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Repeated application of gene therapy in cystic fibrosis patients

Submission date	Recruitment status
15/03/2012	No longer recruiting
Registration date	**Overall study status**
17/05/2012	Completed
Last Edited	**Condition category**
29/01/2018	Nutritional, Metabolic, Endocrine

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Cystic fibrosis (CF) is a common genetically inherited disease caused by mutations in the CFTR gene. Mutations in this gene lead to thick sticky mucus clogging the lungs, infection, inflammation and eventually irreversible lung damage. There is currently no treatment that stops the natural progression of the disease; all available successful treatments merely slow the rate of decline in clinical condition. Gene therapy is a promising new treatment for CF where the faulty CFTR gene is replaced with a working one. The aim of this study is to assess whether CFTR gene therapy can lead to clinical improvement.

Who can participate?
Children aged 12 and above and adults with CF.

What does the study involve?
Participants are randomly allocated to inhale (breathe in) doses of either the gene therapy or a placebo (dummy) treatment every 4 weeks over a 48-week period. A subgroup of at least 20 patients is asked to undergo dosing with a nasal spray. Another subgroup of at least 24 patients is asked to undergo a bronchoscopy, a procedure that allows your doctor to look at your airway through a thin viewing instrument called a bronchoscope.

What are the possible benefits and risks of participating?
If the treatment is effective, the benefits will likely include an increased ability to clear mucus from the lungs, reduced inflammation, improvements in lung function and reduced symptoms. At higher doses, the gene therapy can lead to a systemic inflammatory response (fever), but the side effects are low with the dose used in this study. There is a risk of the side effects increasing with repeated dosing. To ensure that we identify any side effects early, a group of 20 patients will receive three doses before the rest of the group and will be intensively monitored. If there are side effects we will lower the dose for the rest of the study and if there are significant safety concerns the study will be stopped early. As with any treatment, there is a possibility that certain patients may be intolerant or allergic to the treatment. It is possible that there will be an immune response to the treatment but we have seen no evidence for this to date. All dosing will be conducted in hospital with full resuscitation facilities. There is a theoretical risk that the gene therapy could be released into the environment either during dosing or by patient exhalation

(breathing out). All dosing will therefore be conducted in hospital within state of the art, purpose-built rooms. The bronchoscopy will be performed under general anaesthetic. The chance of fever following the procedure will be reduced by using antibiotics.

Where is the study run from?
The Royal Brompton & Harefield, London; The Western General Hospital, Edinburgh and The Hospital for Sick Children, Edinburgh (UK).

When is the study starting and how long is it expected to run for?
March 2012 to March 2014.

Who is funding the study?
National Institute for Health Research (NIHR) and the Medical Research Council (MRC) through the Efficacy and Mechanism Evaluation programme.

Who is the main contact?
Prof. Eric Alton
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Study website
http://www.cfgenetherapy.org.uk/index.html

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

EudraCT/CTIS number
2011-004761-33

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
CRO1881 EudraCT: 2011-004761-33

Study information

Scientific Title
Randomised, double-blind, placebo-controlled phase IIB clinical trial of repeated application of gene therapy in patients with cystic fibrosis

Study objectives
1. To assess the clinical benefit of repeated doses of pGM169/GL67A administered to the lungs of patients with cystic fibrosis (CF) over a period of 48 weeks
2. To assess the safety and tolerability of repeated doses of pGM169/GL67A administered to the lungs of patients with CF over the same period
3. To assess gene expression of the formulation over the same period

More details can be found at http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=12224

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Gene Therapy Advisory Committee, 08/03/2012, ref: GTAC 184
2. Medicines and Healthcare products Regulatory Agency (MHRA), 02/02/2012, ref: 19174/0316 /001-0001

Study design
Randomised double-blind placebo-controlled phase IIB

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Cystic fibrosis

Interventions

Administration of 5 ml pGM169/GL67A or placebo (0.9% saline) via nebuliser to the lungs every 4 weeks for 12 doses
Administration of 2 ml pGM169/GL67A or placebo (0.9% saline) via nasal spray to the nose every 4 weeks for 12 doses (subgroup only)

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
pGM169/GL67A

Primary outcome measure
Relative change in percent predicted FEV1 after 12 doses

Secondary outcome measures
1. Efficacy:
1.1. Relative change in other spirometric measures
1.2. Lung clearance index
1.3. Change in body weight
1.4. Chest CT scan
1.5. Quality of Life Questionnaires
1.6. Exercise capacity
1.7. Activity monitoring
1.8. Serum calprotectin
1.9. Sputum culture
1.10. Sputum weight, cell counts and inflammatory markers
1.11. Frequency of additional antibiotics for increased respiratory symptoms
2. Clinical examination
3. Transcutaneous oxygen saturation
4. Serum inflammatory markers (CRP, white blood cell count, IL-6)
5. Renal and hepatic function
6. Gas transfer
7. Bronchial bood flow
8. Immune response markers (anti-nuclear and double-stranded DNA antibodies, CFTR-specific T cell responses)
9. Endobronchial histology (subgroup only)
10. Gene expression outcomes (subgroups only):
10.1. Transgene mRNA expression in nasal and lower airway brushing samples
10.2. Potential difference measurements in nose and bronchi

Overall study start date
01/03/2012

Completion date
31/03/2014

Eligibility

Key inclusion criteria
1. Cystic fibrosis confirmed by sweat testing or genetic analysis
2. Males and females aged 12 years and above
3. Forced expiratory volume in the 1st second (FEV1) between 50 & 90% predicted inclusive (Stanojevic reference equations)
4. Clinical stability at screening defined by:
4.1. Not on any additional antibiotics (excluding routine, long-term treatments) for the previous 2 weeks
4.2. No increase in symptoms such as change in sputum production/colour, increased wheeze or breathlessness over the previous 2 weeks
4.3. No change in regular respiratory treatments over the previous 4 weeks
4.4. If any of these apply, entry into the study can be deferred
5. Prepared to take effective contraceptive precautions for the duration of their participation in the study and for 3 months thereafter (as stated in Gene Therapy Advisory Committee [GTAC] guidelines)
6. If taking regular rhDNase (pulmozyme), is willing and considered able by independent medical carers, to withhold treatment for 24 hours before and 24 hours after the gene therapy dose (nebulised doses only)
7. Written informed consent obtained
8. Permission to inform general practitioner (GP) of participation in study

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
130

Key exclusion criteria
1. Infection with Burkholderia cepacia complex organisms, Methicillin-resistant Staphylococcus aureus (MRSA) or M. abscessus
2. Significant nasal pathology including polyps, clinically-significant rhinosinusitis, or recurrent severe epistaxis (nose bleeds) (nasal cohort only)
3. Chloride secretory response on nasal PD of > 5 mV (nasal cohort only; will only be known after first measurement)
4. Acute upper respiratory tract infection within the last 2 weeks (entry can be deferred)
5. Previous spontaneous pneumothorax without pleurodesis (bronchoscopic subgroup only)
6. Recurrent severe haemoptysis (bronchoscopic subgroup only)
7. Current smoker
8. Significant comorbidity including:
8.1. Moderate/severe CF liver disease (varices or significant, sustained elevation of transaminases: ALT/ AST>100 IU/l)
8.2. Significant renal impairment (serum creatinine > 150 mol/l)
8.3. Significant coagulopathy (bronchoscopic group only)
9. Receiving second line immunosuppressant drugs such as methotrexate, cyclosporine,

intravenous immunoglobulin preparations
10. Pregnant or breastfeeding

Date of first enrolment
01/03/2012

Date of final enrolment
24/06/2013

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Imperial College London
London
United Kingdom
SW3 6LR

Sponsor information

Organisation
Imperial College London (UK)

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Sponsor type
University/education

Website
http://www3.imperial.ac.uk/

ROR
https://ror.org/041kmwe10

Funder(s)

Funder type
Government

Funder Name
National Institute for Health Research

Alternative Name(s)
National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/07/2016		Yes	No