during the course of the study will be processed for the purpose of the study and for ensuring compliance with medical, ethical, and pharmaceutical laws and regulations. Your information may be made available to regulatory authorities for the purpose of inspecting and validating our work and it may be disclosed on a strict 'need to know' basis in case of medical emergencies.

Members of the research team, other authorised staff from your hospital, the legal sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust), or regulatory authorities may need access to your study documents and medical records. By signing the consent form you will permit authorised staff participating in the research as collaborators or acting on behalf of regulatory authorities to review and use your study documents and/or medical records. Your personal information may be reviewed and copied (your identifying personal data will not be copied) by such people during and after the study to verify clinical and scientific research procedures and/or data to the extent permitted by applicable laws and regulations and without breaching the confidentiality of the records. Even if you withdraw your consent, your personal data may still be processed so that we can verify our work.

Information we collect as part of this study will be held by the research team in paper and electronic format for future reference. Personal data will be held for a maximum of 12 months after the end of the study, and research data for a maximum of 15 years.

Contacting your GP
We will ask you for your permission to contact your GP who will be informed that you are participating in a clinical study.

What will happen to my samples taken as part of the study?

The samples being taken will be treated as a 'gift', and you will not benefit financially if this research leads to the development of a new treatment or medical test. Samples will be sent to Newcastle University for processing and storage. Your name and address will be removed so that you cannot be recognised. After the samples have been analysed, they will be destroyed.

What will happen to the results of the research study?

The results of the study will be published in a peer-reviewed scientific journal. Results may also be presented at clinical conferences. You will not be identified in any publications or reports.

Who is organising and funding the research?

This study was awarded by the Efficacy and Mechanism Evaluation (EME) Programme, and is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC-NIHR partnership. The Newcastle Clinical Trials Unit is managing the study. The Newcastle upon Tyne Hospitals NHS Foundation Trust is the legal sponsor of the study. This means that they are responsible for the conduct and management of the study.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee to protect your safety, rights, wellbeing and dignity. This study has been reviewed and given favourable opinion by NRES Committee North East - Newcastle and North Tyneside 1 Research Ethics Committee.

What should I do now?

If you have any questions about the study, or you think you would like to take part, please contact:
Research Nurses:

Kathryn Houghton, Tel: [redacted] or email [redacted]

Jenny Bainbridge, Tel: [redacted]

Dr Laura Jopson, Tel: [redacted], email: [redacted]

Table of Events Flow Diagram