ADULT PATIENT INFORMATION SHEET

Study title: A randomised, double-blind, placebo-controlled Phase 2B clinical trial of repeated application of gene therapy in patients with cystic fibrosis

Short title: Repeated application of gene therapy in CF patients

Invitation paragraph

You are being invited to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish.

Please ask us if there is anything that is not clear or if you would like more information. Please take as much time as you need to decide whether or not you wish to take part.

Introduction

There is currently no treatment for Cystic Fibrosis (CF) that completely halts the progression of lung damage; all the available therapies help to slow the rate of decline in lung function at best. Because of this, we have formed the UK CF Gene Therapy Consortium, (scientists, doctors & nurses based at Imperial College/ Royal Brompton Hospital, Oxford & Edinburgh Universities & Hospitals, www.**cfgenetherapy**.org.**uk/**) to develop further gene therapy for CF. Gene therapy uses healthy copies of the *CFTR* gene to replace the damaged versions within the nose and lungs of patients with CF. Each of these three centres has previously been involved in clinical gene therapy trials which were designed simply to prove that we could deliver healthy genes in this way. Together, we have designed a programme of research to lead to a large, multi-dose clinical trial. This will be the first trial to give multiple, repeated doses and look for clinical benefit. The gene therapy will consist of the healthy *CFTR* gene, which will be carried into the cells of the airways by a liposome (a fatty substance), called GL67A. This is the same liposome which we used in clinical trials in the 1990s and we, therefore, have results on its safety and efficacy. The gene, however, has been substantially improved and has recently been used in a pilot clinical trial to ensure its safety and to see how long each dose lasts. The gene therapy can cause a brief change in lung function and mild feverish symptoms. We have therefore decided to use a dose of 5mls (a

teaspoonful, delivered by inhalation of a nebulised aerosol) which was found to be the best tolerated in the pilot trial.

What is the purpose of the study?

The purpose of this study is to assess for the first time whether repeated doses of gene therapy administered to the lungs of CF patients can lead to clinical improvement.

Why have I been invited?

You have been invited because you are an adult with CF and you attend the Royal Brompton Hospital, one of the hospitals within the Scottish Adult Cystic Fibrosis Service, or one of our collaborating patient identification centers. You are also relatively well, with mild or moderate lung involvement, however not so well that we will struggle to measure any improvement. This will mean that the nebulised gene therapy has a good chance of reaching the cells lining your airways without being blocked by excessive mucus, and that we will sample from your airways more easily. If you are a patient from one of our collaborating participant identification centres you will attend the Royal Brompton Hospital, Western General Hospital Edinburgh or Royal Hospital for Sick Children Edinburgh for all trial related visits but continue your clinical care at your own centre. Trial visits are not a substitute for your usual clinic visits and we will not make decisions related to your general care, although we will communicate closely with your local team.

If you have been involved in the Run-In study you will be invited for a single screening visit to determine whether you will fit the criteria to participate in the multi-dose trial. If you have been newly recruited, i.e. not participated in the Run-In trial, you will be invited for an introductory visit to talk to you further about the research and assess your eligibility as well as a screening visit.

We think that you may fulfill all of the Inclusion & Exclusion criteria although we will need to go through these lists in detail with you; in particular we will be looking for lung function within the range of 50-90% and for you to be in a stable condition with no recent changes to your CF treatments. If your recent lung function is close to the cut-offs for being included you may wish to perform spirometry to see if you are eligible before discussing all the details of the trial with us, as this is quite time consuming. In this case, we will ask you simply to sign a form consenting to lung function, which in no way commits you to taking part in the trial. If you are unwell at the time you are seen, we may be able to reschedule your visit for once you have recovered and are once again stable.

Do I have to take part?

It is completely 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 and without giving a reason. This will not affect the standard of care you receive.

What will happen to me if I take part?

After the screening visit, all patients volunteering for the main part of this study will receive nebulised doses of either the gene therapy (active) product or placebo (sometimes called the 'dummy drug') at 4 week intervals over a 48 week period. Once you have agreed to take part in the study, you will be assigned by chance (like the flip of a coin, but done by a computer) to receive either gene therapy or placebo. A placebo contains no active ingredient. The probability that you will receive gene therapy is 1 in 2 i.e. there is a 50% chance that you will receive the gene therapy throughout the trial and a 50% chance that you will receive the placebo throughout the trial. Neither you nor your study doctor will know whether you are receiving gene therapy or placebo. This is termed a 'double-blind' study and is extremely important for generating results that are meaningful and which will be believed by the wider scientific community. However, in the event of an emergency, the identity of the nebuliser solution can be determined rapidly.

The first 20 patients (10 active treatment; 10 placebo) will receive a nebulised dose (5ml) on 3 occasions at 4-weekly intervals before any further patients are dosed. This is a safety measure to allow the Data Monitoring and Ethics Committee (DMEC, a panel of medical experts) to review the clinical and laboratory findings to ensure that everything is satisfactory after repeated doses of the active treatment/placebo. If this proves to be the case these patients will continue with subsequent visits and the remaining patients will begin their dosing schedule. Because of the large number of patients (130) involved in the study and the restriction on the facilities (special gene therapy cubicles) used we will have to stagger the dosing visits so it is likely to take at least 5-6 months before all patients have started their dosing schedule.

Were the DMEC to have any concerns with the clinical and laboratory findings, they could recommend that we reduce the dose of the gene therapy product. In this event, and if you belonged to the initial 20 patient group, you would unfortunately have to withdraw from the trial. A further group of 20 patients would then be recruited to receive the reduced dose (2.5ml) of active treatment/placebo on 3 occasions at 4-weekly intervals. The DMEC would again meet to review the clinical and laboratory findings to ensure that everything is

satisfactory. If this proves to be the case these patients will continue with subsequent visits and the remaining patients will begin their dosing schedule. If the DMEC were to have any concerns with the 2.5ml dose the trial would be halted as we do not consider it feasible to administer a smaller dose successfully to the lower airways via nebuliser.

A subgroup (at least 24 patients at the London site) will be asked to undergo nasal dosing. This will involve some additional tests and up to 5 additional short study visits (although we will limit these as much as possible). *This will be explained in detail on another sheet if you wish to consider this (see Appendix 1).*

A subgroup (at least 24 patients at the London site) will be asked to undergo a flexible bronchoscopy (a test to look inside the lungs using a flexible telescope) under general anaesthetic on two occasions (prior to the first dose of gene therapy/placebo and between 29 and 35 days after the 12th dose of gene therapy/placebo). This will involve two additional study visits. *This will be explained in detail on another sheet if you wish to consider this (see Appendix 2).*

You will be monitored before and after each nebulised dose (dosing visit) during 12 scheduled dosing visits. The schedule of visits is 4 weeks +/- 5 days for 48 weeks with further details given below. You will be given a flow chart summarising the sequence of study visits:

1. Introductory visit –new patients only (i.e. those not previously involved in Run-In study) (3-4 hours). This is to help us get to know you and for you to familiarise yourself with the tests before the trial starts. However, it is not essential and, particularly if you have a long distance to travel or other time commitments, we can discuss omitting this visit with you.
2. Eligibility and Consent visit (selected subgroup patients only- see below)* (2-3 hours)
3. Screening visit – all patients (3-4 hours)
4. Pre-dosing nasal PD visits up to 3 (nasal subgroup only)
5. Pre-dosing bronchoscopy (bronchoscopy subgroup only)
6. Dosing visits x 12 (4-6 hours)
7. Post-dosing day 2 visits (1st 3 doses in 1st 20 patients only) (2 hours)
8. Follow up visits on Days 14 and 28 (+/-2days) post-dosing (3-4 hours)
9. Post-dosing bronchoscopy Days 27-36 after dose 12 (bronchoscopy subgroup only)

*As the screening visit must occur within 28 days before the first dosing visit, we will offer people taking part in the nasal or bronchoscopy subgroups the opportunity to plan the additional investigation visits earlier if convenient. This will require an initial, short visit, at

which we assess eligibility, perform a physical examination and limited tests and you will be asked to sign consent for the trial.

Should there be any safety concerns, we have the flexibility to see patients for additional visits at any time during the study; such visits will of course be kept to an absolute minimum.

The procedures performed at each of these visits are summarised below. If for any reason we are unable to perform a test at a certain visit (eg. if you miss a visit or equipment fails), the protocol allows us to consider performing that test at a future visit. A full description of each test follows this summary of visits.

PRE-DOSING VISITS

Introductory visit – if considered necessary for new patients only (i.e. those not previously involved in Run-In study). This visit will take around 3-4 hours and will involve:

- explanation of study
- full medical history
- confirmation that you are medically suitable for the trial
- sign informed consent
- a simple (bedside) examination of your chest, blood pressure, temperature, pulse, and oxygen levels (with a finger probe)
- blood sampling
- urine sampling
- Sputum sample (induction with 7% hypertonic saline if required)
- spirometry (lung function tests, as usually done in clinic)
- lung clearance index (LCI)
- 24 hour sputum weight
- nasal potential difference measurements may be conducted (nasal PD subgroup only)
- we will give you a diary card to take home and instructions on how to complete it
- we will give you a hand-held PiKo-6 device for you to carry out blowing tests (lung function) at home
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Screening visit (all patients)

This visit will take around 3-4 hours and will involve:

- explanation of the study
- confirmation that you are medically suitable for the trial
- sign informed consent (if not already signed at introductory visit)

- quality of life questionnaire
- full medical history and physical examination
- a simple (bedside) examination of your chest, blood pressure, temperature, pulse, and oxygen levels (with a finger probe)
- blood sampling
- urine sampling
- spirometry (lung function tests, as usually done in clinic)
- lung clearance index (LCI)
- exercise bike test
- body worn activity monitor (which we will show you how to use)
- chest CT scan
- gas transfer test
- Sputum sample (induction with 7% hypertonic saline if required)
- 24 hour sputum weight
- nasal potential difference measurements may be conducted (nasal PD subgroup only)
- we will give you a diary card to take home and instructions on how to complete it
- we will give you a hand-held PiKo-6 device for you to carry out blowing tests (lung function) at home

DOSING VISITS

Each of the 12 dosing visits will take around 4-6 hours. If you normally take Pulmozyme, you will be asked to withhold treatment for 24 hours prior to each visit and for 24 hours after dosing.

Predosing, the following will be performed at every visit:

- history (we will ask you how well you have been since the last visit and if any of your medicines have been changed)
- a simple (bedside) examination of your chest, blood pressure, temperature, pulse, and oxygen levels (with a finger probe)
- blood sampling
- spirometry (lung function tests, as usually done in clinic)

At specified visits, the following will also be performed

- lung clearance index (LCI)
- urine sampling
- quality of life questionnaire
- exercise bike test
- body worn activity monitor

- chest CT scan
- gas transfer
- 24 hour sputum weight and collection of fresh sample
- nasal PD (subgroup only)
- bronchial blood flow measurement

Dosing

Approximately 20 minutes before the nebulised dose is administered, you will receive 200-400 µg (2-4 puffs) of inhaled salbutamol to prevent airway narrowing and wheeze, which may be associated with the gene therapy agent / placebo. The nebulised dose will then be given via a mouthpiece from a clinical nebuliser. You will be asked to wear a nose clip for the duration of the nebulisation (3 minutes on, 2 minutes off for 8 cycles) which usually takes around 40 minutes.. The nebuliser will be administered whilst you are sitting in a cubicle to prevent contamination of the immediate environment. You will have contact throughout and will be able to communicate with your research nurse through a glass window. You will be asked to report any new symptoms. Although this environment is not spacious, we will do our best to make you as comfortable as possible. We can provide music or a DVD player should you wish. You will be able to leave the cubicle as required for a toilet break, although we will ask that you wear a mask over your mouth and nose during this time and for 30 minutes after dosing is complete.

If you agree to take part in the nasal dosing subgroup (London site only), we will ask you to administer a nasal spray during the 'off' nebuliser period, with one spray being delivered to each nostril at the beginning and end of the first 6 two minute'off' periods which will deliver a dose of approximately 2 ml.

You will be observed for a minimum of 30 minutes after dosing before leaving the hospital. We will listen to your chest and perform pulse oximetry after the dosing and prior to you leaving the hospital. . If either you or we have concerns about your level of well-being after treatment, we may suggest that you stay in hospital overnight, although we are not expecting this to be the case. We will ask you to take a standard 1g dose of paracetamol immediately after dosing and you will be given another 1g dose of paracetamol to take at home approximately 6 hours after dosing. This is to prevent any mild feverish symptoms that could possibly occur after dosing.

Day 2 post-dosing visits (first 20 patients after each of the first three doses only)

The following will be performed:

- history (we will ask you how you have been since your last visit and if any of your medicines have been changed)
- a simple (bedside) examination of your chest, blood pressure, temperature, pulse, and oxygen levels (with a finger probe)
- spirometry ((lung function tests, as usually done in clinic)
- gas transfer
- blood sampling
- bring in sputum coughed up over last 24 hours and collect fresh sample

Follow up visits

There will be two follow up (F/U) visits that will occur at 14 (+/-2) days and 28 (+/-2) days after your last dosing visit.

At F/U **day 14** we will do the following:

- history (we will ask you how well you have been since the last visit and if any of your medicines have been changed)
- a simple (bedside) examination of your chest, blood pressure, temperature, pulse, and oxygen levels (with a finger probe)
- quality of life questionnaire
- spirometry
- blood sampling
- lung clearance index (LCI)
- nasal PD (subgroup only)
- urine sampling
- bring in sputum coughed up over last 24 hours and collect fresh sample
- diary card check
- download hand-held PiKo-6 device on which you carried out blowing tests

At F/U **day 28** we will do the following:

- history (we will ask you how well you have been since the last visit and if any of your medicines have been changed)
- all the tests performed at the screening visit
- collection of diary card and hand-held PiKo-6 device

Long term follow up: you will be followed up by your clinical team at scheduled CF clinic appointments approximately every 3 months for 2 years.

Description of Tests

- *Full medical history:* we will ask about your medical condition(s) including history of medications (specifically any additional antibiotics required for your chest), operations and allergies plus anything else relevant to the safety of the trial.
- *Clinical examination*: we will listen to your lungs using a stethoscope and measure your height, weight, temperature, pulse, blood pressure and respiratory rate
- *Pulse oximetry (finger probe):* a measurement of the oxygen level in your blood using a finger probe
- *Blood test:* (at each visit where blood is required, up to 25 mls, (5 teaspoons), will be taken for a variety of tests including routine clinical tests e.g. liver and kidney function, full blood count, electrolyte (salt) levels and C-reactive protein (a marker of inflammation). Samples will be stored for future measurement of inflammatory markers and possibly for end-products of gene therapy breakdown. If you wish, we will arrange for you to have local anaesthetic, either cream or spray. If you have a portacath or similar device and your clinical team is happy for this to be used for blood sampling, this may be possible as an alternative. At one single visit at any time during the trial, we will take a sample of blood for DNA (genetic) research. The only tests we will perform on this sample will be:
    - *Testing for your CF gene(s) if these are not known; we will be happy to let you know the results of this test.* ***This sample will not be used to test for any other genetic diseases***
    - *Testing for common, naturally-occurring changes in genes which don't cause disease but might be involved in how individuals respond to gene therapy, eg, inflammatory response genes. This will be most useful in the event that we see that some people respond to gene therapy and others do not, to help us understand this better.*
- *Urine sample*: routine testing with a dipstick for protein, sugar etc; we will also perform a pregnancy test if you are female.Samples will be stored for future measurement of inflammatory proteins and possibly for end-products of gene therapy breakdown
- *Spirometry* (blowing tests, as usually done in clinic).
- *Lung clearance index (LCI)*: this test demonstrates how evenly gas is distributed in the lungs and is a sensitive marker of airway disease. You will be asked to breathe a

tracer gas (SF6) which has no smell or taste and is completely harmless, over a period of several minutes. Once levels in your lungs are stable, you will switch to breathing air and the time taken for the SF6 to leave the lungs is used to calculate the LCI. We will perform the test 3 times, each one taking about 10 minutes.

- *Exercise bike test:* this test will be performed on an exercise bike and is incremental (gets more difficult to pedal as it goes on). Exercise is an event that involves a large number of physiological processes from the heart and lungs, to the blood circulation and the muscle itself. This test will enable us to calculate your exercise capacity. During the test we will record a breathlessness score and a probe will be attached to your finger or ear lobe to measure the oxygen levels in your blood. You will be wearing a nose clip and breathing through a mouthpiece. You will be asked to pedal at a comfortable speed and maintain this speed throughout the test. The resistance to pedalling will automatically increase each minute and you will be encouraged to continue until you either cannot keep up with the speed or feel you have exercised as much as you are able; we will ask you to stop if your oxygen level falls. Once the test is complete you will have a 2 minute cool down period, and we will continue to monitor your oxygen levels until they return to baseline.
- *Sweat test:* Although the diagnosis of CF is not in doubt, some patients, particularly those who were diagnosed many years ago, do not have documented confirmation of a diagnostic test in their notes. If you have neither a confirmed genetic diagnosis (2 mutations) nor a sweat test result, we would like to perform a sweat test as part of the trial. An area of the skin on your forearm will be cleaned and 2 electrodes will be attached with straps. One of these contains a gel which stimulates sweat and the medication is applied to the skin by a weak current; you will feel a little tingling but this is not painful. Following this a collection device will be attached to the skin surface and the sweat collected over a 30 minute period. This will then be analysed by the laboratory for the high levels of salt seen in CF.
- *Activity monitor:* a small band worn on your upper arm that collects step and movement data. You will be asked to wear this for 7 full days after specific study visits.
- *Chest computed tomographic (CT) scan:* Computed tomography uses x-rays to create detailed images of the lungs. It is a good measure of how CF affects the shape and structure of the airways. For each scan you will be asked to lie still on a table which will move slowly through the centre of a large x-ray machine but at no time will you be in an enclosed space. You will be able to communicate with the CT staff if you need to. You will be given breathing instructions at the time of the scan. No

injections are involved and the procedure is completely painless. As x-rays are involved, you will be exposed to a small amount of radiation. However, we will be using as low a dose as is possible for your scans. The estimated maximum dose of all three scans over the entire study period amounts to 4.5 mSV, which is similar to the radiation you would be exposed to as part of natural background radiation over a 2 year period. Because even low levels of radiation can be dangerous to an unborn child, it is a requirement that all females undergo a urine pregnancy test on the day of the procedure.

- *Transfer factor (TLCO)*: this is a lung function test which measures the rate at which gas travels across the lung tissue (alveolus) into the blood stream. Gas transfer is usually normal in patients with CF. We are using this test as a safety measure and in order to assess whether the gene transfer has an effect on this, we need to make a baseline measurement. You will be asked to wear a nose-clip and to breathe out as far as you can through a mouth-piece. You will then breathe in as far as possible, a mixture of air and low concentration of a tracer gas (less than 0.3% carbon monoxide) and hold your breath for 10 seconds before breathing out as far as possible. This will be repeated up to 5 times with rest periods in between tests. This concentration of CO is completely harmless and this is a well-established test used routinely in clinical practice.
- *Sputum sampling:* we will ask you to try and cough up around a teaspoon of sputum; if this is not possible for you, we will obtain secretions for microbiology by asking you to cough onto a sterile swab or brush . At either your introductory or screening visit and at either of your follow up day 14 or day 28 visits if you are unable to cough up a sputum sample, we will use a well-established nebulisation technique to induce sputum. To prevent wheeze (a common side effect), you will be given 200 mcg of salbutamol (Ventolin) or an equivalent drug to open up the airways. After 15 minutes you will receive a 7% saline nebuliser for 5 minutes, and this will be repeated up to 3 times. We will monitor your lung function (FEV_1) throughout, and should we see a significant drop, the test will be stopped. If sputum induction fails, we will obtain secretions for microbiology by asking you to cough onto a sterile swab or brush Samples will be tested for infection and stored for future measurement of inflammatory proteins and possibly for end-products of gene therapy breakdown.
- *CF specific quality of life questionnaire:* this will take a total of 10 minutes to complete.

- *Diary card:* You will be given a diary card which you will be asked to complete for the duration of the study. This will record new symptoms, changes in routine treatments etc.
- *Home lung function:* You will be taught how to use a small lung function device (PiKo-6) and asked to make regular recordings on it at home for the duration of the study period. The machine stores all the readings which will be downloaded onto a computer at each visit.
- *Bronchial blood flow measurement:* (London site only) This test is designed to look at the blood flow to the airways which is often increased in patients with airway disease, probably reflecting inflammation. The test takes about 45 minutes to do and consists of 10 breath-holding manoeuvres of either 8 or 16 seconds. For each manoeuvre you will be seated, wearing a noseclip and breathing in and out through a mouthpiece. After several normal breaths you will need to breathe in a small amount of test gas, which is safe and enriched with oxygen, and hold this breath for 8 or 16 seconds before breathing out again slowly. Your heart rate and oxygen saturation will also be monitored during the test. There is a gap (3-4 min) between each of the manoeuvres to save the data and calibrate the equipment. As the blood flow to the airways may be affected by alcohol and caffeine, it is requested that you do not consume alcohol the night before the test and do not have any caffeine on the day of the test. This test will be undertaken after all other assays / tests if time allows. If you are too tired to do the procedure it will not be done or if during the procedure you feel too tired to continue we will stop the test at any time.
- *Nasal PD and nasal brushings: see Appendix 1* (London site only)
- *Bronchoscopy: see Appendix 2* (London site only)

What else will I have to do?

In addition to the study visits and home monitoring outlined above, we will ask that if you are sexually active, you agree to take contraceptive precautions from enrolment into the study until 3 months after completion. This is a requirement of the Medicines and Healthcare products Regulations Agency (MHRA) and the Gene Therapy Advisory Committee (GTAC) for all clinical trials involving gene therapy. Approved (reliable) methods of contraception include:

- 'the pill'
- long-acting injections or implants
- placement of an intrauterine device (IUD; sometimes called a 'coil') or system (IUS)
- condom or occlusive cap with spermicide

Exceptions to this can be made in the case of:

- male trial participants with CF-related infertility, which has been confirmed on semen testing
- male trial participants who have undergone a vasectomy followed by confirmation of success
- female trial participants whose only male sexual partner has undergone a vasectomy followed by confirmation of success

If you do not already fall into one of these groups, we will ask you to attend your General Practitioner of local Family Planning Clinic to discuss options. You may also find it useful to discuss these issues with your CF Consultant and / or Nurse Specialist who will provide you with information relevant to patients with CF.

There will be no other changes made to your routine clinical care.

We ask that you consent to our informing your General Practitioner about your involvement in the study, including these requirements for contraception.

What is the drug or procedure that is being tested?

We are testing a formulation consisting of a healthy copy of the *CFTR* gene mixed with a fatty substance which helps the gene enter the cells of the airway. The *CFTR* gene has been changed since our original trial in ways that we believed would make it likely to cause less inflammation and last for longer. We did see some flu-like responses and drops in lung function in some people in the Pilot study but by giving a smaller dose (5ml) we were able to reduce these side effects. The research team will be happy to provide you with more specific scientific details should you wish.

What are the alternatives for diagnosis or treatment?

As you will know, conventional treatments for CF have improved greatly over the last few decades. However, they do not correct the basic defect in your cells, which is what we are aiming to do with gene therapy. In general therefore, conventional treatments slow the natural progression of lung disease, rather than stop it altogether. Should you wish not to take part, your standard clinical care will continue as usual.

What are the possible disadvantages and risks of taking part?

We are asking for a large time commitment from you over a period of a year. The study requires you to make a minimum of 15 visits and perform multiple tests. As described above, most of these are straightforward and many of them will be familiar to you from clinics (and, for many of you, your participation in the Run-in).

The risks that we consider likely are as follows:

1. Either the gene therapy or the placebo could cause wheeze or increased cough. To limit this, we will administer salbutamol, to relax the airways, prior to nebulisation. In our previous study, some of the single dose patients had a fall in their lung function several hours after dosing but this was well-tolerated and, for most patients receiving 5 ml, was not associated with any increased symptoms. Lung function had resolved in all dosing groups within 2 days of the dosing visit.
2. In the single dose study, some patients developed a temperature and a mild flu-like illness within a few hours of dosing. These side effects were minimal with the 5 ml dose that we have chosen for this trial and appear to be responsive to paracetamol, which we will ask you to take on two occasions (2hrs and 8 hrs) post-dose whether you have side effects or not. All side effects should have disappeared within 2 days of the dosing visit.
3. The CT scans involve exposure to a small amount of radiation, which in common with all radiation does carry a small risk of causing cancer. We plan to do a type of CT scan using lower radiation doses than a standard CT. The estimated maximum dose of all three scans over the entire study period amounts to around 4.5 mSv. To put this in context, the maximum amount of radiation from all three scans over the entire study period is equivalent to the amount of natural radiation to which everyone is exposed from environmental sources over a period of 2 years. Female patients of a child-bearing age will be required to have a negative pregnancy test on the day of each scan.
4. Please see Appendices 1 and 2 for disadvantages associated with nasal PD and bronchoscopy. (These tests are only being performed at the London site.)

What are the possible benefits of taking part?

Because we are the first research group in the world to administer multiple doses of this gene therapy product, and CF is such a chronic disease, we cannot be sure that there will be any immediate or long-term benefits of participating in the study. You will be helping to advance the field of gene therapy by agreeing to take part. Should this study be successful, we will undertake further trials with a view to developing gene therapy as a treatment.

What happens when the research study stops?

When you have completed your study visits, you will continue to receive your routine clinical care. If you wish, we will keep you informed of any developments that arise from the results of this study.

What if there is a problem?

Throughout the study, we will be happy to talk to you or see you at any point should you have concerns. Should you develop any health problems, we will investigate and treat these after discussion with your usual medical team.

An independent Data Monitoring and Ethics Committee (DMEC) will oversee the safety of the trial as it progresses. Any significant adverse events will be reported to the DMEC.

Complaints : If you have a concern about any aspect of the study, you should ask to speak to a member of your clinical research team (see contact numbers at the end of this Information Sheet) who will do their best to answer your questions. If you remain unhappy and wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you. Details can be obtained from the hospital.

Harm: In the event that something does go wrong and you are harmed during the research due to someone's negligence, then you may have grounds for legal action or compensation, but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Imperial College London holds Public Liability ("negligent harm") and Clinical Trial ("non-negligent harm") insurance policies which apply to this trial. Liability for the gene therapy product design will be accepted by Oxford University and Imperial College London. Liability for the protocol design will be accepted collectively by Oxford University, Edinburgh University and Imperial College London. Clinical negligence insurance / indemnity is provided by the NHS.

Will my taking part in the study be kept confidential?

Yes.

All information collected during the course of the study will be coded and kept strictly confidential. Clinical results and analysis will be collated by the Imperial College Trials Unit. All samples will be stored indefinitely in a coded fashion to preserve confidentiality. Codes will be held by a single investigator at each site. If you consent to take part in the research, any of your medical records may be inspected for purposes of analysing the results. They may also be looked at by people from regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital.

If you agree to take part, your GP will be informed and your hospital notes will be flagged to ensure that other members of the clinical team are also informed.

What if relevant new information becomes available?

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

Also, on receiving new information your research doctor might consider it to be in your best interest to withdraw you from the study. He/she will explain the reasons and arrange for your normal clinical care to continue.

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

You will be free to discontinue the study at any time, without giving a reason, and this will not affect your clinical care in any way. For patients who have commenced dosing we would be grateful if you could attend at least a 14 and 28 day follow up appointment as part of the trial. Samples already obtained will be used for this and other ethically approved studies unless you specifically request samples to be destroyed. In addition we would like to discuss your progress with your clinical team after your routine clinic visits to gather as much information as possible for the trial and ensure continuing patient safety.

What will happen to any samples I give?

Samples will be stored in a coded fashion so that, with the exception of one or two key people, the researchers will not be able to identify individual patients. Many of the samples will be frozen and stored indefinitely. We are working closely with the other members of the UK Gene Therapy Consortium in Oxford, Edinburgh and Southampton Universities and will be sending coded samples to them for analysis and storage. We will also be sending coded blood samples to colleagues at the University of Pennsylvania, USA. We would wish that any spare samples left over could be used in other ethically-approved research protocols and would ask you to agree to this by gifting your samples to us as part of consenting to this study. All of our storage conditions comply with the regulations of the Human Tissue Act and/ or the Human Tissue Act (Scotland) 2006.

What will happen to the results of the research study?

At the end of the study, all results will be analysed, and will be reported at conferences and published in the Medical press. Results of the study will also be made available to study participants on request. You will not be identified in any report/publication.

Will my expenses for taking part in the study be reimbursed?

Yes. We understand the inconvenience involved in taking part in such a study and will be happy to reimburse travel expenses for the visits you will be asked to make.

Who is organising and funding the research?

The study is being funded by the National Institute for Health Research & Medical Research Council. There is no financial gain to either the Hospital or the staff for including and looking after patients in this study.

Who has reviewed this study?

This study has been submitted for review by the Gene Therapy Advisory Committee, the national body charged with assessing the ethical aspects of any clinical trial involving gene therapy.

Thank you for considering taking part in this study

We very much hope that after reading this information and talking to the research team, you feel able to take part, but please be assured that should you not wish to, this will in no way affect your clinical care.

For further information please contact:

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Appendix 1

Nasal dosing Subgroup (London site only)

A group of at least 24 patients in the trial will be asked to undergo nasal dosing and have nasal potential difference (nPD) measured and nasal brushings taken. Because the nostrils are relatively easy to access, and these measurements can therefore be made repeatedly, this offers us a valuable opportunity to study how well the gene is expressing at different time points during the study. This is optional and you do not have to take part in this additional testing if you do not wish to. If you do agree and are considered suitable, there will be a 2 in 3 chance that you will be randomized to receive the active gene therapy rather than placebo.

The section below explains what you will be asked to do in addition to the visits already described in the main Information Sheet

Additional pre-1st dose visits:

Eligibility and Consent (E&C) visit

In certain cases to ease scheduling, we will schedule the nPD tests several months ahead of your planned dosing dates. In this case, the E&C visit will take place, which will include:

- We will confirm that you are eligible to take part and ask you to sign the Consent Form
- We will take a full medical history and perform a standard (bedside) examination including heart rate, breathing rate, blood pressure, pulse oximetry, temperature, and listen to your chest
- blood sampling
- urine sampling
- Spirometry
- Nasal potential difference measurement may be performed at this visit or on separate occasion

Nasal PD visits

You will be asked to have 3 nPD measurements before receiving your first dose of gene therapy. A maximum of 2 measurements can be performed at a visit. These may be performed at E&C, Introductory or Screening visits, or may be scheduled separately to suit you. On a single occasion, either with or after your 3rd nPD, you will undergo a nasal brushing test.

Nasal Dosing: You will be taught how to use the nasal spray and will be asked to administer a nasal spray during the 'off' nebuliser period, with one spray being delivered to each nostril at the beginning and end of the first 6 two minute 'off' periods which will deliver a dose of approximately 2 ml.

Nasal potential difference (nPD)**:** We will perform nasal PD on three occasions before the first dose (this is because we know the measurements are quite variable and want to be as certain as possible that any changes we see are due to the gene therapy and not just this variability), and after the sixth dose and at two time points after the twelfth doseWe may do additional nasal PDs post dose 3, 6 and 9 if opportunity arises and you are agreeable. This test is a sensitive way of measuring salts moving in and out of the cells lining the nose. The readings are different in patients with CF from those without and this test has been used clinically for many years in difficult diagnoses. As gene therapy is directed at correcting these cells, this test can help tell us how well the gene therapy is working. A small abrasion is made with a sterile device on the skin of the forearm; this is not painful. An electrode wire is attached to the abraded skin and a small volume of cream is applied and kept in place with a piece of tape. A soft catheter is inserted about 5-7 cm into one nostril until a stable reading is obtained. This will then be taped in place. A series of solutions is perfused into the nostril; you will be asked to lean forward so that drops fall into a bowl rather than go down the back of your throat. The response to these solutions is measured on a portable computer. The whole test takes approximately 20 minutes. We may wish to perform this on both nostrils (one after the other) depending on the results.

The more common side effects include:

- A slight salty taste from the solutions in your nose
- Sneezing or mild discomfort during insertion of the catheter
- Mild discomfort on your arm for a short while following skin abrasion

Nasal brushing**:** We will obtain cells lining the nose by inserting a small, sterile brush into the nostrils, one at a time. The procedure is not particularly pleasant and makes the eye on that side water slightly. It is however very quick, each nostril taking only approximately 5 seconds. We will perform nasal brushing on one occasion at or after your third nasal PD visit and again at the end of the trial.

Rarely, patients are unhappy to have tests performed on their nose as they find this unpleasant; if you feel this way and are also in the bronchoscopy subgroup, we can include you in the nasal dosing group and perform only a single nPD and brushing pre and post-dosing whilst you are under anaesthetic.

Appendix 2

Bronchoscopy Subgroup (London site only)

A group of at least 24 patients in this trial will be asked to undergo two bronchoscopies, one before the first dose of gene therapy / placebo and the second between day 29 and 35. After the 12th dose of gene therapy / placebo. The purpose of this is to make measurements of the levels and function of the CFTR gene in the hope that we can learn how much gene we need to replace in order to achieve health benefits. As with the nasal group, this is optional and you do not need to take part in this subgroup if you do not want to. If you do agree and are considered suitable, there will be a 2 in 3 chance that you will be randomised to receive the active gene therapy rather than placebo.

The section below explains what you will be asked to do in addition to the visits already described in the main Information Sheet

Additional visits:

Eligibility and Consent (E&C) visit
In certain cases to ease scheduling, we will schedule the bronchoscopy several months ahead of your planned dosing dates. In this case, the E&C visit will take place, which will include:

- We will confirm that you are eligible to take part and ask you to sign the Consent Form
- We will take a full medical history and perform a standard (bedside) examination including heart rate, breathing rate, blood pressure, pulse oximetry, temperature, and listen to your chest
- blood sampling
- urine sampling
- Spirometry

***Flexible bronchoscopy under general anaesthetic (GA)*:**
This will be performed once before you start dosing and again at the end, between 29 and 35 days after your 12th dosing visit.
The bronchoscope allows us a view down into your airways; once you have been anaesthetized and are fully asleep, we will make a general inspection of lung inflammation, plugging etc and will then take 2 biopsies and 10 airway wall brushings from one lung. These are safe procedures, although a small amount of airway wall bleeding is common and you

may notice some blood in your sputum for a few days afterwards. We will also make PD measurements down the bronchoscope onto the airway surface in a fashion similar to that described for the nPD (see Appendix 1). We will, as is usual clinical practice, record the entire procedure onto a DVD, which you may view afterwards with us should you wish.
The samples that we obtain will be tested using:

i. Molecular tests to tell us whether the gene has reached these parts of the lung and successfully entered the airway lining cells
ii. Stains to demonstrate whether the CFTR protein has been produced
iii. Routine histology (examination under a microscope)

We estimate that the whole procedure will take approximately 45-60 minutes. At the end of the procedure, we will give you a single dose of the antibiotic(s) most suited to the bacteria found most recently in your lungs (sputum or cough swab) to limit the chance of a fever after the procedure.
You will have the opportunity to meet and talk to both the Consultant Anaesthetist and Consultant Respiratory Physician performing the procedure beforehand and ask any additional questions you may have. All staff are fully trained and experienced in these procedures, which are performed regularly at this hospital as part of routine clinical management.
You will be monitored and observed for at least 4 hours after the bronchoscopy. We anticipate that most patients will recover fully within this time period and feel able to be discharged. Should this not be the case, we will ask that you remain in hospital overnight for further observation. You will not be able to drive and so should it be more convenient for your travel arrangements, we will arrange for you to stay overnight either at the hospital or at a local hotel.

In summary, bronchoscopy is generally a safe procedure and performed regularly in hospitals.

The more common side effects are;

- Drowsiness after the anaesthetic – this should wear off after a few hours
- A mild, sore throat for a day or so
- Fever (this will be made less likely with the use of an IV antibiotic and the end of the procedure)
- A small amount of blood (specks) may come up when you cough for a day or so due to the biopsies

Rarely, an anaesthetic can lead to an increase in symptoms such as cough and sputum production. Major blood loss or a chest infection after bronchoscopy are very rare.

Many thanks for considering these additional tests; please feel free to ask any questions you may have.