PATIENT INFORMATION SHEET

Study Title: TRANSFORM-UK: A Therapeutic Open Label Study of Tocilizumab in the Treatment of Pulmonary Arterial Hypertension

Invitation
We would like to invite you to take part in our research study. Before you decide, it is important for you to know 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. Feel free to discuss it with others if you wish. Ask us if there is anything that is not clear or if you want more information. Please take your time to read the following information carefully and decide if you wish to participate.

1. What is the purpose of the study?
In pulmonary arterial hypertension there is raised blood pressure in the lungs, which leads to heart failure and early death. Interleukin-6 is a protein involved in pulmonary arterial hypertension. Tocilizumab blocks interleukin-6, and is demonstrated to be safe and effective in trials of other diseases like rheumatoid arthritis. The purpose of this study is to explore the therapeutic response of intravenous administration of Tocilizumab by measuring heart function and blood pressure in the lungs. The study will also assess its safety in patients with Pulmonary Arterial Hypertension.

2. Why have I been invited?
You have been asked to take part in our study because you have pulmonary arterial hypertension. Approximately 21 patients are expected to take part in the study, recruited from sites across the UK.

3. Do I have to take part?
No. Your participation in this study is entirely voluntary and you are under no pressure to take part.

Talk with your family, friends and your GP to help you make your decision. You can take as much time as you like.

If you do decide to take part we will ask you to sign a consent form. If you later change your mind, you are free to withdraw from the study at any time without having to explain why. If you do not wish to take part in this study, the standard of care that you receive will not be affected.

4. What will happen to me if I take part?
Having carefully considered the information form and asked the questions you would like to have answered, the first thing you need to do is to confirm that you are willing to take part in the study by completing and signing the consent form that we have provided. Please keep this information leaflet to remind you what we have asked you to do. You will be free to withdraw at any time and 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.

You will be in the study for up to 24 weeks. During this period we will ask you to attend 8 study visits at the hospital, 2 of which may involve an overnight stay.
If you do decide to take part the following will happen:

Screening visit
To assess your eligibility for the study a screening visit will be performed which will involve the following investigations:

- A detailed medical history
- Female patients of child bearing age will have a urine pregnancy test
- Pulmonary Function tests (only if you have NOT had these done within the 24 weeks prior to the screening visit)
- A six minute walk test
- Sampling of blood (approximately 20 ml) for routine blood tests.
- Vital signs (weight, blood pressure, heart rate, temperature and oxygen levels)

If you meet all the criteria for the study and still wish to take part you will be enrolled and the following visits will be performed:

Baseline, Week 0 (to take place within 30 days of screening visit)
You will be admitted to hospital for two days to have the following investigations:

- Right heart catheterisation (usually via a vein in your arm or just above your collar bone)
- A physical examination
- An ECG will be recorded
- Vital signs (e.g. heart rate, blood pressure, height, temperature and weight) will be measured
- You will be asked to complete a quality of life questionnaire
- A six minute walk test
- Sampling of blood (approximately 50 ml) for routine and research blood tests.
- Female patients of child bearing age will have a pregnancy test (urine)

After you have completed all the investigations you will receive an intravenous infusion of Tocilizumab in your arm which will take up to one hour.

Week 4
You will be asked to attend the hospital to have the following procedures:

- A physical examination
- Vital signs (weight, blood pressure, heart rate, temperature and oxygen levels) will be measured
- You will be asked to complete a quality of life questionnaire
- A six minute walk test
- Sampling of blood (approximately 20 ml) for routine blood tests.
- Female patient of child bearing age will have a pregnancy test (urine)

After you have completed all the investigations you will receive an intravenous infusion of Tocilizumab in your arm that will take up to one hour.

This visit will be repeated every four weeks (Weeks 8, 12, 16 and 20).

Week 24 – End of Study visit
You will be admitted to hospital for two days to have the following investigations:

- Right heart catheterisation (usually via a vein in your arm or just above your collar bone)
- A physical examination
- An ECG will be recorded
- Vital signs (weight, blood pressure, heart rate, temperature and oxygen levels) will be measured
- You will be asked to complete a quality of life questionnaire
- A six minute walk test
- Sampling of blood (approximately 50 mls) for routine and research blood tests.
- Female patient of child bearing age will have a pregnancy test (urine)

**Telephone follow up**
A telephone follow up will be performed 30 days after the End of Study Visit. You will be asked questions about your general wellbeing and if there have been any changes to your medication.

**Safety Follow up visit**
A safety follow up visit will be performed 4 months after the End of Study Visit. You will be asked to attend the hospital for the following investigations:

- A physical examination
- Vital signs (e.g. heart rate, blood pressure, height, temperature and weight) will be measured
- You will be asked to complete a quality of life questionnaire
- Sampling of blood (approximately 20 mls) for routine blood tests.

Please see table 1 for an overview of the visit and assessment schedule.

**5. How will being part of this study affect my lifestyle?**
You will be asked to attend hospital once a month for six months to receive your IV infusion and other clinical tests. Two of the visits may require an overnight stay.

If you are a woman who can get pregnant, you will need to have a urine pregnancy test every month. You must not get pregnant and in taking part in this study you will agree to use 2 reliable different methods of birth control from the baseline visit until completion and at least 3 months after your last dose. This is standard advice and clinical care for all women of child bearing age with pulmonary hypertension. This is because historically half of patients with established pulmonary arterial hypertension die during or shortly after pregnancy.

Your study doctor will inform you of the risk that you will be undertaking if you get pregnant while you are receiving the study drug.

**6. Expenses and payments**
You will not be paid for participating in this study, but you will be reimbursed for any travel expenses incurred.

**7. What are the alternative treatments available?**
Your study doctor can tell you about other treatment choices for your pulmonary hypertension.

**8. What are the possible disadvantages and risks of taking part?**
Tocilizumab has been shown to be well tolerated and associated with minimal risk of adverse reactions in other clinical trials. The most commonly reported side effects are:

- Upper respiratory tract infections
- Headaches
- Increased blood pressure

**Cardiac catheterisation**
Cardiac catheterisation can be a stressful and uncomfortable procedure, but is an essential step in the diagnosis and management of pulmonary arterial hypertension. Two cardiac catheterisations may be additional to standard care, but are required for clinical trials for the investigation of a new treatment in PAH which is necessary to demonstrate a reduction in pulmonary vascular resistance.
You will be exposed to radiation during the course of the cardiac catheterisation. The total dose of radiation you will receive during the course of the study is equivalent to the amount of background radiation the average UK resident receives over 5-6 years. The risk of inducing fatal cancer from this exposure in a 70 year old person suffering from heart failure is 1 in 8,300. This reflects their poor prognosis and the risk is considered to be minimal.

Some people may experience chest pain or palpitations during the procedure which is usually short lived. Serious complications are rare, but do sometimes occur. Potentially serious complications include a punctured lung or a heart attack. In very rare instances (1 in 2000), some people have died as a consequence of one of these serious complications.

**Venepuncture**

There is minimal risk associated with having your blood taken. If can cause brief discomfort and bruising, which might last for several days, and will therefore be performed by experienced members of the healthcare team.

We may not be aware of all the side effects, risks and inconveniences of participating in this study, so it is important that you tell the study doctor of any problems or symptoms that occur during the study. If you are at all worried about your symptoms then you can contact the study doctor at any time.

**9. What are the possible benefits of taking part?**

Taking part in this study may or may not make your health better, and may or may not have direct benefit to you. However, the information we get from this study will potentially help improve the treatment of people with pulmonary arterial hypertension in the future.

**10. What happens when the research study stops?**

At the end of the study, the study drug will be discontinued. Your study doctor will discuss your options with you.

**11. What if relevant new information becomes available?**

Sometimes we get new information about the treatment being studied. If this happens, your study doctor will tell you and discuss whether you should continue in the study. If you decide to continue in the study you may be asked to sign an agreement outlining the discussion. If the study is stopped for any other reason, we will tell you and arrange your continuing care.

**12. What will happen if I don’t want to carry on with the study?**

You can withdraw from the study at any time. If you withdraw from the study prematurely we would ask you to attend a termination visit. The visit would include the same tests as the Week 24 End of Study visit detailed in section 4.

**13. What if there is a problem?**

If you are concerned about any aspect of this study you should ask to speak to one of the researchers (contact details below) who will do their best to answer your questions.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the Patient Advice and Liaison Service (PALS) (contact details below). If something goes wrong and you are harmed during the study due to someone’s negligence then you may have grounds for a legal action for compensation against the hospital involved, but you may have to pay your legal costs. The normal NHS complaints mechanisms will still be available to you.

NHS hospitals are unable to agree in advance to pay compensation for non-negligent harm (situations where no one can be blamed for what happened). However, NHS Trusts are able to consider offering an ex-gratia payment in the case of a claim.

**14. Will my taking part in this study be kept confidential?**

All information that is collected about you during the course of this study will be kept strictly
confidential according to the Data Protection Act 1998. Information on paper will be kept in locked filing cabinets and where possible behind security coded, locked doors. Electronic information will be kept on computers that are protected by passwords.

The electronic data we store for this study will be kept on a database, but we will not keep any details of your name or address, the data will be stored only under your hospital number on a secure computer on hospital premises.

Any information about you that leaves the hospital will be anonymised and anything that could identify you (name, date of birth, address, hospital number) will be removed and you will only be identified by a study code. When the study is reported to the funding body, published in medical journals or presented at conferences it will not be possible to identify you personally.

Representatives from regulatory authorities may need to look at your medical records and the data collected in the study to check that the study was carried out correctly. All will have a duty of confidentiality to you.

15. Involvement of the General Practitioner
Your GP will be notified regarding your participation in this trial. A letter will be sent along with a copy of this information leaflet.

16. What will happen to any samples I give?
If you take part in this study you will be asked to give blood samples for laboratory testing. Most blood samples will be processed on site and are routine tests taken for your safety. At your baseline and end of study visit research bloods will be taken as well as routine blood tests. The research bloods will be frozen and sent to a central laboratory in Cambridge for further tests. Some of this blood may be kept for future research. These blood samples will be given the same unique study code as your other study information.

17. What will happen to the results of the research study?
Results of the study will be made available to the public through scientific publications. Under no circumstances would identities of research participants be disclosed in any publication.

18. Who is organising and funding the research?
The study is funded by Roche Products Ltd and the National Institute of Health Research and jointly sponsored by Cambridge University, Papworth Hospital and Roche Products Ltd.

19. Who has reviewed the study?
All research in the NHS is reviewed at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and approved by the NRES Leicester Central Research Ethics Committee and the Research and Development Department at Papworth Hospital NHS Foundation Trust.

20. Further information and contact details
For further information, you can speak to one of the study team:

Principal Investigator: Local principal investigator
Study Coordinator: Local Study nurse or coordinator

Alternatively, you can speak to an independent contact:
Local independent contact details

Thank you for considering taking part in this study.

If you decide to participate you will be asked to sign a consent form and will be given a copy of this information sheet and the consent form to keep.
<table>
<thead>
<tr>
<th>Assessment</th>
<th>Screening</th>
<th>Baseline</th>
<th>Week 4, 8, 12, 16 + 20</th>
<th>Week24 End Of Study</th>
<th>Safety Follow up</th>
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* not Required if done less than 24 weeks prior to screening visit