MOVING LENTIVIRAL-BASED GENE THERAPY INTO A FIRST-IN-MAN CF TRIAL

Griesenbach, D.[1,8]; Alton, E. [1,8]; Beekman, J.[2,5]; Boyd, A.[3,8]; Chan, M. [1,8]; Davies, J.C.[1,8]; Davies, L.[4,8]; Davidson, H.[3,8]; Dekkers, F.[5]; Gea-Sorli, S.[1,8]; Gill, D.[4,8]; Hasegawa, M.[6]; Higgins, T. [1,8]; Hyndman, L.[3,8]; McLachlan, G.[7,8]; Inoue, M.[6]; Hyde, S.C.[4,8]; Moran, C. [1,8]; Meng, C. [l,8]; Paul-Smith, M. [l,8]; Pringle, I.[4,8]; Pytel, K. [1,8]; Rodriguez-Martinez, A. [1,8]; B.[3,8]; Tsugumine, S.[6]

1. Department of Gene Therapy, Imperial College, London, London, United Kingdom; 2. Department of Pediatric Pulmonology, University Medical Centre, Utrecht, Netherlands; 3. Medical Genetics Centre for Genomic and Experimental Medicine, University of Edinburgh, Edinburgh, United Kingdom; 4. Gene Medicine Group, NDCLS, John Radcliffe Hospital, Oxford University, Oxford, United Kingdom; 5. Laboratory of Translational Immunology, Wilhelmina Children's Hospital, University Medical Centre, Utrecht, Netherlands; 6. DNAVEC Corporation, Tsukuba, Japan; 7. Developmental Biology Division, The Roslin Institute Roslin, Edinburgh, United Kingdom; 8. UK Cystic Fibrosis Gene Therapy Consortium, London, United Kingdom

The UK CF Gene Therapy Consortium has developed a pipeline of vectors to deliver CFTR into the airway epithelium. The first of these (plasmid/liposome complexes) recently completed a Phase IIb trial. Anticipating that increased efficiency of gene transfer will be required, we have developed an F/HN-pseudotyped lentivirus which is ~2 logs more efficient in lung gene transfer than non-viral vectors, a single administration lasts for the lifetime of a mouse, and can be repeatedly administered. This vector is targeted for a first-in-man study in 2016, and in preparation for this we have assessed (1) selection of the most efficient promoter/enhancer for lung gene transfer, (2) assessment of toxicity "benchmarked" against the leading non-viral formulation including mapping of integration sites, (3) determination of transduction efficiency which will be used to inform dose-ranging in the trial and characterisation of the cell types transduced by the vector, (4) understanding the impact of pre-existing and acquired anti-viral immunity on transduction efficiency and toxicity, (5) confirmation of CFTR expression and function in relevant models, and (6) comparison of vector stability in a jet and single-pass mesh nebuliser. Data will be presented for each of these components, which we believe support progression into

human studies. Trial design as well as a regulatory-compliant toxicology study will also be discussed.