SUBJECT INFORMATION FORM AND INFORMED CONSENT FORM

Study Title: A Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study Investigating the Optimal Dose Regimen, Efficacy, and Safety of Adding Oral Cysteamine in Adult Patients with Cystic Fibrosis (CF) Being Treated for an Exacerbation of CF-associated Lung Disease

Protocol Number: NBTCS02
EudraCT Number: 2011-002750-31
Sponsor: NovaBiotics, Ltd.

Principal Investigator: **Insert**
Address: **Insert**
Telephone: **Insert**
Emergency Telephone: **Insert**

Subject Initials:
Subject Number:

Introduction

Dear _____,

We would like to invite you to take part in a research study into Cystic Fibrosis (CF). You have received this letter because you have CF and you are either currently experiencing an acute worsening (exacerbation) of your CF, or you are well but you may have an exacerbation of your CF in the future.

Before you decide to take part in this research study, it is important for you to understand why the study is being done and what it involves. Please take your time to read the following information carefully and discuss it with relatives, friends, and your doctor(s) if you wish. If there is anything that is not clear or if you would like more information, please ask the study doctor. Ask the study doctor as many questions as you want until all your questions have been answered. Take your time to decide whether or not you wish to take part in this study.

This study has been designed by NovaBiotics, Ltd. and is being carried out by chest doctors at various hospitals in the United States of America and Europe. NovaBiotics, Ltd. is paying for the costs of this study and is also referred to as the sponsor. About 120 subjects from different countries will participate in the study. XX patients will take part in the study in your country.

1. Purpose of the study

As you know, people with CF have problems with thick sticky mucus and chest infections. At the moment there is a limited range of antibiotics that we can use, and the bugs in the sputum are often resistant.

Recently NovaBiotics Ltd has discovered that a drug called cysteamine could possibly help in the treatment of exacerbations of CF. Cysteamine has been used for over 20 years to treat a rare genetic condition called cystinosis that damages the kidneys. What has been discovered is that cysteamine may make mucus thinner so that it is easier to cough up sputum and clear the lungs. Cysteamine has also been shown to be an antibiotic and it may also make existing antibiotic treatments for CF work better.

The purpose of this study is to identify the best dose of cysteamine to add to standard antibiotic treatment when people with CF have an exacerbation. To do this the effects of five different doses of cysteamine will be compared to the effects of a placebo. The study treatment (cysteamine or placebo) is always in addition to antibiotic treatments chosen by your doctor to treat your exacerbation.

The study is also aiming to identify which is the best symptom questionnaire to use in future studies of exacerbations of CF. To do this, the answers to several symptom questionnaires will be analysed to see which questionnaire is the most sensitive in detecting changes in symptoms.

2. Do I have to take part?

You do not have to take part. Taking part in the study is voluntary. This means you may choose to take part or not and your decision will not affect the medical care you receive. You do not need to provide a reason for your decision. If you decide not to take part, it will not cause any penalty or loss of benefits to which you are otherwise entitled. If you decide to take part in this research study, you need to sign and date this document. We will give you a copy of the Patient Information Sheet and Informed Consent Form to keep.

3. What will happen to me if I take part?

This is a randomized, double-blind, parallel group, placebo-controlled study. “Randomized” means that the treatment (cysteamine or placebo) you will get will be determined by chance (like tossing a coin) by a computer. “Double-blind” means that neither you nor your study doctor will know what treatment you will be receiving. “Parallel Group” means that the treatment will be given to the separate groups at the same time. “Placebo-controlled” means that some of the patients in the study will receive a placebo, which is medication that does not contain active drug. Placebo and the investigational drug will be called “study drugs”. You will receive your standard treatment for your exacerbation that your doctor prescribes regardless of whether you are randomized to receive placebo or study drug.

If you meet all entry criteria you may take part in the study. Your involvement will last at least 3 weeks (from Baseline/Day 0) and you will be required to come to the hospital for examinations (assessments) and tests every week (Screening/Baseline, Day 7, Day 14, Day 21).

Screening

We will first see if you meet all of the entry criteria. To do this we will measure your weight, height, blood pressure and heart rate. We will also ask you about your medical history and previous exacerbations (chest infections).

Baseline/Day 0

The baseline/Day 0 visit will take place on the day your doctor determines that you have an exacerbation of your CF that needs treatment with a course of antibiotics. Taking part in the study will not change the treatments chosen by your doctor.

We will do the following during the baseline (Day 0) visit:

1) check entry criteria again
2) randomly assign to either cysteamine or placebo
3) perform a physical examination
4) measure your weight, blood pressure and heart rate
5) measure your lung function by blowing tests in the same way you were used to in the past
6) take 7ml (1-2 teaspoons) of blood from a vein in your arm
7) test a urine sample (8ml, 1-2 teaspoons) that we will ask you to provide
8) test a sputum sample that we will ask you to provide in the same way you provided it in the past
9) ask you to complete three different symptom questionnaires
10) if you are a woman of childbearing potential we will do a urine pregnancy test
11) give you the study drug and the instructions on how to use it.

If the screening and baseline visits cannot be done on the same day, the entry criteria and you weight, blood pressure and heart rate will need to be repeated at the Baseline visit.

Day 7

On the 7th day after your baseline (day 0) visit, we will

1) measure your weight, blood pressure and heart rate
2) measure your lung function by blowing tests in the same way you were used to in the past
3) take 7ml (1-2 teaspoons) of blood from a vein in your arm
4) test a urine sample (8ml, 1-2 teaspoons) that we will ask you to provide
5) test a sputum sample that we will ask you to provide in the same way you provided it in the past
6) ask you to complete three different symptom questionnaires

7) ask you to return all packaging of your used medication and the unused study medication to the clinic. The site staff will give the unused medication back to you before you leave the clinic.

Day 14

On the 14th day after your baseline (day 0) visit, we will

1) measure your weight, blood pressure and heart rate
2) measure your lung function by blowing tests in the same way you were used to in the past
3) take 14ml (2-3 teaspoons) of blood from a vein in your arm
4) test a urine sample (8ml, 1-2 teaspoons) that we will ask you to provide
5) test a sputum sample that we will ask you to provide in the same way you provided it in the past
6) ask you to complete three different symptom questionnaires
7) ask you to complete an additional questionnaire about how you are feeling compared to how you felt after previous exacerbations.
8) ask you to return all packaging of your used medication and the unused study medication. The site staff will keep this at the clinic.

Day 21

On the 21st day after your baseline (day 0) visit, we will:

1) perform a physical examination
2) measure your weight, blood pressure and heart rate
3) measure your lung function by blowing tests in the same way you were used to in the past
4) take 7ml (1-2 teaspoons) of blood from a vein in your arm
5) test a urine sample (8ml, 1-2 teaspoons) that we will ask you to provide
6) test a sputum sample that we will ask you to provide in the same way you were used to in the past
7) ask you to complete three different symptom questionnaires
8) if you are a woman of childbearing potential we will do a urine pregnancy test.

Treatments

In addition to the standard (antibiotic) treatment which you will receive for your current exacerbation, you will receive study medication for two (2) weeks. The study medication will be in the form of capsules and you will be asked to take three (3) capsules three (3) times a day.

To make sure that the cysteamine and placebo are spread equally across the treatment groups, each person taking part in the study will be put into one of six groups selected randomly by a computer. One group will receive 150mg cysteamine once per day (along with

two doses of placebo per day), the second group will receive 450mg cysteamine twice per day (along with one dose of placebo per day), the third group will receive 450 mg cysteamine three times per day (no placebo), the fourth group will receive placebo three times per day, the fifth group will receive 150 mg cysteamine three times per day (along with placebo at each dose) and the sixth group will receive 300 mg cysteamine three times a day (along with placebo at each dose).

You have an equal chance (17%) of being assigned to each of the six treatment groups. The dose of cysteamine is less than that recommended for use in people with cystinosis. Neither you nor the investigator will know which group you are in. This can be found out immediately if this is important for your health.

4. What is expected of you

In order to carry out the study properly and for your own safety, it is important that you follow the study instructions. The study instructions require that you:

- take the study medication as instructed
- do not participate in another medical study for which you take medication
- attend all study visits
- bring all study medication (including empty medication packages) to the clinic on Day 7 and Day 14 for review
- carry your participant card for the study with you at all times. This card states that you are taking part in this study. It also states whom to contact in the event of a medical emergency. Show this card if you visit any other doctor.

It is important that you contact the investigator:

- before you start using other medicines or if the dose is changed. Even if they are homeopathic or natural remedies, vitamins and/or medicines that you can buy at stores.
- if you are admitted to hospital or are going for treatment there
- if you suddenly develop any health problems
- if you no longer want to take part in the study
- if your contact details change.

Pregnancy

Women who are pregnant or breast-feeding cannot take part in this study. Women and female partners of men participating in the study must not get pregnant during the study.

If you are a woman of childbearing potential (not surgically sterile for at least 6 months or postmenopausal for at least 1 year) or a man with a female partner of childbearing potential you must use a medically accepted method of contraception. If you are a woman you must continue use of this method of contraception for the duration of the study and for 30 days

after the last dose. If you are a man you must agree to this for the duration of the study and until 90 days after the last dose.
Acceptable methods of contraception for men and women include abstinence, barrier method (condom or diaphragm) with spermicide, intrauterine device (IUD), vasectomy (at least 6 months ago), bilateral tubal occlusion, or hormonal contraceptive (oral, transdermal, implanted, injected) in conjunction with a barrier.
Men are not permitted to donate sperm from first study drug dose until 90 days after dosing.

This is because the study medication may have consequences for an unborn child. The consequences are not known. The investigator will talk to you about the most suitable contraceptives. If you or if you are a man, your female partner, still become(s) pregnant during the study, you must immediately tell the investigator and if you are a woman participating, stop study treatment. In both cases, the pregnancy will be monitored closely and reported to the sponsor of this study.

5. Possible side effects or discomforts

The study medicine may have side effects. The most common events are nausea, vomiting, stomach pain, loss of appetite, fever, diarrhea, loss of energy, tiredness, headache and rash. Cysteamine has occasionally been associated with reversible leukopenia (a reduction in the number of white cells in your blood) and abnormal liver function in cystinosis patients.
You may experience some discomfort when taking part in this study. The study medication may cause a non-pleasant body odor (including bad breath).

It may be necessary to induce a sputum sample if you are not able to produce a sputum sample so that we can test for bacteria. The most common methods for sputum induction are a non-invasive procedure using an ultrasonic nebulizer or with the assistance of a physiotherapist.

Even though cysteamine has been used for other conditions for 20 years it may have side effects in CF that are unknown.

Please report any side effects you may experience to the investigator.

Blood Tests

In total, we will take 35ml (10 teaspoons) of blood from you over the course of the study. The risks of taking the blood samples include temporary discomfort from the needle in your arm, bruising, swelling at the needle site and, in rare instances, dizziness, fainting or infection.

6. Possible advantages and disadvantages

It is possible that you will receive little or no benefit from taking part in this study and your exacerbation may not change or may get worse. The study medication plus antibiotic treatment may resolve your infection and/or relieve your symptoms quicker and more

effectively than antibiotic treatment alone, but this is not certain. The information gained in this study may be useful in helping people with CF in the future.

Disadvantages of taking part in the study may be:

- The additional time it will take for you;
- Additional tests and questionnaires;
- Instructions you need to follow (e.g. when to take the study medication);
- Possible side effects.

All these aspects have been described above under points 3, 4 and 5.

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

If you do decide to take part in the study, you can always change your mind. You are free to withdraw at any time during the study and without giving a reason. You will then be treated as usual for your exacerbation. You do need to tell the investigator immediately that you wish to stop.

The data collected until that time will still be used for the study.

If there is any new information about the study that is important for you, the investigator will let you know. You will then be asked whether you still want to carry on taking part.

8. End of the study

Your participation in the study stops when:

- you have completed all the visits according to the schedule as described under point 3
- you choose to stop
- you become pregnant
- the investigator considers it best for you to stop, regardless of your consent
- the ethics committee, government or NovaBiotics, Ltd. decides to stop the study.

The study is concluded once all the participants have completed the study. The investigator will discuss the options for further medical care with you.

After processing the data, the investigator will inform you about the most important results of the study. The investigator will also tell you which study treatment you had. If you do not want this to happen, please tell the investigator. He/she will then not tell you.

9. Usage and storage of your data and bodily material

For this study it is necessary to collect and use your blood, urine and sputum plus your medical and personal data. Each person taking part will receive an anonymous identification code that will be attached to the laboratory samples and the other collected data. Your name will be deleted so that you cannot be identified.

Your data

All your data will remain confidential. The investigator and the sponsor NovaBiotics, Ltd. (represented by a Clinical Research Organisation named (*[PSR and Agility]*) are the only

people who will know about your participation. We will share your data with the sponsor of the study for analysis, but we will only using the anonymous code, never your name. The key to the code will stay with the local investigator. In the reports about the study only this code will be used. Some people may access your medical and personal data. This is to check whether the study is done properly and that the information is reliable. General information about this can be found in the general brochure on medical research. People who may access your data are: the study team, the sponsor, the safety committee supervising the study, a monitor working for *[PSR or Agility]*, the *[Healthcare Inspectorate (or local Healthcare Authorities)]* or an Auditor appointed by the sponsor. They will also keep your data confidential. If you sign the consent form, you consent to having your medical and personal data collected, stored and accessed.

The investigator will store your data for 15 years. The sponsor of the study will receive a copy of the data without your name and will store the data for 25 years.

Your bodily material

Blood and urine samples will be analysed at a central laboratory for routine safety assessments. Blood and urine samples will be destroyed once the final study report of the study has been written.

Sputum samples will be tested by the central laboratory to assess if there is bacteria present and if so, which kind and how many. The sputum samples may be frozen and stored. Your stored samples may be used by the sponsor for gaining information about your illness. Your samples will have an unique code, but not your name or other information that could identify you. At the end of this study, these samples may be kept in storage by NovaBiotics for a period up to 15 years.

If you do not want your sputum samples to be kept until after the study, please tell your study team and check the appropriate box in the Informed Consent Form at the end of this document. You will still be able to take part in this study even if you do not want your samples to be stored.

This study is listed in a clinical trial registry to be found on the website http://www.ClinicalTrials.gov. This website does not contain any information that can identify you. The website may contain a summary of the results. You can find this study under reference *NBTCS02*.

10. What will happen to the results of the research study?

The results of the study will used by Novabiotics Ltd to further develop cysteamine for use in people with CF. The results be published in scientific journals and presented at scientific meetings. We will also send you a summary of the findings.

11. Study subject insurance

If you believe that you have been harmed in any way by taking part in this study, you have the right to pursue a complaint and seek compensation through the research sponsors of the study (NovaBiotics Ltd).

Insurance has been taken out for everyone participating in this study. The insurance covers damage due to participation in the study. This applies to damage manifesting during the study or within four years of the end of the study. You must notify the insurance company about the damage within those four years.

The insurance does not cover all damages. The damages that are not covered are listed briefly at the end of this text.

In the event of damage please contact the insurance company [or claims adjustor] directly. *<also indicate here how the study subject must act/report damage: by telephone/e-mail/post, other instructions?>*

The insurance company for the study is: Name: … Address: … Telephone number: … E-mail: … (Policy number: ...) (Contact person: …)

<include only if there is a claims adjustor - this is compulsory if the insurance company is located outside of [country] The claims adjustor for the study is: Name: … Address: … E-mail: Telephone number: …

The insurance offers a cover of <copy policy amount, this must be at least €650,000> per study subject and <copy policy amount, this must be at least €5,000,000> for the entire study (and <copy policy amount, this must be at least €7,500,000> annually for all studies from the same sponsor).

The insurance policy does **not** cover the following damage:

- damage as a result of a risk that you were informed about in the written information. This does not apply if the risk occurs in a more severe form than envisaged, or if the risk was very unlikely to occur;
- damage to your health that would also have occurred if you had not participated in the study;
- damage resulting from not or not entirely following directions or instructions;

- damage to descendants as a result of a negative effect of the study on you or your descendants;
- damage as a result of an existing treatment method for research into existing methods of treatment.

12. Will my primary care physician or general practitioner be informed if I take part?

If you decide to take part and if you agree, your general practitioner will be informed about your participation in the study. Please inform the study team if you do not want your general practitioner to be informed, or if you want another doctor to be informed about your participation in the study and check the appropriate box in the Informed Consent Form at the end of this document.

13. Compensation for participation

The study medication, additional tests and treatment for the study are free of charge for you. You will receive an expense allowance of *[€ amount]* per visit for your participation in this study and a reimbursement of your travel cost (*[€ amount/km]* plus *[€ amount]* *[other costs (e.g. parking)]*. This reimbursement should be communicated to the Tax Authorities as income. If you stop before the study is completed, you will receive a smaller amount.

14. Who has reviewed the study?

The study has been reviewed by an NHS Research Ethics Committee, which has responsibility for scrutinising proposals for medical research on humans. In this case, the reviewing committee was < details EC>, who have raised no objections to the study.

In addition, the study has also been reviewed and approved by the Medicines and Healthcare Products Regulatory Agency. The <hospital department/other reviewers> has also reviewed and approved the study.

15. Any questions?

The study doctor is the person in charge of this study. You can call him/her at the phone number(s) listed in this consent form. You can also call the study staff with questions about this research study. Ask questions as often as you want. If you have questions about the scheduling of appointments or study visits, also call the study staff at the phone number(s) listed below.

[Investigator]: [for principal investigator of centre: name, contact details and times of availability]

[Study nurse/study doctor/study Staff]: [optional for a second person to contact: name, contact details and times of availability]

If you want to speak with someone not directly involved in this study, please contact at , or at .

You can talk to them about:

- your rights as a research subject
- your concerns about the research
- a complaint about the research

Independent [doctor/expert]: [name, type of doctor/expert, contact details and times of availability]

Complaints: [department or person with contact details and times of availability]

<if applicable, add the contact details of e.g. coordinating investigator and/or emergency number/24-hour number>

Thank you for taking the time to read this information leaflet

Subject Consent Form

Study Title: A Randomized, Double-Blind, Parallel Group, Placebo-Controlled Study Investigating the Optimal Dose Regimen, Efficacy, and Safety of Adding Oral Cysteamine in Adult Patients with Cystic Fibrosis (CF) Being Treated for an Exacerbation of CF-associated Lung Disease

Protocol Number: NBTCS02
EudraCT Number: 2011-002750-31
Sponsor: NovaBiotics, Ltd.

Principal Investigator: **Insert**
Address: **Insert**
Telephone: **Insert**
Emergency Telephone: **Insert**

Subject Initials:
Subject Number:

SUBJECT AGREEMENT

Please initial the boxes if you agree:

1. The study, as well as the risks and possible benefits, have been explained to me in detail, and I have had a chance to ask any question I had and all my questions have been answered to my satisfaction. ☐

2. I have read and understood this Patient Information Sheet **(Version number___, date___/___/___).** and Informed Consent Form. I will receive an original copy of this signed and dated informed consent form. My study doctor keeps the other original copy. ☐

3. By signing this document I freely volunteer to take part in this study and confirm that I am aware of the conditions of participation and withdrawal. ☐

4. I agree to strictly cooperate with the study doctor and study staff and follow their instructions. ☐

5. **I agree to share my information as described in this form.** I agree that personal data obtained in connection with this study may be recorded and transferred to NovaBiotics, Ltd. and its national and international representatives in anonymous form (i.e. without referring to my name) for scientific analysis. These data may also be shown to representatives of the sponsor, of relevant authorities or of Ethics Committees to allow examination ☐

of proper conduct of the study. The data may also be transferred to other countries. I am also aware that standards of data protection may differ in these countries.

6. I understand that the results of this study may be published or sent to the responsible authority in those countries where the drug is to be registered and approved for marketing. ☐

7. **I authorise the direct access** to my personal medical files for specialists commissioned by NovaBiotics, Ltd., by Ethics Committees or by national and international regulatory authorities responsible for clinical studies oversee. ☐

8. **I give permission for my sputum samples to be stored for futher analyses by the sponsor after the study has ended.**

YES	NO

9. **I give permission for my general practitioner to be informed of my participation in the study.**

YES	NO

If YES please provide name and contact details of your general practitioner:

_____

If you would like another doctor to also be informed, please provide his specialty, name and contact details.

_____

10. With my signature I declare that I participate in this study voluntarily. My study doctor / the study staff did not put any pressure on me. I do not waive my legal rights as a study patient.

Subject name (block letters):.....

Subject's Signature: ..... Date __ __ / __ __ __ / __ __ __ __
D D M M M Y Y Y Y

Study Doctor

I herewith confirm that I discussed the clinical study with the participant using language and expressions comprehensible for the patient. I have informed the patient completely on the nature of the study and possible benefits and risks. I believe that the patient understood my explanations.

Study Doctor's Name (block letters):…….

Study Doctor's Signature: …… Date: __ __ / __ __ __ / __ __ __ __

D D M M M Y Y Y Y