

APPENDIX IV**CLINICAL TRIAL INFORMATION LEAFLET 1
(FOR ADULTS)
Version 001; Dated 26/06/03**

A randomised, open label study to compare the safety and efficacy of a dry powder formulation of inhaled Colomycin (colistimethate sodium) and nebulised TNSFI (tobramycin nebuliser solution for inhalation, Tobii®) in cystic fibrosis patients with *Pseudomonas aeruginosa* lung infection

PROTOCOL NO: COLO/DPI/02/06**Why have I received this leaflet?**

You are being invited to take part in a research study. Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and to discuss it with someone if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not to take part.

What is the purpose of the study?

As you know, Tobii® (tobramycin nebuliser solution for inhalation), is an antibiotic medicine which is used to treat *Pseudomonas aeruginosa* chest infections in cystic fibrosis patients. You have been receiving Tobii® in a cycle of 28 days active therapy (nebulised tobramycin twice a day), followed by 28 days rest from treatment.

Colistimethate sodium (Colomycin) is another antibiotic medicine that is used for the treatment of *Pseudomonas aeruginosa* chest infections in cystic fibrosis patients. Colomycin has been marketed in some countries for over 40 years and has been used to treat chest infections for about 20 years. At the moment, patients can either inhale Colomycin through a nebuliser, or be given Colomycin by injection. Colomycin is used in many European countries and you may have taken this in the past.

The company that makes Colomycin has developed a new way for patients to inhale the medicine. Colomycin can now be inhaled as a powder (contained in capsules) which is sucked in through a newly developed pocket-sized, hand held device. Colomycin powder is made of the same active ingredient as standard Colomycin, but has been made into a much finer powder so that you can use it in a special inhaler device.

Before you decide whether to take part, your doctor will show you the inhaler device and explain how this is used to inhale powder from the capsules.

We are doing this study because we would like to see whether giving Colomycin powder in this way is just as good as Tobii® in maintaining lung function. We will also be comparing the convenience and ease of use of these two different ways of taking an antibiotic to treat *Pseudomonas aeruginosa* chest infections.

We have already given Colomycin powder to 12 healthy people and 22 people with cystic fibrosis at a single dose of 125 mg (1 capsule) on two occasions (all of these people were aged 18 years and



over). No serious side effects were reported, although mild side effects such as cough, throat irritation and unpleasant taste were found.

We have also given Colomycin powder to at least 6 cystic fibrosis patients at a dose of 1 capsule twice a day for 4 weeks. At least three of these patients were children between the ages of 8 and 13 years. The results of this study were looked at very closely by a group of doctors. They told us they think it is safe for cystic fibrosis patients to receive Colomycin powder at this dose twice every day.

Why have I been chosen?

You are a cystic fibrosis patient who is currently suffering from a lung infection with bacteria called *Pseudomonas aeruginosa*. If you agree to take part, you will be one of about 300 patients taking part in the study. The Colomycin powder medication is intended for all cystic fibrosis patients aged 8 years or older, so we need to evaluate it in adults and children.

Do I have to take part?

NO. Entry into the study is entirely voluntary. 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 do decide to take part, you are still free to withdraw at any time and you would not have to give a reason. If you decide not to take part or if you withdraw at any time, the standard of medical care that you receive either now or in the future will not be affected. Your doctor is also able to withdraw you from the study at any point if they feel there is good reason (for example, if it is in your interests to do so).

What will happen if I take part?

Sometimes, because we do not know which way of treating patients is best, we need to make comparisons. People are randomly put into groups and then the results are compared. The groups are selected by a computer which has no information about the individual – the selection is by chance. (This process is called randomisation, and means that you will not be able to choose which medication you are allocated to).

On starting the study, you will be entered into one of two groups of patients by randomisation.

One group of patients will receive 3 cycles of Tobin[®] - each cycle consisting of 28 days active therapy with nebulised tobramycin 300mg twice daily, followed by 28 days rest from treatment. The other group of patients will receive 125mg Colomycin powder twice a day, every day for 6 months by the new inhalation device.

The study has been designed so that there will be an equal number of patients in each group. Therefore, you have an equal chance of receiving the Colomycin powder using the new inhalation device or of receiving tobramycin by nebulisation, as you have done in the past.

If you are allocated to the Colomycin powder group, the first time you take your medicine in this way will be supervised by your doctor. You will also be given simple instructions for cleaning the device.

This study is an open label study, which means that you and your doctor will know which treatment group you are in. It is important that you answer any questions as honestly as possible for the study to work.



The only person who will not know which treatment group you are in is the person who performs lung function tests. Again, for the study to work, it is important that you do not tell the person doing the lung function testing which treatment you are taking.

The study will last for 6 months.

Will I have to alter my lifestyle to take part?

The study has been designed so that you will experience the minimum amount of additional discomfort and inconvenience. However, the nature of a clinical study does mean that some changes will be necessary.

1. Clinic visits You will be required to attend the clinic on six or seven occasions [at the screening visit (today), at the beginning of study treatment (this might be the same day as the screening visit), after 1 month of treatment, after 2 months, after 4 months, after 5 months and after 6 months (at the end)]. During these clinic visits you will be seen so that the doctor can:

- Check your health. (past and present medical conditions, medicines you have taken/ are taking, height and weight measurements)
- Perform lung function tests to see how well your treatment is working.
- At three or four of these visits we would also like to collect a blood sample (up to 15ml, about 1 tablespoon) and urine sample (at least 40ml, about 3 tablespoons) so that we can monitor your general health. If you are receiving Colomycin powder, some of these samples will also be used as a safety procedure for checking the levels of drug in your body.
- At most of these visits we would also like to collect a sputum sample so that we can monitor whether the bacteria causing the infection develops resistance to the antibiotic (this measures whether the bacteria survive despite antibiotic use). Again, if you are receiving Colomycin powder, some of the sputum samples will be used for checking the levels of drug in your body.

2. Taking the study medication If you are in the group of patients that receive Colomycin powder, probably the biggest change in your everyday routine is that you will be asked to take the study medication twice a day every day for 6 months. If you are in the other group of patients, you will receive 3 cycles of Tobin[®] - each cycle consisting of 28 days active therapy with nebulised tobramycin 300mg twice daily, followed by 28 days rest from treatment.

3. Completing a questionnaire You will be asked to complete a questionnaire about your health at most visits. You may like to ask to see what this looks like before agreeing to take part in the study. The way in which you complete this questionnaire is very important for us to say whether the study has been a success or not.

If at any time you decide you no longer want to take part in the study, you will be asked to return to the clinic for a final study visit.

FEMALE PATIENTS ONLY: Pregnancy and Contraception

With many treatments for cystic fibrosis, the benefits to the mother far outweigh the risks to the unborn child. However, the possible side effects of the study medicines are not known for certain in pregnant women. We feel it is best to minimize the possibility of the medicine causing any harm.

Because of this, if you are pregnant or breast-feeding, or if there is a real possibility of you becoming pregnant during the course of the study, you will not be able to participate. A urine sample at your first and at your last visit will be tested to ensure that you are not pregnant. If you are sexually active, your doctor will also check that you are using an effective method of



contraception whilst participating in the study. If you were to become pregnant during the study period, your doctor would withdraw you from the study.

Will travel and other expenses be reimbursed?

Costs of travel expenses for clinic visits and reasonable personal expenses (such as refreshments) will be reimbursed.

What are the alternatives for diagnosis or treatment?

There are other antibiotic treatments that are currently used in the treatment of lung infection with *Pseudomonas aeruginosa*. Your doctor will prescribe appropriate antibiotic treatment for you, if you do not want to take part in the study or if you want to withdraw earlier. However, there is currently no other antibiotic that can be inhaled as a dry powder. Using antibiotics other than Colomycin increases the risk that the bacteria causing the infection will develop resistance to the antibiotic (survive despite antibiotic use). Colomycin is somewhat different from other antibiotics in the way in which it 'attacks' bacteria and over the 40 years that Colomycin has been used, resistance levels remain extremely low.

Are there any side effects or disadvantages of taking part?

Like most medicines, both Tobir[®] and Colomycin powder can cause side effects in some people. During the study, you will be monitored very closely for any signs of side effects. As with any treatment, you should tell your doctor if you have any new symptoms or if any symptoms become worse.

Possible side effects of Colomycin

- Following inhalation of Colomycin through a nebuliser, patients have reported symptoms such as wheezing, chest tightness, shortness of breath, breathing difficulties, throat irritation, new cough/ increase in cough, chest tightness, chest pain.
- Patients in previous studies have reported that Colomycin powder causes similar symptoms. Following inhalation of Colomycin powder, some patients have experienced increased symptoms of cough and throat irritation compared to nebulised. Inhalation of the Colomycin powder is also associated with a mildly unpleasant taste.
- Most of the symptoms reported by patients are mild and do not last very long.
- When Colomycin has been given by injection (not the way of giving Colomycin in this study), there is the possibility of side effects such as dizziness, pins and needles or numbness. Following injections of Colomycin, kidney problems may occur in patients with existing kidney failure if too high doses are given or if it is given with certain other antibiotics. In almost all cases these injection-related problems will normally get better if treatment is stopped or the dose reduced.
- However, on the basis of about 20 years use of nebulised Colomycin, it is extremely unlikely that you will experience these injection related side effects during this study as we do not expect there to be much absorption of Colomycin from the lungs to the bloodstream.

Possible side effects of Tobir[®]

- Uncommonly patients have reported voice alteration (hoarseness), increased cough, shortness of breath and sore throat after inhaling this medicine.



- Rarely, patients may experience chest tightness or difficulty breathing, chest pain, pain, inflammation of the voice-box, ringing in the ears, mouth ulceration, rash, weakness, fever, headache, feeling sick, being sick, loss of appetite, dizziness, increased sputum quantities, coughing up blood, nose bleeds, runny nose and taste disturbances.
- Rarely, patients who have received Tobir[®] at the same time as, or following repeated courses of, injected tobramycin or related drugs have developed hearing loss. Injections of tobramycin or certain other antibiotics (aminoglycosides) have been associated with allergic reactions, hearing problems and kidney problems.
- Very rarely, patients may experience abdominal pain, ear pain, diarrhoea, back pain, fungal infections (e.g. thrush), swelling of lymph glands, sleepiness, hyperventilating, ear problems or sinusitis.
- People with cystic fibrosis experience many symptoms of the disease. These may still occur while taking Tobir[®], but should not be any more frequent or seem any worse than before. Patients have commonly reported symptoms such as sputum colour changes, chest infection, muscle pain, nasal polyps and ear infections whilst taking Tobir[®].

(Please note these details are also included in the patient information booklet contained in each box of Tobir[®]).

What to do if you experience breathing problems (wheezing, chest tightness for example) after taking your study medication

With both Tobir[®] and Colomycin powder, there is a possibility you may experience some side effects after inhaling the medicine. These include coughing, wheezing, shortness of breath, chest tightness, difficulty breathing and chest pain.

If you experience side effects like these after taking your study medication, you can take 1-2 puffs on your usual bronchodilator inhaler. If you need to take more than 8 puffs from your inhaler within 1 hour of taking study medication, you should contact your doctor. Your doctor will then decide whether you should carry on taking part in the study.

The particular treatment in the study may also involve risks to you which are currently unforeseeable.

Are there any benefits of taking part?

If you take part, you will have the chance to help us compare two different antibiotics used to treat *Pseudomonas aeruginosa* chest infections.

If the study proves successful, it may benefit you and other cystic fibrosis patients in the future since a different and new method of taking the antibiotic medication may become available.



What if new information becomes available?

Sometimes during the course of a research study, new information becomes available about the medicine that is being studied. If this happens, your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw, your doctor will make arrangements for your standard care to continue. If you decide to continue in the study you may be asked to sign an updated consent form.

Also, on receiving new information, your 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 care to continue.

What if something goes wrong?

In the event of something going wrong, the legally prescribed insurance cover has been arranged for this study.

[Section to be completed in the country specific PIS in accordance with country-specific requirements].

Will taking part be kept confidential?

We know that you would want your medical records to be kept confidential. By giving your consent to participate in the study you will also agree that certain officials [authorised representatives of the sponsor and the contract research organisation who are strictly bound to confidentiality (monitor, auditor), authorised representatives of Government Regulatory Authorities and of Ethics Committees] will look at your medical notes for purposes of analysing the results and to check that the study is being carried out correctly. All information which is collected about you during the course of research will have your name and address removed so that you cannot be recognised from it.

Your consent will also include permission for your GP (the doctor who normally is treating you) to be informed that you are taking part in the study.

What will happen to the results of the study?

The results of the study will be put together in a report. If this study shows that inhalation of Colomycin powder is both safe and successful in treating lungs infected with *Pseudomonas aeruginosa*, we hope to obtain marketing approval to make this new product available to all cystic fibrosis patients.

The results of the study may also be published in a journal. But you will not be identified in any way in any report or publication.

Who is organising and funding the research?

Your doctors will get a fee for conducting the research, but they will **not** profit from including you in this study.



Designing and organising the study has been, and will continue to be, a joint undertaking. The companies involved are the sponsor [Forest Laboratories UK Limited] which is responsible for the study, which is funding the project, and which sells Colomycin and a Contract Research Organisation [Chiltern International]. This company has employees who will be able to closely monitor and work on this study in countries throughout Europe.

Who has reviewed the study?

The study has been reviewed and approved by [in country specific translation insert name of the national regulatory authority] and further regulatory authorities in Europe and has been approved by centralised Ethics Committees and local Ethics Committees, in accordance with local regulations.

Who can I contact for further information?

Your doctor and his/ her staff are always available to answer any questions you may have in connection with this study.

Dr. [to be completed]

Telephone: [to be completed]

24 hour contact telephone number for use in case of emergency: [to be completed]

If you agree to take part in this study, you will receive a copy of the information sheet to keep and a signed copy of the consent form.

Thank you once again for reading this information



APPENDIX V**CONSENT FORM 1 (For Adults)**

Version 001; Dated 26/06/03

A RANDOMISED, OPEN LABEL STUDY TO COMPARE THE EFFICACY AND SAFETY OF A DRY POWDER FORMULATION OF INHALED COLISTIMETHATE SODIUM AND NEBULISED TNSFI (TOBRAMYCIN NEBULISER SOLUTION FOR INHALATION, TOBI®) IN CYSTIC FIBROSIS PATIENTS WITH PSEUDOMONAS AERUGINOSA LUNG INFECTION.**PROTOCOL NO: COLO/DPI/02/06**

Patient Number

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Patient Initials

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Parts A, B & C MUST be completed before the patient is entered into the study.**PART A**

1. Have you read the clinical trial information leaflet provided?
2. Has the nature and purpose of the study been explained to you?
3. Have you had the opportunity to ask questions and discuss the study?
4. Have you received satisfactory answers to your questions?
5. Have you received enough information about the study?
6. Have you had adequate time in which to decide whether to participate in the study?
7. Who has spoken to you about the study? Prof./Dr/Mr./Mrs./Ms _____

Please tick

YES

NO

☐☐☐☐☐☐☐☐☐☐☐☐☐☐**PART B**

1. Do you understand that participation in the study is voluntary and that you are free to withdraw at any time (you do not have to give a reason for withdrawing and it will not affect your future medical care)?
2. We know that you would want your medical records to be kept confidential. However, during the study it will be necessary for certain officials [i.e. authorised representatives of the sponsor and the contract research organisation (monitor, auditor), and of Government Regulatory Authorities, and of Ethics Committees] to look at your medical notes (these people understand the need for confidentiality). In addition to this, do you authorise your doctor to contact your GP to make known your participation in this study and to disclose details of your relevant medical and drug history, in confidence?
3. Do you understand that if you should suffer injury as a result of participating in this study the sponsor has arranged the legally prescribed insurance cover for this study?

Please tick

YES

NO

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PATIENT: I _____ hereby consent to take part in the above-titled study, the nature and purpose of which I understand.
(Patient's full name – in their own handwriting)

Signed: _____ Date: _____
(Patient's signature)

INVESTIGATOR: I hereby declare that I have discussed the above-titled study in accordance with GCP Guidelines. The patient has understood all the information he/she has been given and freely chooses to participate in this study.

Signed: _____ Date: _____
(Investigator's Signature)

Name (Print): _____

