Patient information for adults

Title of the study:

Prospective randomized, placebo-controlled, double blind, multicenter study (phase III) to evaluate clinical efficacy and safety of avian polyclonal anti-Pseudomonas antibodies (IgY) in prevention of recurrence of Pseudomonas aeruginosa infection in cystic fibrosis patients Study code: PsAer-IgY

Hospital or practice stamp:

Investigator:_____

Patient name (first name and surname): _____

Date of birth: _ _/_ _/_ _ _ _

Dear Patient

We would like to invite you to participate in a clinical study. A clinical study is carried out to obtain additional knowledge about a new medication or a new form of treatment. A clinical study is thus a part of clinical medical research. In the following pages we would like to inform you about the aims and course of the clinical study, to give you information about the study procedures and to explain why this study is so important. We ask that you carefully read this information and then decide yourself if you would like to take part in this clinical study. If you do decide to participate, you will receive an informed consent document. After you have reviewed the document with the cystic fibrosis doctor (known as the 'investigator' for the rest of the patient information), please sign it.

You can of course decide not to participate in the study. Even if you do decide to participate in the study now, you have the right to end your participation at any time during the study without having to provide any reasons and without incurring any penalties.

However you decide your decision will not have any effect on your future medical care. If you decide to end your participation during the course of the study, please inform the responsible investigator promptly. You will then be asked to attend some follow-up appointments. These are important to prevent the results of the study being compromised. Of course, your investigator is available to answer any other questions you may have. Thank you for your interest!

The following text is intended to explain the goals and course of the study. An investigator will then review the information with you. Please do not hesitate to discuss any points that are not clear to you. You will then be given enough time to consider your decision about your participation.

Introduction

The clinical study named above will be carried out in accordance with the rules of the World Medical Association, the Declaration of Helsinki and in accordance with the relevant local laws and guidelines. In Ireland the study will be evaluated by the Irish Medicines Board (IMB) and the Clinical Resaerch Ethics Committee of the Cork Teaching Hospitals.

Aim of the study

Patients with cystic fibrosis are at risk of developing a respiratory tract and lung infection caused by the bacterium *Pseudomonas aeruginosa* (known in the following as *Pseudomonas*). This bacterium can lead to deterioration in the course of the cystic fibrosis. *Pseudomonas* bacteria can often be detected in the respiratory tract as early as preschool age. This early infection was previously treated with antibiotic tablets and an additional inhaled antibiotic. In many cases *Pseudomonas* can be kept out of the respiratory tract for a certain period. However, the probability is high, that *Pseudomonas* reinfects the respiratory tract. Over time there is the risk that these bacteria become resistant to various antibiotics and become established permanently in the lungs and respiratory tract. This is then referred to a chronic *Pseudomonas* infection. The bacteria can no longer be removed completely from the respiratory tract; only the number of bacteria can be reduced. It is therefore important to keep the lungs and respiratory tract free from *Pseudomonas* for as long as possible.

The study medication, Immunoglobulin Y (IgY) is an antibody against *Pseudomonas* produced from eggs. Antibodies are proteins that are formed as a response to certain substances. Antibodies form part of the immune system. The IgY antibody is intended to form a barrier against *Pseudomonas* bacteria. The aim of this study is therefore to test if IgY can delay reinfection with these bacteria. Previous studies with small patient numbers indicated that IgY did has potential to do this. In the current study the efficacy of IgY will be investigated in a larger number of patients with cystic fibrosis.

Information about the study design:

This study is financed as part of the EU FP7 programme (enacted on 19 November 2009).

The sponsor is Mukoviszidose Institut gGmbH, Bonn. According to the guidelines for Good Clinical Practice, the sponsor of a clinical study is a person, a company, an institution or an organisation that is responsible for the initiation, management and/or financing of a clinical study.

The study medication is manufactured by Cobra Biologics (Sweden) in accordance with the currently valid manufacturing standards.
One hundred and eighty patients from different countries in Europe in various cystic fibrosis study centres will participate in the study.

Each patient will participate in the study until *Pseudomonas* is again detected in the patient's sputum/throat cough swab or endolaryngeal suction. The maximal duration of the study during which the patient is administered the study medication is limited to 2 years for each patient. If possible, patients will not need to attend any additional outpatient appointments for the study but rather the examinations needed for the study will be carried out during the normal quarterly outpatient visits.

Randomisation (random allocation)

In the further course of the study, you will be allocated (randomised) to one study arm (active ingredient or placebo). One group of the study participants will receive a solution with IgY (active ingredient) and another group will receive a similar solution without IgY (placebo). In the following patient information, the term 'study medication' means both IgY and the placebo.

The study participants will be randomly distributed into one of the two groups. This is necessary to be able to objectively compare the groups with one another and to be able to draw conclusions about the efficacy of the IgY. Neither you nor your doctor can influence or know which study arm you will be included in (double-blind study). You may only have this information at the end of the study. If during the study there is an urgent reason to remove this blinding, your investigator has an envelope in which it is documented in which study arm you were included. This envelope must only be opened in such an emergency and in consultation with the sponsor, the Mukoviszidose Institut gGmbH.

Which reactions can occur during the course of the study?

For the participants who receive the placebo it is likely that nothing will change. For the group who receives IgY, it is expected that reinfection with *Pseudomonas* will be delayed.

If *Pseudomonas* is detected in the course of the study in the sputum/throat cough swab or endolaryngeal suction, patients in either group will be treated using approved methods (antibiotics) in accordance with the decisions of your doctors. Your participation in the study is ended with a reinfection.

The antibody/the medication

Manufacture:
IgY is, as described above, an antibody that is specifically active against *Pseudomonas*. It is obtained from the egg yolk of chicken eggs. To obtain these antibodies, hens are inoculated with the weakened bacterium (active immunisation). As a result the hens develop antibodies to the pathogen and these antibodies are also found in the eggs. These antibodies are purified from the egg yolk using a special washing method. Only normal water is needed for this method. The solution obtained is used as a medication for gargling. Generally, all eggs that we eat contain IgY antibodies but because of the active immunisation, the hens form specific IgY antibodies that are active against *Pseudomonas*.

Use:
You should gargle the study medication every evening after brushing your teeth. After gargling, you must not eat or drink until the next morning. Please gargle with the solution for at least two minutes and then swallow it afterwards. You can divide the contents of the bottle into a number of portions and gargle each one.

IgY is stored in the freezer. Each day (in the morning) a bottle is thawed for use in the evening.

As an exception, it is possible to thaw and refreeze the unopened bottle up to two times. The solution can be kept in the refrigerator in the closed bottle for one week once thawed. Any exceptions should be discussed carefully between patient and investigator in advance.

The solution can be kept at room temperature for 2 days. Once the bottle is opened the solution must be used within 2 hours. Please follow the instructions in the enclosed package insert when using the solution!

If you have difficulties with gargling or swallowing the solution, please contact your doctor or the responsible study nurse.

Interactions:

All medications that you usually need or that you may need during the study are allowed. You should not, however, take any antibiotics that are active against *Pseudomonas* or other similar (Gram negative) bacteria before such an infection is confirmed by detection in sputum/throat cough swabs or endolaryngeal suction. Please inform the doctor about any medications you are currently taking and about any changes in your medication (see 'Documentation').

Side effects:
The risk of any negative side effects is low. If you suffer from an allergy to chicken eggs, however, you cannot participate in this study. It is essential in all cases that you inform your doctor about any suspicious reaction or any unusual symptom.

Pregnancy:
According to current knowledge, the active substance of the study medication is not absorbed. Therefore, the risk for mother and child during pregnancy is considered low. However, since no experience is available in this regard, pregnant women should not participate in the study. All female participants who are older than 10 years of age and have secondary sexual characteristics must carry out a pregnancy test using a urine sample. The investigator will decide if you have to carry out this test. The test is carried out in the outpatient clinic. Pregnancy during the study period should be avoided and the responsible investigator must be immediately informed should you become pregnant. Your investigator will be happy to advise you regarding contraception options.

Documentation:
So that we are able to confirm that you have taken the study medication, it is necessary that you bring all used, partly used and unused bottles with you to your appointments in the cystic fibrosis outpatient clinic. Please do not throw away any of the bottles!

You will receive a diary. In this diary please enter the following:

- Gargling and swallowing of the daily study medication (IgY/placebo)
- Any change in your medication, particularly if you took any antibiotics
- Visits to the cystic fibrosis outpatient clinic or hospital in addition to the standard appointments
- Any unusual reaction
- Any suspicious symptom

In case of doubt, suspicious reactions or symptoms should be reported to the contact address of the study centre or the investigator as well.

Course of the study

If you decide to take part in the study you will be ordered for an outpatient visit for inclusion into the study. The investigator must confirm that you satisfy the inclusion and exclusion criteria of the study. You will have a blood draw and another sputum sample, throat cough swab or endolaryngeal suction taken. A central laboratory will

examine these samples to confirm that your lungs and respiratory tract are currently not infected with the *Pseudomonas* bacterium. You can only be included in the treatment phase of the study if no *Pseudomonas* is found and if infection with the bacterium is not suspected on the basis of the blood draw.
The further appointments that are necessary for the study should coincide as much as possible with your normal outpatient appointments. They will take place every three months in line with these appointments. At each of these appointments you will undergo a physical examination and a lung function test.

Sputum sample, throat cough swab, endolaryngeal suction
All outpatient appointments will include a sputum sample or throat cough swab/ endolaryngeal suction if a sputum sample is not possible. These samples are sent to the local laboratory of your cystic fibrosis outpatient clinic to be examined for *Pseudomonas* bacteria. In addition, three samples are normally sent to Copenhagen during the course of the study: The first sample at the screening into the study, the second after one year, and the third at the end of the study. Should your health significantly deteriorate during the study or should you not have used the study medication in the manner prescribed, you will be scheduled for an additional outpatient appointment during which an additional sample will be taken and sent to Copenhagen. Should the local laboratory detect *Pseudomonas* during the study, the laboratory will send a culture of the detected microbe to the central laboratory. In Copenhagen, the samples are also tested for *Pseudomonas*.

Blood draws:
The studies normally require three blood draws: The first takes place during the pre-inclusion visit, the second after one year, and the third at the regular conclusion of your study participation after two years. A fourth draw is only required if infection with the *Pseudomonas* bacterium is suspected before conclusion. The second and third blood draws should be performed with your regular annual blood draw. For the study, 2 ml of whole blood are required. The samples are sent to the central laboratory in Copenhagen. There, they are examined for serum antibodies against *Pseudomonas*. Half of the submitted 1 ml serum will be stored in Copenhagen until the end of the study and then sent to the laboratory of Uppsala University when all study participants have completed the study. In this laboratory, all samples are tested using a particularly sensitive procedure for the so-called C-reactive protein (CRP) and for antibodies against the study medication IgY. CRP plays an important role in the human immune system. For instance, it recognises bacteria and initiates the body's defence mechanisms in concert with other proteins. Therefore, it is an important inflammatory marker.

Can the samples be linked to the participants, and what happens with the sample remnants?
The blood and secretion samples are sent pseudonymised with a patient code. Only your investigator has this code, so that the laboratories cannot make any inferences about you personally.

The sample remnants are destroyed after the tests described above are completed. Should you decide to leave the study before completion, the existing samples are tested as described, and any remnants are then destroyed.

Additional tests are only done if there has been a serious deterioration in your state of health. The time needed for each visit is expected to be 45 minutes with the doctor/study nurse and a further 45 minutes for the lung function test. The treatment phase of the study lasts for no more than 2 years for each patient.

Once a month, you will be called by the study nurse of your cystic fibrosis outpatient clinic and surveyed about your use of the study medication. If this survey reveals indications of a possible reinfection with *Pseudomonas*, the study nurse will make an appointment for you to visit the outpatient clinic to take an additional sputum sample or throat cough swab or endolaryngeal suction.

If you are being treated by other doctors, particularly your general practitioner or lung specialist, you must inform them about your participation in the clinical study. Likewise, your investigator must be informed about any medical treatment administered to you by any other doctor during the clinical study. In the consent and data protection forms, you can give or deny consent to the investigator informing your general practitioner or lung specialist.

What do you have to watch out for when participating in the study?

During the study, study participants should not sleep in the same room as other people with cystic fibrosis (apart from siblings). Patients who want to travel during the study should discuss this in detail with their doctor before travelling.

What benefits does participation in the study have for you?

If you are randomised in the active ingredient group and therefore gargle the IgY antibody, you will receive a medication that we expect will delay reinfection with the *Pseudomonas aeruginosa* bacterium. The advantage to you is that you will be sick less often and will need fewer antibiotics.

The group that receives the placebo will not have a personal benefit. These participants help to check the efficacy of the IgY and to verify it if necessary. This is possible so that, if the efficacy has been proven, the medication can be placed quickly on the market. We expect to be able to better help CF patients in the near future in this way.

Will there be costs associated with the study for you?

There will be no costs for participants in the study. Any additional examinations during the normal outpatient appointments and the study medication are free of

charge. You will receive a 30 € allowance for the inclusion visit and for possible additional study visits.
The study medication must be stored frozen. At the start of the study you will receive seven packages with 15 bottles which each contain 70 ml of solution with the IgY antibody or the placebo. Every three months after this you will again receive six packages with the appropriate quantity. You will find the exact instructions for taking the study medication on the package insert that is enclosed in each package. In case you do not have a freezer or your freezer does not have enough room, we will provide you with a freezer. In this case your doctor or the responsible study nurse will manage the order of a freezer by mail-order business. You may keep the freezer after the end of the study.

Voluntary participation, right to refuse treatment and withdrawal of informed consent

Participation in this clinical study is voluntary. Your consent can be withdrawn at any time and without the need to give any reasons. If you do withdraw your consent, this will not have any consequences for your future medical care.
The use of pseudonymised data already collected before your withdrawal cannot be withdrawn to ensure that the correctness of the study evaluation is not compromised. It will, however, be checked which data are required for this. Pseudonymised means data are not used with names or initials but only a number and/or a letter code, possibly with the addition of your year of birth. Only your investigator has access to this code. The remaining data collected about your disease as part of the study will be immediately deleted after your withdrawal from the study.
Your participation can also be ended by the treating doctor, by the sponsor of the study (study management/sponsor or protocol committee) or by a regulatory authority (e.g., the Irish Medicines Board). The study can be cancelled completely for safety reasons, for example. Some patients must end their participation in the study because they have not followed the instructions of the doctor or to protect the patient. This can be done without the consent of the participant.

Contacting the investigator

If you should have any questions during the clinical study, you can contact the following person(s) at any time (please insert name)

_____ phone number _____/_____

The following number is for emergencies: _____/_____

If you have any questions, you can contact the principal investigator of the study at any time:
Professor Antje Schuster, MD:

Address:
Department of Paediatrics,
Heinrich-Heine-University of Duesseldorf,
Phone: +49 / 0 211 / 811-8297
Fax: +49/ (0) 211 / 811-6539
Email: Schuster@med.uni-duesseldorf.de

Insurance

In accordance with the S.I. 190 (2004), the Irish law for Clinical Trials, all participants in a clinical study on a drug are insured. The scope of the coverage is defined in the insurance documents you will receive. Should you suspect that your participation in the clinical study adversely affected your health or worsened existing illnesses, you must immediately directly notify the insurer:

Name and address of insurer:

Great Lakes Reinsurance (UK) PLC

Plantation Place
30 Ferrchurch Street
London EC3M 3AJ

A subsidiary of: Munich RE
Contact details: Dr Volker Kraus
Phone: +49 89 3 891 5752
Munich Re Group
Am Münchner Tor 1
80805 Munich

Insurance no.: DE 100-01-11

to avoid jeopardising your coverage. If necessary, ask your investigator to assist you in this process. Should you receive assistance from your investigator, you will receive a copy of the notification. Should you directly notify the insurer, please also inform your investigator.
You must collaborate in the clarification of the cause or extent of any injury and you must take any measures necessary to prevent or minimise the injury.

For the duration of the clinical study, prior consultation of the investigator is required for any medical treatment – with the exception of emergencies. You must inform the investigator immediately after any emergency treatments.

You will receive a copy of the insurance confirmation, including the terms and conditions of insurance. *Please particularly note section 1.4 (on exclusions), section 3.1 (on the scope of benefits) and sections 4.3 and 4.4 (on your obligations).*

Please also note that the insurance provides no accident coverage for your travel to and from the study centre.

Will you be informed about new information during the clinical study?

You will be informed about any new information concerning this clinical study that becomes known and that may be crucial for your willingness to participate further. You may reconsider your decision to continue participating in this clinical study based on this information.

Confidentiality, data protection and transfer of data

We would like to ask for your consent to the data about your treatment being documented and scientifically evaluated. The data are stored in the study centre for 10 years. The medical files are confidential. Neither your name nor personal information is used in scientific publications, meaning no inferences can be made about you or your disease.
All persons who care for you as part of this clinical study are bound by medical confidentiality and are also bound by the German data protection/data privacy act. The results of examinations carried out as part of the study are kept in the case report forms (CRF) developed for the study. They are used in pseudonymised form for scientific publications.

Note

As required by law, this clinical study was checked by the responsible ethics committee and approved.

Who do I ask if I have other questions?

Consultations at the study centre
You always have the opportunity to have an additional consultation with the investigator named on page 1 or with another investigator.
Contacts
You can also contact the Irish Medicines Board. Participants in clinical studies, their legal representatives or proxies can contact the following:

Irish Medicines Board
Kevin O'Malley House,
Earlsfort Centre,
Earlsfort Terrace,
Dublin 2
Tel: 01-6764971/ 01-6764976

Email: imb@imb.ie

I acknowledge with my signature that I have been informed in an interview with the investigator about the PsAer-IgY study.
I have read and understood the Patient information. All questions have been answered by the investigator.

I have kept a copy of the patient information, the informed consent form and the insurance conditions. A copy remains in the study centre.

Patient's name in block letters

Date Signature of the **patient**

I conducted the explanatory consultation and have obtained the consent of the guardians and the patient.

Investigator's name in block letters

Date Signature of **investigator** providing the explanation