84 Pulmosphere™ DPI technology reduces time burden in cystic fibrosis: the lesson of tobramycin inhalation powder (TIP™)

D.E. Geller[1], S. Heuerding[2], M. Higgins[3], J. Weers[4]. [1]*Nemours Children's Clinic, Orlando, United States;* [2]*Novartis, Basel, Switzerland;* [3]*Novartis, Horsham, United Kingdom;* [4]*Novartis, California, United States*

Background: CF patients take many inhaled drugs and thus have a large treatment burden. Dry powder inhalers (DPI) can deliver drugs faster than liquid nebulizers, but have been limited to low-dose asthma drugs. The T-326 DPI delivers a high payload of the novel tobramycin PulmoSphere™ formulation, which was developed to improve the convenience of administration of inhaled tobramycin.
Methods: We review the development of TIP™, the PulmoSphere particle engineering process and the key features and benefits of this novel formulation.
Results: TIP PulmoSphere particles are produced by spray-drying an emulsion-based feedstock, resulting in small (median diameter: 1.7–2.7 μm) spheroidal, highly porous, sponge-like particles. These characteristics favor dispersibility by minimizing the area of particle-to-particle contact. The T-326 DPI was designed to reduce administration time vs nebulization. In two clinical studies (EAGER and EVOLVE trials), patients with CF ⩾6 years of age with chronic *Pseudomonas aeruginosa* and airway obstruction (FEV_1 between 25–75% of predicted) were able to use the drug/device combination successfully. Compared to tobramycin inhalation solution via jet nebulizer, the TIP/T-326 Inhaler combination provides about a 3-fold more efficient deposition of tobramycin to the lung, with faster delivery (4–6 vs 15–20 min), no thorough cleaning requirement, and greater convenience.
Conclusion: TIP reduces treatment burden and may improve treatment adherence, a key factor for clinical outcomes in CF. Pulmosphere technology may also be applied to other drugs (small molecules, peptides, proteins) with applications in CF.

85 Aztreonam 75 mg powder and solvent for nebuliser solution (AZLI) in cystic fibrosis (CF) patients with chronic *Burkholderia* species (*Burk*) infection: baseline demographics and microbiology from a randomized, placebo-controlled trial

E. Tullis[1], J.L. Burns[2], G. Retsch-Bogart[3], M. Bresnik[4], S. Lewis[5], A.B. Montgomery[5], J.J. LiPuma[6]. [1]*University of Toronto, Toronto, ON, Canada;* [2]*University of Washington, Seattle, WA, United States;* [3]*University of North Carolina, Chapel Hill, NC, United States;* [4]*Gilead Sciences, Foster City, CA, United States;* [5]*Gilead Sciences, Seattle, WA, United States;* [6]*University of Michigan, Ann Arbor, MI, United States*

Objectives: *Burk* infections cause significant morbidity/mortality in CF patients (pts). *Burk*-infected CF pts have been excluded from prior aerosolized antibiotic trials. Aztreonam has in vitro activity vs *Burk* and there are anecdotal reports of responses to compassionate use AZLI in *Burk*-infected pts. A 1 yr randomized placebo-controlled trial of AZLI, conducted at 35 sites in the US and Canada, is fully enrolled (*ClinicalTrials.gov NCT01059565)*. Baseline demographic and microbiology data are presented.
Methods: CF pts ⩾6 yrs with chronic *Burk* infection (>50% of respiratory cultures positive in past year, isolate confirmed *Burk* by reference research lab) and stable pulmonary disease were enrolled. Pts were randomized to receive 6 mos of blinded AZLI 75 mg or placebo TID every day via Pari Investigational eFlow® Nebuliser System, followed by 6 mos of open label AZLI for all pts. Endpoints include change in FEV_1 and *Burk* CFU, use of systemic antibiotics and hospitalizations.
Results: 100 pts (males 61%) were randomized and treated. Mean age was 26.3 yrs (83% >18 yrs). Mean FEV_1 57% predicted. *B. cenocepacia* (42%) and *B. multivorans* (28%) were the most common of the 9 *Burk* spp isolated. *Pseudomonas aeruginosa (PA)* was isolated in 29% of pts. Mean *Burk* $\log_{10}$ CFU/gm was 6.9. Aztreonam MIC_{50} was 64 μg/mL; MIC_{90} 1024 μg/mL.
Conclusions: This is the largest randomized controlled trial evaluating the safety and efficacy of aerosolized antibiotic treatment in *Burk*-infected CF pts. Baseline demographics of *Burk*-infected pts are similar to those of CF pts in *PA* infection trials. 70% of *Burk*-infected pts had either *B. cenocepacia* and *B. multivorans*.
Supported by Gilead Sciences

86* Lung function improvement with aztreonam 75 mg powder and solvent for nebuliser solution (AZLI) in a single-arm extension of a randomized trial of inhaled antipseudomonal antibiotics in patients with cystic fibrosis (CF) and *Pseudomonas aeruginosa* infection

B.M. Assael[1], R. Chiron[2], R. Fischer[3], M. Bresnik[4], S. Lewis[5], A.B. Montgomery[5], T. Pressler[6]. [1]*Cystic Fibrosis Center, Verona, Italy;* [2]*CHU de Montpellier, Montpellier, France;* [3]*University of Munich, Munich, Germany;* [4]*Gilead Sciences, Foster City, CA, United States;* [5]*Gilead Sciences, Seattle, WA, United States;* [6]*National University Hospital, Copenhagen, Denmark*

Objectives: In a 6 month randomized trial of three 28-day on/off courses of AZLI vs tobramycin nebuliser solution (TNS) in 268 CF patients (pts) with *Pseudomonas aeruginosa (PA)* infection, AZLI was superior to TNS at 28 days and over 3 treatment courses in lung function (FEV_1) improvement. A single-arm extension phase (EXT) evaluated safety and efficacy of AZLI for 3 additional 28-day on/off treatment cycles (*ClinicalTrials.gov NCT00757237)*. FEV_1 responses for the first 2 EXT courses of AZLI are presented.
Methods: CF pts ⩾6 yrs, baseline FEV_1 ⩽75% predicted, chronic *PA* and stable pulmonary disease were enrolled. EXT was open to European pts completing ⩾1 course of AZLI or TNS during the randomized phase (RAND) of the study. The start of RAND followed 14–28 days off antibiotics. All pts in EXT received AZLI 75 mg TID via Pari Investigational eFlow® Nebulizer System for 3 cycles (28 days on/28 days off). Mean % changes from RAND baseline in FEV_1 % predicted at end of 1st and 2nd EXT course were calculated using observed case data.
Results: Of 174 European pts in RAND, 133 (76%) enrolled in EXT. Mean age 24.7 yrs.
Mean % changes from RAND baseline in FEV_1 % predicted:
65 TNS-treated pts after 3 RAND courses: −1.2; Switched to AZLI in EXT course 1 and 2: +4.9 and +4.7 respectively
68 AZLI-treated pts after 3 RAND courses: +8.6; Continued AZLI in EXT course 1 and 2: +6.5 and +5.1 respectively
No new safety issues were noted.
Conclusions: CF pts on AZLI showed sustained FEV_1 improvements after each of 5 treatment courses. CF pts showed no FEV_1 improvements after 3 courses of TNS but had marked improvements after switching to AZLI.
Supported by Gilead Sciences

87* Effects of inhaled MP-376 (Aeroquin™, levofloxacin inhalation solution) on cystic fibrosis patients with both *Staphylococcus aureus* (SA) and *Pseudomonas aeruginosa* (PA) lung infection

P.A. Flume[1], D.E. Geller[2], J.S. Loutit[3], M.N. Dudley[3], D. Conrad[4], Mpex 204 Study Group. [1]*Medical University of South Carolina, Charleston, United States;* [2]*Nemours Children's Clinic, Orlando, United States;* [3]*Mpex Pharmaceuticals, San Diego, United States;* [4]*University of California San Diego, San Diego, United States*

Introduction: Approved inhaled antibiotics have been tested in patients with PA lung infection, but patients frequently have multiple pathogens identified in sputum cultures. This study assessed the efficacy of MP-376 in CF patients with chronic PA lung infection who were also infected with SA at baseline.
Methods: Randomized, double-blind, placebo controlled trial of 3 dose groups of MP-376 (120 mg QD, 240 mg QD, 240 mg BID) vs. placebo for 28 days, delivered by a customized investigational PARI eFlow nebulizer. Inclusion criteria: age ⩾16 years, chronic PA airways infection, FEV_1 25–85% predicted, and ⩾3 courses of inhaled antibiotics over the past 12 months. Data for the subset of MITT patients with SA at baseline were analyzed.
Results: The mean baseline characteristics of the 151 enrolled patients were age 29 years, FEV_1 52% of predicted, and 4.8 courses of inhaled antibiotics over last 12 months. Forty-four percent of patients were co-infected with SA (25% with methicillin-resistant; MRSA) at baseline. The improvement in FEV_1 (L) for patients co-infected with PA and SA for the 240 mg BID group ($n = 13$) compared to placebo ($n = 17$) at Day 28 was 11.3% ($p = 0.03$); the improvement in FEV1 with MP-376 over placebo was similar in the 15 patient subset coinfected with MRSA (15.2%; $p = 0.11$).
Conclusion: Nebulized MP-376 demonstrated statistically and clinically significant improvement in lung function in this heavily-treated CF patient population, including patients with both PA and SA lung infection.