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REVIEW

Tobramycin administered by the TOBI® Podhaler® for persons with cystic fibrosis: a review

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Abstract: From its introduction, the antibiotic tobramycin has been an important tool in the management of persons with cystic fibrosis (CF) and chronic *Pseudomonas aeruginosa* lung infections. Initially an intravenous rescue treatment for pulmonary exacerbations, tobramycin delivered by inhalation has become a mainstay of chronic suppressive CF infection management. Platforms for tobramycin aerosol delivery have steadily improved, with increased lung deposition complimented by decreased device complexities, loaded tobramycin doses, delivery times, and treatment burdens. Most recently, a unique tobramycin inhalation powder (TIP) formulation with a portable delivery system, the TOBI® Podhaler® (Novartis AG, Basel, Switzerland) has been developed and approved in Europe, Canada, and Chile. Four capsules, each containing 28 mg of TIP are successively pierced and inhaled via the T-326 Dry Powder Inhaler Device (Novartis AG, Basel, Switzerland). No external power source is required to deliver an efficacious tobramycin dose in minutes. By comparison, tobramycin inhalation solution (TIS) (TOBI®; Novartis), is delivered by LC® Plus (PARI Respiratory Equipment Inc, Midlothian, VA) jet nebulizer powered by an air compressor over 15–20 minutes. Comparative pharmacokinetics, safety, and efficacy studies of TIS and TIP in CF subjects with *P. aeruginosa* ≥ 6 years old demonstrate that: tobramycin lung deposition with 112 mg TIP is comparable to that attained with 300 mg TIS, TIP is more effective than placebo and not inferior to TIS with respect to pulmonary function benefit, and TIP has significantly faster treatment times and achieves higher patient satisfaction than TIS. TIP is associated with an increased frequency of mild to moderate local adverse events (cough, dysphonia, and dysgeusia) compared with TIS, however, these become less frequent as subjects gain TIP experience. These results suggest that the TOBI Podhaler may better meet the needs of many CF patients and families by reducing treatment time and complexity and improving patient satisfaction compared with TIS.

Keywords: dry powder inhaler, tobramycin, cystic fibrosis

Cystic fibrosis and *Pseudomonas aeruginosa* lung infections

Cystic fibrosis (CF) is a life-shortening autosomal recessive genetic disease, affecting an estimated 80,000 individuals worldwide. Mutations of the CF transmembrane conductance regulator (*CFTR*) gene result in dysfunction or absence of CFTR protein activity on the apical surfaces of epithelia in multiple organ systems, including the airways.[1,2] One in 20 Caucasians carries an abnormal *CFTR* allele, with progressively lower prevalence of carriage in persons of Hispanic, African, and Asian descent.[3] More than 1800 mostly rare mutant *CFTR* alleles have been identified to date;[4] the F508del mutation accounts for more than two thirds of mutant alleles.[5–9] Though CFTR acts

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as a chloride channel, it also regulates transport of sodium and bicarbonate across epithelial membranes. In the airways, dysfunction of CFTR leads to depletion of the airway surface liquid, and thick, sticky airway secretions, resulting in decreased mucociliary clearance.[10] These factors, along with increasing epithelial adherence of inspired microorganisms[11] and a profound host inflammatory response, become self-sustaining as infection is established.[12] Currently, ~80% of CF deaths are the direct or indirect result of loss of lung function,[9] driven by chronic airway obstruction, complex lung infections, and inflammation.[1,12] Accumulation of multiple strains and species of microbial opportunists creates complex communities within conducting airways,[13] whereas invasion beyond the airway lumen and subsequent systemic infection are relatively rare. CF airway infections are unique in this respect (and many others) and tenets of traditional infectious disease biology often do not lend themselves well to either their characterization or management.

Pseudomonas aeruginosa, a notable CF pathogen associated with poorer overall outcomes, is the most frequently isolated bacterial species from CF respiratory tract specimens; in 2009, >51% of US Cystic Fibrosis Foundation Patient Registry patients had at least one airway culture positive for *P. aeruginosa*.[9] Infection prevalence increases with age and, if not treated within a few months of detection, *P. aeruginosa* becomes refractory to eradication with antipseudomonal antibiotics. Once established, chronic *P. aeruginosa* lung infections can be carried by persons with CF for their lifetimes[14–17] and are associated with worsening nutritional status, accelerated lung disease, and earlier death.[17–22]

Chronic suppressive antipseudomonal antibiotic therapy

The clinical course of CF lung disease is typically one of chronic progression interrupted by intermittent episodes of acute worsening of symptoms, termed "pulmonary exacerbations." In addition to recommended supportive treatments for CF lung disease,[23] antibiotics targeting *P. aeruginosa* respiratory infections to prevent and/or suppress bacterial growth and to decrease pulmonary inflammation and tissue injury are commonly used in CF.[24–27] Along with the classic use of antipseudomonal antibiotics in response to acute exacerbations associated with *P. aeruginosa*,[28,29] CF clinicians regularly schedule oral, aerosolized, and/or intravenous (IV) antipseudomonal antibiotic maintenance treatments in clinically stable patients.[23,30] Controlled trials of chronic suppressive antibiotic treatments have demonstrated significant reductions in exacerbation rates and significant improvements in both pulmonary function and patient and clinician assessments of global quality of life.[31–37]

Of the three possible routes of administration of chronic suppressive antipseudomonal antibiotic therapies (oral, inhaled, or IV), topical administration by aerosol inhalation has become predominant. Between 1995 and 2005, use of inhaled antibiotics in the US CF population increased from 6.5% to 43.1%.[38] The emergence of inhaled antipseudomonal antibiotics as the primary choice of CF clinicians for the suppression of chronic *P. aeruginosa* infections has several root reasons, some practical and some experiential. The earliest report of the benefits of chronic suppressive antipseudomonal therapies in patients with *P. aeruginosa* lung infection was published in 1983 and based on 2-week IV antibiotic courses administered every 3 months.[39] Despite initial reports of impressive clinical benefit, scheduled inpatient IV antibiotic treatments have obvious cost and quality of life liabilities, and there has been subsequent questioning of the true benefit of this approach compared with IV treatment guided by increased symptoms.[40] Although oral antibiotics are associated with a lower treatment burden, there are few orally bioavailable antipseudomonal antibiotics (fluoroquinolones) and no controlled trials demonstrating the safety and efficacy of chronic oral fluoroquinolones in CF. Beyond these limitations, the safety and efficacy of both oral and IV suppressive antibiotic therapies are limited by a common problem: use of the systemic circulation to access the site of infection within the lumen of the airways. Antipseudomonal antibiotics have dose-limiting systemic toxicities that affect the amount of drug that can reach the infection site via the systemic circulation. In contrast, inhalation of antibiotic aerosols allows topical delivery and results in peak concentrations at the infection site that are orders of magnitude higher than those achieved by IV or oral delivery, which should theoretically increase antibiotic efficacy. Although systemic exposure results from absorption of inhaled antibiotics from the lung, peak serum drug levels are substantially lower than those observed with systemic antipseudomonal antibiotic treatments.[41] This distinction, combined with an ability to administer inhaled antibiotics to outpatients, has led to the extensive study of inhaled antipseudomonal antibiotics as suppressive agents in CF.[31–33,36,42–54] While most of the earlier studies had significant limitations (small numbers; different drugs, doses, and aerosol delivery systems; heterogeneous patient populations; different study designs), they tended to demonstrate benefits such as improved lung function, reduced *P. aeruginosa* density, and fewer exacerbations.[55]

These positive early experiences caught the attention of pharmaceutical companies and, now, the commercial registration of several antipseudomonal antibiotic formulations developed specifically for administration as aerosols to patients with CF and *P. aeruginosa* infection have dramatically improved access to this treatment modality.

Topical administration of tobramycin in CF

Aminoglycosides are antipseudomonal antibiotics that have several characteristics that have lent themselves to use as inhaled CF therapies.[31,32,36,43,44,46,48,49,53,56–58] These characteristics include good solubility, relative stability in aqueous solution, physicochemical properties conducive to aerosolization, systemic as opposed to local dose-limiting toxicities, and bacterial killing proportional to maximum drug concentration achieved at the infection site.[59]

Tobramycin is the most extensively studied and utilized inhaled aminoglycoside. In normal volunteers, systemic tobramycin is eliminated by glomerular filtration, while tobramycin clearance is accelerated in persons with CF[60] due to additional diffusion into the lung, sputum binding, and expectoration.[61] At levels achieved by IV delivery, more than 90% of tobramycin in CF sputum is bound and inactive, but this binding is saturable and higher tobramycin concentrations retain activity in sputum.[62] For this reason, relatively large doses of tobramycin have been delivered to the lung by inhalation to improve antibacterial activity.[48,49]

Improvements in tobramycin aerosol delivery

Early methods for delivery of high dose tobramycin were plagued by complicated protocols, poor device efficiency, and substantial treatment burden. Patients were required to dissolve tobramycin sulfate in saline, transfer an aliquot to an ultrasonic nebulizer, and dilute with saline.[48] The aerosol generator had to be activated well before inhalation and patients were required to inhale 200 breaths.[48] Investigators in a subsequent study using the same protocol observed that more than 50% of midday doses were not received by patients.[49]

Recognizing that this system had substantial room for improvement, investigators subsequently studied a variety of different tobramycin aerosol delivery platforms.[63,64] As nebulizer efficiency improved, the dose of tobramycin loaded into the nebulizer was correspondingly reduced. By the time of the large multicenter Phase III CF studies of tobramycin inhalation solution (TIS), (TOBI®; Novartis, Basel, Switzerland), the delivery system consisted of 5 mL of a 60 mg/mL tobramycin solution loaded into a LC® Plus (PARI Respiratory Equipment, Inc, Midlothian, VA) jet nebulizer coupled with a PulmoAide® (DeVilbiss Healthcare, Somerset, PA) compressor.[32] Randomized, blinded, placebo-controlled studies of TIS demonstrated a significant mean relative improvement in forced expiratory volume in 1 second (FEV_1) among subjects receiving TIS (Figure 1A), as well as a significant reduction in the risk of hospitalization or treatment with IV antibiotics for pulmonary exacerbation.[32] Adverse events noted to be significantly higher in subjects receiving TIS relative to subjects receiving placebo were tinnitus (3.1% versus 0%, $P = 0.003$) and dysphonia (12.8% versus 6.5%, $P = 0.02$).[32] Despite the relatively low serum tobramycin levels associated with TIS treatment compared with IV tobramycin administration, at least one incident of acute renal failure associated with tobramycin inhalation powder (TIP) use has been reported since regulatory approval,[65] indicating that acute systemic tobramycin toxicity remains an important (if relatively rare) risk associated with TIS. In addition, at least one instance of hypersensitivity to tobramycin presenting as persistent bronchospasm and associated eosinophilia has been linked to TIS administration.[66]

Although the TIS platform that has received regulatory approval represented a marked improvement over earlier tobramycin aerosol delivery methods, shortcomings remain. First, TIS administration takes at least 15 minutes per dose under the best of circumstances, and substantially longer for patients with poorly functioning compressors. When this is included with nebulizer set up, cleaning of the unit required after each administration, and daily disinfection, the time burden is substantial. In addition, the LC Plus has a residual volume that results in waste of about 1.5/5 mL TIS dosing solution. The jet nebulizer/compressor combination is not very compact or portable, and requires an AC power source. Finally, TIS requires refrigeration during storage.

Since the regulatory approval of TIS, a number of in vitro and in vivo delivery studies of tobramycin aerosols have been reported that address shortcomings of the approved TIS platform. These include studies of alternative air compressors,[67,68] behavioral modifications that can increase tobramycin lung deposition and reduce variability,[69] and alternative aerosol delivery systems[70–72] and/or tobramycin formulations[70,73–75] to increase aerosol output and reduce administration time. Taken together, these reports make it clear that there is substantial room for improvement in the mechanics of tobramycin wet aerosol delivery over the original TIS delivery platform.

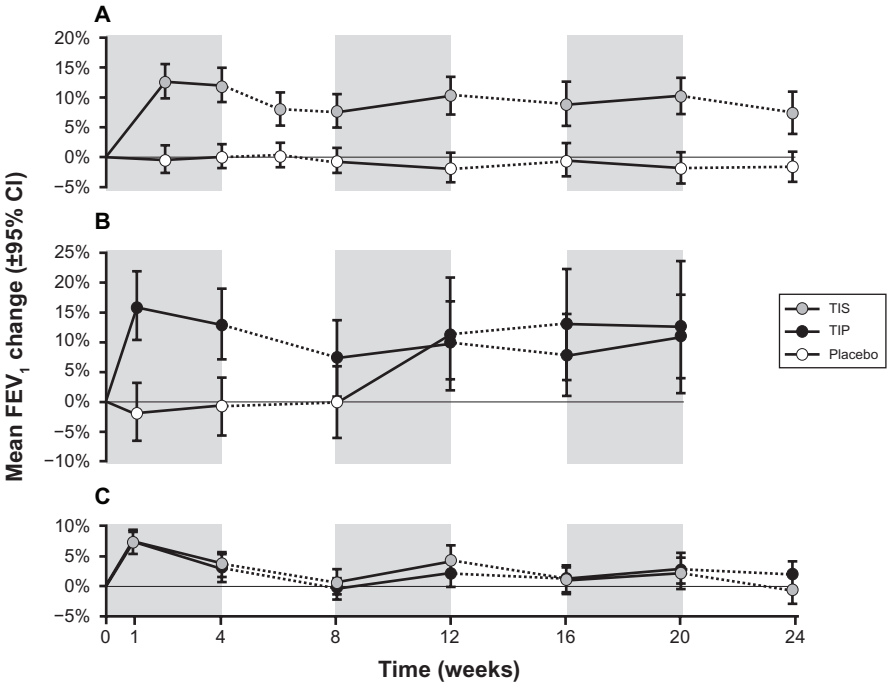

Figure 1 Pulmonary function outcomes from randomized, controlled, blinded inhaled-tobramycin studies. (**A**) Comparison of TIS to placebo.[32] (**B**) Comparison of TIP to placebo for 1 treatment cycle followed by two cycles of treatment with TIS.[77] (**C**) Comparison of TIS to TIP for 3 treatment cycles.[87]

Notes: Gray circles, subjects randomized to receive 112 mg TIP twice daily; black circles, subjects randomized to receive 300 mg TIS twice daily; open circles, subjects randomized to receive matching placebo treatment twice daily; gray zones and solid lines, 28-day periods where subjects were receiving study treatments; dashed lines, 28-day periods where subjects were not receiving study treatments; bars represent 95% confidence intervals for means. **A** adapted with permission from Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med*. 1999;340(1):23–30; © 1999 *New England Journal of Medicine*. **B** adapted with permission from Konstan MW, Geller DE, Minić P, Brockhaus F, Zhang J, Angyalosi G. Tobramycin inhalation powder for P. aeruginosa infection in cystic fibrosis: the EVOLVE trial. *Pediatr Pulmonol*. 2011;46(3):230–238. **C** adapted from *Journal of Cystic Fibrosis*, Vol 10, Issue 1, Michael W Konstan, Patrick A Flume, Matthias Kappler, Raphaël Chiron, Mark Higgins, Florian Brockhaus, Jie Zhang, Gerhild Angyalosi, Ellie He, David E Geller, Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial, Pages 54–61, Copyright 2011, with permission from Elsevier.

Tobramycin PulmoSphere® technology

Many inhaled medications currently on the market for asthma and COPD are formulated as dry powders and delivered by dry powder inhalers (DPIs). DPI drug delivery is considerably more convenient than wet aerosol administration, as devices are portable, do not require external power, have short administration times, and do not require refrigeration, rigorous cleaning, or disinfection. Pharmaceutical powders are hygroscopic, requiring manufacturing and packaging under conditions that exclude water. Traditional powders are formed by milling the drug into small particles that have large relative surface areas and strong cohesive forces between particles. This requires the addition of large carrier particles such as lactose to improve disaggregation of the powder into a respirable aerosol, a modification that severely limits the quantity of active drug that can be packed into a dose. Typical DPIs deliver between 18 and 550 μg of active drug per dose, several orders of magnitude less than the quantity of tobramycin delivered by TIS to persons with CF. For this reason, traditional DPI technologies have not been suitable for the delivery of tobramycin to the lungs in the past.

Recently, an alternative method for the manufacture of a dry powder tobramycin formulation, termed PulmoSpheres® (Novartis AG, Basel, Switzerland), has been developed.[76] PulmoSpheres of tobramycin inhalation powder (TIP) are produced by an emulsion-based spray-drying process that yields light porous tobramycin particles with improved flow and dispersion properties and more uniform particle size distributions when compared with traditional milled powders.[76] With improved flow and dispersion, TIP can be delivered using modest inspiratory efforts from capsules with the portable breath-actuated T-326 Dry Powder Inhaler Device (Novartis AG). When compared to TIS delivery, the T-326 inhaler/TIP combination offers faster tobramycin delivery[77] and improved intrapulmonary deposition in a convenient, portable format.[76]

The chemistry and manufacture of TIP PulmoSpheres are complex and have been extensively reviewed.[76] Briefly, submicron oil-in-water emulsion droplets are created by homogenization of perfluorooctyl bromide (perflubron) in water. The dispersed oil droplets are then stabilized with a monolayer of the long-chain phospholipid distearoylphosphatidylcholine (DSPC).

Tobramycin sulfate and $CaCl_2$ are then added to the water phase of this feedstock, which is atomized into a hot air stream, with each atomized droplet containing a large number of submicron emulsion droplets. As water evaporates from atomized droplets in the hot air stream, tobramycin diffuses to the center of the droplet while the submicron oil droplets migrate to the periphery of the droplets. Eventually, shells consisting primarily of DSPC, $CaCl_2$, and perflubron are formed on the exterior of the droplets. Further drying causes perflubron evaporation, leaving dry particles with a porous exterior shell of DSPC and $CaCl_2$ and amorphous solid tobramycin within that are collected from the airstream by cyclone separators. The process of conversion of atomized feedstock droplets to dried particles of TIP occurs within milliseconds. The final TIP formulation contains tobramycin sulfate as the active ingredient and DSPC and $CaCl_2$ as excipients, with only trace levels of perflubron remaining. TIP is chemically very stable, with a long shelf life and no need for refrigeration. As with all powders, TIP is extremely hygroscopic and must be packaged in unit-dose blister packs to avoid hydration and retain flow and dispersion properties.

The physical characteristics of TIP PulmoSpheres are quite different from those of traditional dry powders that are created by the milling of crystallized compounds (Figure 2A).[76] PulmoSphere size distributions are considerably more uniform, and their spheroidal shape and DSPC surface composition result in much lower interparticle cohesive forces (Figure 2A), meaning that PulmoSpheres are substantially less prone to agglomeration than milled powders and the amount of force necessary to suspend them as dry aerosols is lower, allowing the facilitating of their use in younger patients or those with low levels of pulmonary function.[76] For instance, it has been estimated that a patient could essentially empty a TIP capsule in a T-326 inhaler with a single 1.0 L inhalation at a 40 L/min flow rate or with two 0.6 L inhalations using a 30 L/min flow rate.[78] These volumes and rates are well within the capabilities of most (but perhaps not all) persons with CF aged ≥6 years.[79] Low agglomeration and easy dispersal of PulmoSpheres obviates the need for carrier particles such as lactose, allowing a much higher payload of active drug per capsule.

The T-326 inhaler is pictured in Figure 2B. A hypromellose capsule containing tobramycin PulmoSpheres is loaded into the device by removing the mouthpiece and inserting the capsule into the chamber. The mouthpiece is screwed back onto the body, the button is depressed to pierce the capsule, and the patient inhales through the mouthpiece. During inspiration, the capsule rotates rapidly in the T-326 chamber, which causes TIP to be emptied from the capsule.

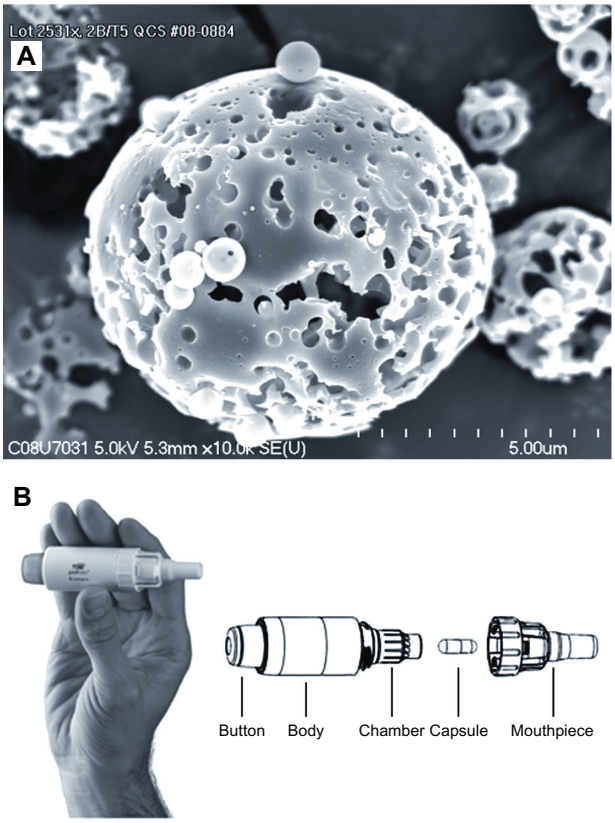

Figure 2 TIP PulmoSpheres® (Novartis AG, Basel, Switzerland) and the T-326 Dry Powder Inhaler Device (Novartis AG). (**A**) Electron micrograph of PulmoSpheres, which are light, hollow, porous, particles that are less dense than milled powders, and travel more slowly in the inspiratory airstream, thus avoiding impaction in the upper airways. (**B**) The T-326 inhaler is a simple, capsule-based dry powder inhaler that is portable, inexpensive, and disposable.[76]

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The T-326 has relatively low airflow resistance to allow patients to generate high airflow rates and produce reliable dose delivery.[76,80] Although most CF patients, including those as young as 6 years of age, can empty more than 90% of the contents of a capsule in a single inhalation,[78] treatment instructions call for a second inhalation from the T-326 inhaler to ensure that capsules are completely emptied. The lowest values for respiratory parameters used to test capsule emptying in the lab were a 0.6 L inspiratory volume and a 30 L/min peak inspiratory flow.[78] It is likely that some patients with very severe limitation in lung function may not be able to empty the capsules to achieve lung deposition. Patients can confirm that the entire capsule dose has been delivered by inspecting the capsule after inhalation.

Dosing of inhaled tobramycin by dry powder delivery

Development of the TOBI® Podhaler® (Novartis, Basel, Switzerland) – TIP/T-326 inhaler combination – represents a

potentially significant advance in the delivery of tobramycin aerosols to persons with CF. Presumably, the greater convenience and portability of this format compared with TIS will be associated with a lower treatment burden and should afford greater treatment adherence. However, the improvements in tobramycin formulation and delivery that make the TOBI Podhaler an attractive treatment alternative to TIS also require determination of the dose of TIP that is "equivalent" to the 300 mg tobramycin dose of TIS. An equivalent TIP dose should contain substantially less than 300 mg tobramycin, as the fraction of TIP dose deposited in the lungs of healthy volunteers by T-326 inhaler is approximately three times higher than that of TIS delivered by the LC Plus.[83,87]

Unfortunately, determination of a TIP dose that is clinically equivalent to the 300 mg TIS is not simple, for several reasons. Although it is presumed that clinical efficacy of TIS results from deposition of tobramycin at the site of *P. aeruginosa* infection, the endobronchial space, tobramycin levels measured in CF sputum following TIS delivery are highly variable.[63,64,69,84] This variability probably reflects both true differences in tobramycin deposition driven by patient-related variables as well as sampling inhomogeneity. Due to variability in sputum tobramycin concentrations, investigators have employed serum tobramycin levels after aerosol delivery as surrogates for lung deposition when comparing different delivery devices and/or formulations.[63,64,85,86] This approach seems logical, in that systemic tobramycin presumably originates from absorption across the lung epithelia. However, serum tobramycin concentrations may not be ideal surrogates for tobramycin lung deposition, as different aerosol delivery devices can yield substantially different ratios of peak sputum to serum tobramycin levels,[64] and relative tobramycin absorption may differ by lung region (eg, peripheral versus central). Recognizing these caveats, investigators have determined that consecutive inhalation of four TIP capsules containing a total of 112 mg tobramycin by T-326 inhaler produces a comparable tobramycin serum pharmacokinetic profile to deliver 300 mg TIS by LC Plus in a dose-escalation study in CF patients.[83] Further, a scintigraphy study of healthy volunteers demonstrated a similar distribution of tobramycin among central and peripheral airways between TIP and TIS, and showed that intersubject variability in tobramycin deposition with the TIP/T-326 system was lower than that of TIS.[82] It is possible that a portion of this difference in intersubject variability resulted from the controlled inhalation associated with TIP administration, as controlled inhalation has been previously shown to reduce deposition variability among TIS-treated subjects.[69] The average time required to administer four TIP capsules by T-326 inhaler is about 4–6 minutes versus about 20 minutes required for TIS administration ($P < 0.001$).[77,83,87]

TIP clinical efficacy studies

Comparisons of serum pharmacokinetics between 112 mg TIP delivered by T-326 inhaler and 300 mg TIS delivered by LC Plus are insufficient to infer either clinical efficacy of TIP or equivalency to TIS. This is because there are no dose-proportionality data defining relationships between serum or sputum tobramycin levels in TIS-treated patients and magnitude of clinical benefit experienced (as measured by improved lung function or decreased risk of exacerbation). Further, treatment-related adverse events identified in TIS Phase III studies (tinnitus and dysphonia) were not correlated with differences in systemic tobramycin exposure.[32]

Two Phase III studies have now been conducted in subjects aged ≥6 years with CF and *P. aeruginosa* lung infections to characterize the clinical efficacy and safety of TIP delivered by the T-326 inhaler. The EVOLVE (EValuate tObramycin inhaLed dry powder efficacy Versus placebo in cystic fibrosis patiEnts) study was a randomized, double-blind, placebo-controlled trial in subjects that were relatively naïve to prior TIS treatment.[77] A total of 105 subjects from 38 treatment centers in Europe, Latin America, and the USA were randomized to receive either 112 mg TIP or placebo delivered twice daily by T-326 inhaler for 28 days followed by a 28-day off-treatment period. Two subsequent 28 day on/off treatment cycles of twice-daily 112 mg TIP were administered to all subjects. Enrollment in the study was halted when an interim analysis determined that the primary efficacy endpoint had been reached. Subjects receiving TIP experienced a statistically significant improvement in mean FEV_1% predicted at the end of the first treatment period compared to those receiving placebo (Figure 1B).[77] Improvement in FEV_1 in TIP-treated subjects compared with subjects receiving placebo was retained after 28 days off treatment. Subjects receiving TIP also had a reduced mean density of *P. aeruginosa* in their sputum, fewer hospitalizations related to respiratory events, and used fewer concomitant antipseudomonal antibiotics than their peers receiving placebo in the first treatment cycle.[77] Although changes in CF practice patterns and standards of care made it impossible for EVOLVE investigators to employ the same three-cycle placebo controlled design of the Phase III TIS studies,[32] TIP efficacy results observed during the first 56 days of the EVOLVE study were comparable to those observed in the first 56 days of the TIS Phase III studies (Figure 1A and B).[32,77]

Table 1 Evolution of tobramycin aerosol delivery platforms

Characteristic	UltraNeb® 100/99[a]	TIS/LC PLUS[b]	TIP/T-326[c]
Average delivery time	15–20 minutes	15–20 minutes	4–6 minutes
Daily treatments	3	2	2
Daily treatment time	45–60 minutes	30–40 minutes	8–12 minutes
Tobramycin load	600 mg	300 mg	112 mg
Daily tobramycin load	1800 mg	600 mg	224 mg
Dose preparation required?	Yes	No	No
Aerosol generator type	Ultrasonic nebulizer	Jet nebulizer	Dry powder inhaler
Cleaning	Washing/drying Disinfection regimen	Washing/drying Disinfection regimen	Wiping/tapping
Set-up/clean-up time	>30 minutes	10–15 minutes	1–2 minutes
Requirements	AC power	AC power, refrigeration	None

Notes: [a]Smith et al, 1989;[48] UltraNeb®, DeVilbiss Healthcare, Somerset, PA. [b]Marketed as TOBI®[32] (Novartis, Basel, Switzerland). [c]Marketed as TOBI® Podhaler® (Novartis).[77,87]
Abbreviations: TIS, tobramycin inhalation solution; TIP, tobramycin inhalation powder.

A more direct comparison of TIP and TIS safety and efficacy was achieved in the open-label, randomized EAGER (Establish A new Gold standard Efficacy and safety with tobramycin in cystic fibRosis) study, which compared twice-daily 112 mg TIP treatment with twice-daily TIS treatment for three consecutive cycles of 28 days treatment followed by 28 days off treatment.[87] The study was conducted in 127 CF treatment centers in 15 countries. Of 553 subjects randomized, 308 received at least one dose of TIP and 225 (73.1%) of those completed the study, while 209 subjects received at least one dose of TIS and 171 (81.8%) of those completed the study. The primary objective of the study was to identify any adverse event associated with TIP not already identified in previous TIS studies. Inclusion of 300 TIP subjects was estimated to provide > 99% probability of observing at least one adverse event with a true incidence of 2% in subjects receiving TIP. The study was also designed to provide 96% power to demonstrate noninferiority of TIP to TIS with regard to relative change from baseline in FEV_1% predicted after three treatment cycles, based on a noninferiority margin of 6% and a one-sided significance level of 0.15 (assuming 1% true TIS–TIP treatment difference, and a 20% standard deviation).[87]

A higher percentage of EAGER subjects receiving TIP reported adverse effects than did subjects treated with TIS (90.3% versus 84.2%, $P < 0.05$). Most adverse effects were mild or moderate in intensity, and more subjects experienced adverse events in the first treatment cycle in both groups, with adverse events decreasing with each successive cycle. Cough (not including productive cough) was the most frequently reported adverse event in subjects treated with either TIP (48.4%) or TIS (31.1%), with post hoc analyses showing this difference to be statistically significant ($P < 0.001$). Most cough events were reported as being mild or moderate in intensity, with frequency of severe cough events low and similar between treatment groups (2.6% for TIP versus 1.9% for TIS)[87] and an insignificant difference (post hoc $P = 0.558$). Only 12/308 TIP-treated subjects (3.9%) discontinued due to cough compared with 2/209 (1.0%) TIS-treated subjects. Important, incidence of acute bronchospasm as measured by precipitous drop in FEV_1 was low, and the same for each group. Adverse events other than cough that were more commonly reported in the TIP group were dysphonia (13.6% versus 3.8%; post hoc $P < 0.001$) and dysgeusia (3.9% versus 0.5%; post hoc $P = 0.019$).

Efficacy, as measured by mean increase in FEV_1% predicted from baseline to Day 28 of the third cycle, was similar between treatment groups, with the 1.1% difference in relative change falling within the predefined 6% margin for noninferiority of TIP to TIS (Figure 1C).[87] Study investigators concluded that (a) the safety profile of TIP was comparable with TIS, with the exception of cough, dysphonia and dysgeusia; (b) patient-reported satisfaction was significantly higher with TIP than TIS, which was related to the ease of use and convenience of TIP; and (c) TIP was not inferior to TIS with respect to clinical efficacy.

Conclusion

The clinical studies described formed the basis for an application for marketing authorization for the 112 mg tobramycin TIP/T-326 inhaler combination under the commercial name TOBI Podhaler. To date, marketing authorization has been granted in the European Union, Chile, and Canada. Dry powder formulation of tobramycin represents a significant advance in the logistics of inhaled tobramycin treatment for persons with CF (Table 1). Not only is this format faster, less cumbersome, and more portable than previous platforms, but it also involves the loading and disposition (including environmental disposal) of substantially less tobramycin. These attributes, combined with

evidence that this format is not inferior to the widely utilized wet aerosol formulation TIS with respect to efficacy (Figure 1) and is associated with only mild to moderate increases in local adverse events, suggest that dry powder tobramycin may be an attractive alternative to patients and caregivers. Important, because a minimum inspiratory flow and lung volume are required for TIP/T-326 use, as well as the cognitive ability to use a DPI correctly, TIS will continue to be the treatment of choice for younger patients or patients who are more ill, who may use simple tidal breathing for tobramycin aerosol treatment.[58,88]

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Dr VanDevanter has relationships with Baxter Healthcare, Genentech, Gilead, Kalobios, NanoBio, Pulmatrix, Rempex, and Vertex.

Dr Geller has relationships with Aires, Genentech, Gilead Sciences, Inc, Insmed, MAP Pharmaceuticals, NanoBio, Novartis, Pharmaxis, Philips Respironics, Rempex, Teva, Talecris, and Vertex.

References

1. Davis PB, Drumm M, Konstan MW. Cystic fibrosis. *Amer J Respir Crit Care Med*. 1996;154(5):1229–1256.
2. Ratjen F, Döring G. Cystic fibrosis. *Lancet*. 2003;361(9358):681–689.
3. National Newborn Screening and Genetics Resource Center. *National Newborn Screening Report*: *2000*. San Antonio, TX: National Newborn Screening and Genetics Resource Center; 2003. Available at http://genes-r-us.uthscsa.edu/resources/newborn/00/2000report.pdf. Accessed Aug 19, 2011.
4. Cystic Fibrosis Mutation Database. CFMDB statistics [web page on the Internet]. Toronto: Cystic Fibrosis Centre at the Hospital for Sick Children; nd [updated Apr 25, 2011]. Available from: http://genet.sickkids.on.ca/StatisticsPage.html. Accessed Aug 19, 2011.
5. European Cystic Fibrosis Society. *ECFS Patient Registry Report 2007 Data*. Karup: European Cystic Fibrosis Society; 2010. Available at: http://www.ecfs.eu/files/webfm/webfiles/File/ecfs_registry/ECFRreport2007final.pdf. Accessed Aug 19, 2011.
6. Cystic Fibrosis Trust. *UK CF Registry Annual Data Report 2009*. Bromley, London: Cystic Fibrosis Trust; 2011. Available at: http://www.cftrust.org.uk/aboutcf/publications/cfregistryreports/Final_UK_Cystic_Fibrosis_Registry_Report_2009.pdf. Accessed Aug 19, 2011.
7. Cystic Fibrosis Canada. *Canadian Cystic Fibrosis Patient Data Registry Report*: *2009*. Toronto: Cystic Fibrosis Canada; 2011. Available at: http://www.cysticfibrosis.ca/assets/files/pdf/CPDR_ReportE.pdf. Accessed Aug 19, 2011.
8. Cystic Fibrosis Australia. *Cystic fibrosis in Australia 2009*: *12th Annual Report from the Australian Cystic Fibrosis Data Registry*. North Ryde: Cystic Fibrosis Australia; 2011. Available at: http://www.cysticfibrosis.org.au/projects/dataregistry/. Accessed Aug 19, 2011.
9. Cystic Fibrosis Foundation. *Patient Registry*: *Annual Data Report 2009*. Bethesda, MD: Cystic Fibrosis Foundation; 2010. Available at: http://www.cff.org/UploadedFiles/research/ClinicalResearch/Patient-Registry-Report-2009.pdf. Accessed Aug 19, 2011.
10. Donaldson SH, Boucher RC. Update on pathogenesis of cystic fibrosis lung disease. *Curr Opin Pulm Med*. 2003;9(6):486–491.
11. Knowles MR, Gilligan PH, Boucher RC. Cystic fibrosis. In: Mandell GL, Bennett JE, Dolin R, editors. *Mandell*, *Douglas*, *and Bennett's Principles and Practice of Infectious Diseases*. Vol 1. 5th ed. Philadelphia, PA: Churchill Livingstone; 2000:767–772.
12. Konstan MW, Berger M. Infection and inflammation in the lung in cystic fibrosis. In: Davis PB, editor. *Cystic Fibrosis*. New York, NY: Marcel Dekker; 1993:219–276.
13. Lipuma JJ. The changing microbial epidemiology in cystic fibrosis. *Clin Microbiol Rev*. 2010;23(2):299–323.
14. Gilligan PH. Microbiology of airway disease in patients with cystic fibrosis. *Clin Microbiol Rev*. 1991;4(1):35–51.
15. Govan JR, Nelson JW. Microbiology of lung infection in cystic fibrosis. *Br Med Bull*. 1992;48(4):912–930.
16. Govan JR, Deretic V. Microbial pathogenesis in cystic fibrosis: mucoid Pseudomonas aeruginosa and Burkholderia cepacia. *Microbiol Rev*. 1996;60(3):539–574.
17. Høiby N, Flensborg EW, Beck B, Friis B, Jacobsen SV, Jacobsen L. Pseudomonas aeruginosa infection in cystic fibrosis: diagnostic and prognostic significance of Pseudomonas aeruginosa precipitins determined by means of crossed immune electrophoresis. *Scand J Respir Dis*. 1977;58(2):65–79.
18. Henry RL, Mellis CM, Petrovic L. Mucoid Pseudomonas aeruginosa is a marker of poor survival in cystic fibrosis. *Pediatr Pulmonol*. 1992;12(3):158–161.
19. Emerson J, Rosenfeld M, McNamara S, Ramsey B, Gibson RL. Pseudomonas aeruginosa and other predictors of mortality and morbidity in young children with cystic fibrosis. *Pediatr Pulmonol*. 2002;34(2):91–100.
20. Pedersen SS, Høiby N, Espersen F, Koch C. Role of alginate in infection with mucoid Pseudomonas aeruginosa in cystic fibrosis. *Thorax*. 1992;47(1):6–13.
21. Demko CA, Byard PJ, Davis PB. Gender differences in cystic fibrosis: Pseudomonas aeruginosa infection. *J Clin Epidemiol*. 1995;48(8):1041–1049.
22. Li Z, Kosorok MR, Farrell PM, et al. Longitudinal development of mucoid Pseudomonas aeruginosa infection and lung disease progression in children with cystic fibrosis. *JAMA*. 2005;293(5):581–588.
23. Flume PA, O'Sullivan BP, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2007;176(10):957–969.
24. Burns JL, Ramsey BW, Smith AL. Clinical manifestations and treatment of pulmonary infections in cystic fibrosis. *Adv Pediatr Infect Dis*. 1993;8:53–66.
25. Marks MI. Antibiotic therapy for bronchopulmonary infections in cystic fibrosis. The American approach. *Antibiot Chemother*. 1989;42:229–236.
26. Ramsey BW. Management of pulmonary disease in patients with cystic fibrosis. *N Engl J Med*. 1996;335(3):179–188.
27. Denton M, Wilcox MH. Antimicrobial treatment of pulmonary colonization and infection by *Pseudomonas aeruginosa* in cystic fibrosis patients. *J Antimicrob Chemother*. 1997;40(4):468–474.
28. Ferkol T, Rosenfeld M, Milla CE. Cystic fibrosis pulmonary exacerbations. *J Pediatr*. 2006;148(2):259–264.
29. Flume PA, Mogayzel PJ Jr, Robinson KA, et al. Cystic fibrosis pulmonary guidelines: treatment of pulmonary exacerbations. *Am J Respir Crit Care Med*. 2009;180(9):802–808.
30. Döring G, Conway SP, Heijerman HG, et al. Antibiotic therapy against Pseudomonas aeruginosa in cystic fibrosis: a European consensus. *Eur Respir J*. 2000;16(4):749–767.

31. MacLusky IB, Gold R, Corey M, Levison H. Long-term effects of inhaled tobramycin in patients with cystic fibrosis colonized with Pseudomonas aeruginosa. *Pediatr Pulmonol*. 1989;7(1):42–48.
32. Ramsey BW, Pepe MS, Quan JM, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med*. 1999;340(1):23–30.
33. Høiby N. Prospects for the prevention and control of pseudomonal infection in children with cystic fibrosis. *Paediatr Drugs*. 2000;2(6):451–463.
34. Moss RB. Administration of aerosolized antibiotics in cystic fibrosis patients. *Chest*. 2001;120(3 Suppl):107S–113S.
35. Quittner AL, Buu A. Effects of tobramycin solution for inhalation on global ratings of quality of life in patients with cystic fibrosis and Pseudomonas aeruginosa infection. *Pediatr Pulmonol*. 2002;33(4): 269–276.
36. Murphy TD, Anbar RD, Lester LA, et al. Treatment with tobramycin solution for inhalation reduces hospitalizations in young CF subjects with mild lung disease. *Pediatr Pulmonol*. 2004;38(4):314–320.
37. Oermann CM, Retsch-Bogart GZ, Quittner AL, et al. An 18-month study of the safety and efficacy of repeated courses of inhaled aztreonam lysine in cystic fibrosis. *Pediatr Pulmonol*. 2010;45(11):1121–1134.
38. Konstan MW, VanDevanter DR, Rasouliyan L, et al. Trends in the use of routine therapies in cystic fibrosis: 1995–2005. *Pediatr Pulmonol*. 2010;45(12):1167–1172.
39. Szaff M, Høiby N, Flensborg EW. Frequent antibiotic therapy improves survival of cystic fibrosis patients with chronic Pseudomonas aeruginosa infection. *Acta Paediatr Scand*. 1983;72(5):651–657.
40. Elborn JS, Prescott RJ, Stack BH, et al. Elective versus symptomatic antibiotic treatment in cystic fibrosis patients with chronic Pseudomonas infection of the lungs. *Thorax*. 2000;55(5):355–358.
41. Geller DE. Aerosol antibiotics in cystic fibrosis. *Respir Care*. 2009; 54(5):658–670.
42. Di Sant'Agnese PE, Andersen DH. Celiac syndrome; chemotherapy in infections of the respiratory tract associated with cystic fibrosis of the pancreas; observations with penicillin and drugs of the sulfonamide group, with special reference to penicillin aerosol. *Am J Dis Child*. 1946;72:17–61.
43. Hodson ME, Penketh AR, Batten JC. Aerosol carbenicillin and gentamicin treatment of Pseudomonas aeruginosa infection in patients with cystic fibrosis. *Lancet*. 1981;2(8256):1137–1139.
44. Kun P, Landau LI, Phelan PD. Nebulized gentamicin in children and adolescents with cystic fibrosis. *Aust Paediatr J*. 1984;20(1):43–45.
45. Jensen T, Pedersen SS, Garne S, Heilmann C, Høiby N, Koch C. Colistin inhalation therapy in cystic fibrosis patients with chronic Pseudomonas aeruginosa lung infection. *J Antimicrob Chemother*. 1987;19(6):831–838.
46. Stead RJ, Hodson ME, Batten JC. Inhaled ceftazidime compared with gentamicin and carbenicillin in older patients with cystic fibrosis infected with Pseudomonas aeruginosa. *Br J Dis Chest*. 1987;81(3):272–279.
47. Carswell F, Ward C, Cook DA, Speller DC. A controlled trial of nebulized aminoglycoside and oral flucloxacillin versus placebo in the outpatient management of children with cystic fibrosis. *Br J Dis Chest*. 1987;81(4):356–360.
48. Smith AL, Ramsey BW, Hedges DL, et al. Safety of aerosol tobramycin administration for 3 months to patients with cystic fibrosis. *Pediatr Pulmonol*. 1989;7(4):265–271.
49. Ramsey BW, Dorkin HL, Eisenberg JD, et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N Engl J Med*. 1993; 328(24):1740–1746.
50. Hodson ME, Gallagher CG, Govan JR. A randomised clinical trial of nebulised tobramycin or colistin in cystic fibrosis. *Eur Respir J*. 2002; 20(3):658–664.
51. McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. *Am J Respir Crit Care Med*. 2008;178(9):921–928.
52. Retsch-Bogart GZ, Quittner AL, Gibson RL, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. *Chest*. 2009;135(5):1223–1232.
53. Nasr SZ, Sakmar E, Christodoulou E, Eckhardt BP, Streetman DS, Strouse PJ. The use of high resolution computerized tomography (HRCT) of the chest in evaluating the effect of tobramycin solution for inhalation in cystic fibrosis lung disease. *Pediatr Pulmonol*. 2010;45(5):440–449.
54. Wainwright CE, Quittner AL, Geller DE, et al. Aztreonam for inhalation solution (AZLI) in patients with cystic fibrosis, mild lung impairment, and P. aeruginosa. *J Cyst Fibros*. 2011;10(4):234–242.
55. Conway SP. Nebulized antibiotic therapy: the evidence. *Chron Respir Dis*. 2005;2(1):35–41.
56. Wiesemann HG, Steinkamp G, Ratjen F, et al. Placebo-controlled, double-blind, randomized study of aerosolized tobramycin for early treatment of Pseudomonas aeruginosa colonization in cystic fibrosis. *Pediatr Pulmonol*. 1998;25(2):88–92.
57. Ratjen F, Döring G, Nikolaizik WH. Effect of inhaled tobramycin on early *Pseudomonas aeruginosa* colonisation in patients with cystic fibrosis. *Lancet*. 2001;358(9286):983–984.
58. Ratjen F, Munck A, Kho P, Angyalosi G; ELITE Study Group. Treatment of early Pseudomonas aeruginosa infection in patients with cystic fibrosis: the ELITE trial. *Thorax*. 2010;65(4):286–291.
59. Craig WA, Ebert SC. Killing and regrowth of bacteria in vitro: a review. *Scand J Infect Dis Suppl*. 1990;74:63–70.
60. Levy J, Smith AL, Koup JR, Williams-Warren J, Ramsey B. Disposition of tobramycin in patients with cystic fibrosis: a prospective controlled study. *J Pediatr*. 1984;105(1):117–124.
61. De Groot R, Smith AL. Antibiotic pharmacokinetics in cystic fibrosis. Differences and clinical significance. *Clin Pharmacokinet*. 1987; 13(4):228–253.
62. Mendelman PM, Smith AL, Levy J, Weber A, Ramsey B, Davis RL. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. *Am Rev Respir Dis*. 1985;132(4):761–765.
63. Weber A, Smith A, Williams-Warren J, Ramsey B, Covert DS. Nebulizer delivery of tobramycin to the lower respiratory tract. *Pediatr Pulmonol*. 1994;17(5):331–339.
64. Eisenberg J, Pepe M, Williams-Warren J, et al. A comparison of peak sputum tobramycin concentration in patients with cystic fibrosis using jet and ultrasonic nebulizer systems. Aerosolized Tobramycin Study Group. *Chest*. 1997;111(4):955–962.
65. Izquierdo MJ, Gomez-Alamillo C, Ortiz F, et al. Acute renal failure associated with use of inhaled tobramycin for treatment of chronic airway colonization with Pseudomonas aeruginosa. *Clin Nephrol*. 2006;66(6):464–467.
66. Santos RP, Awa E, Anbar RD. Inhaled tobramycin solution-associated recurrent eosinophilia and severe persistent bronchospasm in a patient with cystic fibrosis: a case report. *BMC Pediatr*. 2007;7:11.
67. Standaert TA, VanDevanter DR, Ramsey BW, et al. The choice of compressor affects the aerosol parameters and the delivery of tobramycin from a single model nebulizer. *J Aerosol Med*. 2000;13(2):147–153.
68. Westerman EM, Boer AH, Touw DJ, et al. Aerosolization of tobramycin (TOBI) with the PARI LC PLUS reusable nebulizer: which compressor to use? Comparison of the CR60 to the PortaNeb compressor. *J Aerosol Med Pulm Drug Deliv*. 2008;21(3):269–280.
69. Dopfer R, Brand P, Müllinger B et al. Inhalation of tobramycin in patients with cystic fibrosis: comparison of two methods. *J Physiol Pharmacol*. 2007;58 Suppl 5(Pt 1):141–154.
70. Geller DE, Rosenfeld M, Waltz DA, Wilmott RW; AeroDose TOBI Study Group. Efficiency of pulmonary administration of tobramycin solution for inhalation in cystic fibrosis using an improved drug delivery system. *Chest*. 2003;123(1):28–36.
71. Hubert D, Leroy S, Nove-Josserand R, et al. Pharmacokinetics and safety of tobramycin administered by the PARI eFlow rapid nebulizer in cystic fibrosis. *J Cyst Fibros*. 2009;8(5):332–337.

72. Coates AL, Denk O, Leung K, et al. Higher tobramycin concentration and vibrating mesh technology can shorten antibiotic treatment time in cystic fibrosis. *Pediatr Pulmonol*. 2011;46(4):401–408.
73. Lenoir G, Antypkin YG, Miano A, et al. Efficacy, safety, and local pharmacokinetics of highly concentrated nebulized tobramycin in patients with cystic fibrosis colonized with Pseudomonas aeruginosa. *Paediatr Drugs*. 2007;9 Suppl 1:11–20.
74. Chuchalin A, Csiszér E, Gyurkovics K, et al. A formulation of aerosolized tobramycin (Bramitob) in the treatment of patients with cystic fibrosis and Pseudomonas aeruginosa infection: a double-blind, placebo-controlled, multicenter study. *Paediatr Drugs*. 2007;9 Suppl 1: 21–31.
75. Poli G, Acerbi D, Pennini R, et al. Clinical pharmacology study of Bramitob, a tobramycin solution for nebulization, in comparison with Tobi. *Paediatr Drugs*. 2007;9 Suppl 1:3–9.
76. Geller DE, Weers J, Heuerding S. Development of an inhaled dry-powder formulation of tobramycin using PulmoSphere technology. *J Aerosol Med Pulm Drug Deliv*. 2011;24(4):175–182.
77. Konstan MW, Geller DE, Minić P, Brockhaus F, Zhang J, Angyalosi G. Tobramycin inhalation powder for P. aeruginosa infection in cystic fibrosis: the EVOLVE trial. *Pediatr Pulmonol*. 2011;46(3):230–238.
78. Standaert TA, Speirs RJ, Rao N, et al. Young cystic fibrosis patients can effectively use a novel high-payload capsule-based dry powder inhaler with tobramycin powder for inhalation (TPI). *Pediatr Pulmonol*. 2004;38(Suppl 27):67–91.
79. Tiddens HA, Geller DE, Challoner P, et al. Effect of dry powder inhaler resistance on the inspiratory flow rates and volumes of cystic fibrosis patients of six years and older. *J Aerosol Med*. 2006;19(4): 456–465.
80. Haynes A, Nakamura J, Heng C, Heuerding S, Thompson G, Malcolmson R. Aerosol performance of tobramycin inhalation powder. In: Dalby RN, Byron PR, Peart J, Suman JD, Farr SJ, Young PM, editors. *Respiratory Drug Delivery 2010*. River Grove, IL: Davis Healthcare International; 2008: 701–706.
81. Challoner PB, Flora MG, Hirst PH, et al. Gamma scintigraphy lung deposition comparison of TOBI in the PARI LC Plus nebulizer and the Aerodose inhaler. *Am J Respir Crit Care Med*. 2001;163:A83.
82. Newhouse MT, Hirst PH, Duddu SP, et al. Inhalation of a dry powder tobramycin pulmosphere formulation in healthy volunteers. *Chest*. 2003;124(1):360–366.
83. Geller DE, Konstan MW, Smith J, Noonberg SB, Conrad C. Novel Tobramycin inhalation powder in cystic fibrosis subjects: pharmacokinetics and safety. *Pediatr Pulmonol*. 2007;42(4):307–313.
84. Geller DE, Pitlick WH, Nardella PA, Tracewell WG, Ramsey BW. Pharmacokinetics and bioavailability of aerosolized tobramycin in cystic fibrosis. *Chest*. 2002;122(1):219–226.
85. Weber A, Williams-Warren J, Ramsey B, Smith AL. Tobramycin serum concentrations after aerosol and oral administration in cystic fibrosis. *Am J Ther*. 1995;2(2):81–87.
86. Geller DE, Rosenfeld M, Waltz DA, Wilmott RW; AeroDose TOBI Study Group. Efficiency of pulmonary administration of tobramycin solution for inhalation in cystic fibrosis using an improved drug delivery system. *Chest*. 2003;123(1):28–36.
87. Konstan MW, Flume PA, Kappler M, et al. Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *J Cystic Fibros*. 2011;10(1):54–61.
88. Gibson RL, Emerson J, Mayer-Hamblett N, et al. Duration of treatment effect after tobramycin solution for inhalation in young children with cystic fibrosis. *Pediatr Pulmonol*. 2007;42(7):610–623.