A randomised, double-blind, placebo-controlled trial of repeated nebulisation of non-viral cystic fibrosis transmembrane conductance regulator (*CFTR*) gene therapy in patients with cystic fibrosis

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Declared competing interests of authors: All authors report grants from the National Institute for Health Research, grants from Cystic Fibrosis Trust, grants from Just Gene Therapy, grants from Medicor Foundation and report that Genzyme, a Sanofi company, manufactured and provided Lipid 67. Ian A Pringle also has a patent WO200711062 issued. Ronald K Scheule also reports other funding from Genzyme, a Sanofi company, outside the submitted work and has a patent US5783565 issued, a patent US5840710 issued, and a patent US5935936 issued. Michelle C Manvell also reports grants from Royal Brompton Biomedical Research Unit (National institute for Health Research funds), outside the submitted work. Steve Cunningham also reports personal fees from Gilead, outside the submitted work and is a principle investigator for Vertex Pharmaceuticals studies in children with cystic fibrosis. Nicholas J Simmonds also reports personal fees from cystic fibrosis Adherence Steering Committee, personal fees from Vertex advisory board, personal fees from Pharmaxis advisory board and lecture fee, personal fees from Gilead advisory boards and lecture fee, personal fees from Eumedica lecture fee, personal fees from Forest Laboratories honorarium, outside the submitted work. Eric WFW Alton also has a patent WO2013061091 pending. Christopher Boyd also has a patent WO2013061091 pending. Alexandra L Quittner is a member of the advisory board for Genentech Inc., reports consulting for AbbVie Pharmaceuticals, grants from Cystic Fibrosis Foundation, grants from Vertex Pharmaceuticals and grants from Novartis Pharmaceuticals, outside the submitted work. Uta Griesenbach also has a patent WO2013061091 pending, and a patent European Patent Application Number 12784648.3 pending. Seng H Cheng is an employee of Genzyme, a Sanofi Company and also has a patent US5650096 issued, a patent US5747471 issued, and a patent US5840710 issued. David J Porteous also has a patent WO2013061091 pending. J Alastair Innes also has a patent WO2013061091 pending. Jane C Davies also reports fees paid to employing institution from Vertex for her role as clinical trials lead, educational meetings and advisory board participation, fees paid to employing institution from Novartis for advisory board participation and fees paid to employing institution from Proteostasis for advisory board participation, outside the submitted work, and has a patent WO2013061091 pending. Stephen C Hyde also has a patent WO200711062 issued, and a patent WO2013061091 pending. Lee A Davies has a patent US 20140242690 A1 pending, and a patent WO2013061091 pending. Deborah R Gill also has a patent WO200711062 issued, and a patent WO2013061091 pending. James M Wilson is a founder of, holds equity in, an advisor to and grant recipient from, REGENXBIO and Dimension Therapeutics. He is an advisor to Solid Gene Therapy. He is an inventor on patents licensed to various biopharmaceutical companies.

Published July 2016
DOI: 10.3310/eme03050

Plain English summary

Repeated nebulisation of non-viral CFTR gene therapy

Efficacy and Mechanism Evaluation 2016; Vol. 3: No. 5
DOI: 10.3310/eme03050

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Plain English summary

Cystic fibrosis (CF) is an inherited disease that significantly shortens life because of severe lung disease. Only one treatment aimed at the underlying cause is currently available and this is suitable for only the 4% of patients who have specific types of gene mutations; standard care for all other patients targets the symptoms of the disease rather than the cause.

Gene therapy aims to insert a normal copy of the gene back into the lungs' cells and restore function. In the UK CF Gene Therapy Consortium we have (1) identified the best vector with which to gain cell entry; (2) designed a piece of genetic material capable of safely expressing the missing protein for a prolonged duration; (3) found out how we can deliver this to the lungs using a clinical nebuliser; (4) tested safety in two animal models; and (5) confirmed a safe dose in a single-administration trial.

In this trial, CF patients (aged $\geq$ 12 years) randomly received gene therapy or placebo every month for 1 year. The primary outcome was a change in lung health, measured by a standard breathing test [forced expiratory volume in the first second (FEV_1)]. In addition, we included a number of secondary and safety outcomes.

One hundred and sixteen patients received at least nine doses and were analysed for efficacy. After 12 months, a statistically significant, but modest, difference was observed between the two groups for FEV_1; this was supported by trends in other outcomes. Effects were independent of gene mutation, age and sex. There were no significant safety concerns.

We suggest the results reported here provide proof of concept that repeated administration of CF transmembrane conductance regulator (*CFTR*) gene therapy can alter clinically relevant outcomes, providing another step along the path of translational CF gene therapy.

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

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This report

The research reported in this issue of the journal was funded by the EME programme as project number 11/14/25. The contractual start date was in March 2012. The final report began editorial review in February 2015 and was accepted for publication in October 2015. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

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