101* Inhaled tobramycin nebulizer solution for treatment of early *Pseudomonas aeruginosa* infection: the ELITE study

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The benefit of early antibiotic intervention in treating *P. aeruginosa* in patients with cystic fibrosis (CF) is increasingly acknowledged. However, the effect of different treatment periods in this early intervention is unclear.
In the open-label, randomized, multicentre ELITE (EarLy Inhaled Tobramycin for Eradication) study, CF patients ⩾6 months of age with early *P. aeruginosa* infection were treated twice daily with tobramycin nebulizer solution (TNS; 300 mg in 5 ml) for 28 or 56 days and followed up for 27 months. The primary objective was to determine the median time to recurrence of any strain of *P. aeruginosa*. Secondary objectives were (a) assessment of the proportion of patients free of *P. aeruginosa* 1 month after completion of TNS treatment and (b) a safety evaluation of TNS.
All patients were initially given TNS for 28 days. Eligible patients were then randomized 1:1 either to stop TNS treatment or to receive a further 28 days of treatment. The study recruited 123 patients at 21 European CF centres; 35 patients were not randomized due to the presence of *P. aeruginosa* antibodies at baseline. Of the 88 randomized patients, 46 received 28 days and 42 received 56 days of treatment. Genotyping of *P. aeruginosa* isolates obtained at baseline and on recurrence was conducted using random amplified polymorphic DNA polymerase chain reaction and pulsed-field gel electrophoresis for similar strains. Safety monitoring assessed treatment-emergent adverse events, serum tobramycin levels, renal function, and audiometry. Study recruitment was completed in November 2005, and the last patient completed follow-up in January 2008. Final results of the study will be presented at the meeting.
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102* A randomized placebo-controlled study of nebulized liposomal amikacin (Arikace™) in the treatment of cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection

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Objective: Arikace™ is a sustained-release liposome formulation of amikacin for inhalation being developed for the treatment of *P. aeruginosa* (Pa) infection in CF patients (pts). The primary objective of this study was to evaluate the effects of 28-day (d) exposure of Arikace™.
Methods: This is a Phase2a study conducted in 15centers in Europe. Patients were stratified by baseline FEV1(%pred) and randomized 2:1 to Arikace™ or placebo (1.5% NaCl). Cohort1 received 280 mg and Cohort2, 560 mg of active drug or placebo for 28d by inhalation with PARIeFlow® nebulizer, and were followed for 28d. Safety; pharmacokinetics; Pa sputum density; Quality of Life (CFQ-R) and exacerbation rate were evaluated weekly during the study period of 56d.
Results: 66pts were enrolled. 32 Cohort1 pts have completed study:10adults;12pts aged 13–18 yr;10pts aged 6–12 yr. Baseline FEV1(%pred) was 40–75% in 19pts and >75% in 13pts. A review of safety and efficacy data by the DSMB recommended enrollment in Cohort2, and 34pts have enrolled:13 adults;13 pts aged 13–18 yr; 8pts aged 6–12 yr. Baseline FEV1(%pred) was 40–75% in 24pts and >75% in 10pts. All pts in Cohort2 have received >17d of treatment and 29pts have completed 28d of treatment. Final study data available in April for submission to ECFS.
Conclusion: Arikace™ given once daily for 28d at a dose of 280 mg was well tolerated in CFpts. To date 29pts in Cohort2 (560 mg) have completed treatment and others are being evaluated. Baseline characteristics and clinical parameters of pts enrolled in this randomized, placebo-controlled study of Arikace™ for inhalation provides an initial profile of the population that may benefit from this treatment.

103* Pharmacokinetics of ciprofloxacin PulmoSphere® inhalational powder

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Introduction: Ciprofloxacin has proven anti-pseudomonal activity. An inhaled formulation – Ciprofloxacin PulmoSphere® Inhalational Powder (CPIP) has been developed to maximise bactericidal activity in lung endothelia of cystic fibrosis (CF) patients.
Methods: In a Phase I single-centre, randomised, single-blind placebo-controlled study of healthy male volunteers, subjects inhaled a single 50 mg dose of CPIP (32.5 mg ciprofloxacin betaine) followed by 50 mg placebo. Vital signs, electrocardiogram, lung function (total specific resistance, thoracic gas volume and FEV1) and adverse events (AE) were assessed. Systemic absorption was measured in blood and urine. PK parameters were calculated from plasma concentration vs time data. A physiological PK model of inhalation administration was used to estimate CPIP deposition in the lungs. A further study in CF patients is on-going.
Results: CPIP was well tolerated with no clinically relevant AE and no clinically relevant changes in vital signs, ECG outputs or lung function. Compared with historic data for a single IV/PO dose (e.g. Cmax 3–5 mg/L), a minimal total systemic exposure was seen (AUC 0.354 mg*h/L, median tmax 0.6 h; Cmax 0.06 mg/L). Terminal half life (9.5 h), clearance (91.7L/h) and volume of distribution (1262L) data indicate that CPIP was delivered effectively to the lungs. PK modelling showed ~20% of the inhaled dose was deposited in the trachea/bronchi.
Conclusion: In healthy male subjects, inhaled CPIP is well tolerated, has minimal systemic exposure and is delivered in an active form to the lungs.
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104 Single-dose pharmacokinetics of aerosol MP-376 (levofloxacin solution for inhalation) in cystic fibrosis patients: PK–PD implications

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Objective: Pulmonary delivery of anti-infectives provides the potential to attain PK-PD indices in the lung that exceed those which can be achieved with systemic dosing. MP-376 is a novel formulation of levofloxacin (LVX) that enables safe, rapid delivery, and provides taste masking. This analysis compares LVX sputum and serum pharmacokinetics following aerosol MP-376 with an oral 750 mg LVX dose.
Methods: Eight stable CF patients were enrolled in a single ascending dose study of MP-376 loaded doses of 78, 175, and 260 mg using the PARI eFlow nebulizer. In a separate group of 8 CF patients, oral LVX 750 mg was administered. Serum and sputum samples were assayed for LVX concentration using HPLC.
Results: The mean LVX Cmax in the sputum following aerosol MP-376 doses of 78, 175, and 260 mg, or oral LVX were 388, 714, 1 112, and 9 mg/L, respectively. Mean sputum LVX AUCs following aerosol MP-376 doses or oral LVX were 851, 656, 1 448, and 93 mg-h/L, respectively. Mean serum LVX AUCs for aerosol MP-376 or oral LVX were 2.0, 4.5, 6.5, and 77 mg-h/L, respectively. Aerosol doses of MP-376 were well-tolerated, with no drug-related serious adverse effects.
Conclusions: Aerosol administration of MP-376 results in markedly higher LVX exposures in sputum compared to maximum oral doses, thus increasing key PK-PD indices for antibacterial effects. Serum LVX levels are at least 10-fold lower with aerosol administration of MP-376 compared to oral doses. Multiple-dose safety and efficacy studies of MP-376 in CF patients are in progress.