

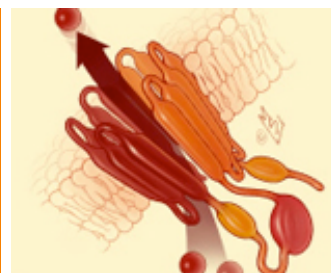


# eLITERATURE REVIEW

## eCysticFibrosis Review

Presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing

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### October 2010: VOLUME 2, NUMBER 11

#### New Inhalation Therapies

#### In this Issue...

New inhalation therapies are being developed to combat CF lung disease on multiple fronts. The availability of novel agents that suppress or eradicate infection, reduce inflammation, and restore the physiologic underpinnings of mucus clearance are expected to bring significant improvements in the duration and quality of life to CF patients. In this issue, we review recent studies of inhaled aztreonam lysine, dry powder mannitol, and denufosal tetrasodium, and discuss how these new agents may fit into existing and future treatment schemes.



#### Program Information

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#### Length of Activity

- Physicians: 1 hour
- Nurses: 1 contact hour
- Dieticians: 1 contact hour
- Physical Therapists: 1 contact hour

#### Release Date

October 26, 2010

#### Expiration Date

October 25, 2012

#### Podcast Release

November 9, 2010

#### Next Newsletter Issue

TBA

## LEARNING OBJECTIVES

After participating in this activity the participant will demonstrate the ability to:

- Evaluate the data used to support the approval of aztreonam lysine for inhalation in cystic fibrosis.
- Describe the underlying rationale and data from clinical trials of dry powder mannitol in cystic fibrosis.
- Describe the rationale and data from clinical trials supporting the use of denufosal tetrasodium in cystic fibrosis.

### IMPORTANT CME/CE INFORMATION

▼ Program Begins Below

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### Program Directors

**Michael P. Boyle, MD, FCCP**  
Associate Professor of Medicine  
Director, Adult Cystic Fibrosis Program  
The Johns Hopkins University  
Baltimore, MD

**Peter J. Mogayzel, Jr., MD, PhD**  
Associate Professor of Pediatrics  
Director, Cystic Fibrosis Center  
The Johns Hopkins University  
Baltimore, MD

**Donna W. Peeler, RN, BSN**  
Pediatric Clinical Coordinator  
Cystic Fibrosis Center  
The Johns Hopkins University  
Baltimore, MD

**Meghan Ramsay, MS, CRNP**  
Adult Clinical Coordinator  
Cystic Fibrosis Center  
The Johns Hopkins University  
Baltimore, MD

## GUEST AUTHOR OF THE MONTH



Commentary & Reviews:

**Scott H. Donaldson, MD**

Associate Professor of  
Medicine  
Associate Director, Adult CF  
Center  
Division of Pulmonary and  
Critical Care Medicine  
University of North Carolina at  
Chapel Hill  
Chapel Hill, NC

**Guest Faculty Disclosures**

**Scott H. Donaldson, MD** discloses that he receives grants and research support from Gilead Sciences, Inspire Pharmaceuticals and Vertex Pharmaceuticals. Dr. Donaldson also works as a consultant to Parion Sciences, Inspire Pharmaceuticals, Pulmatrix and Novartis.

**Unlabeled/Unapproved Uses**

The author has indicated that there will be a reference to unlabeled or unapproved uses of denufosol and mannitol for treatment of CF in the presentation.

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## NOVEMBER PODCAST



**eCysticFibrosis Review is happy to offer our accredited PODCASTS, to be sent to you in November.**

The eCysticFibrosis Review podcast complements the topic presented in this issue by applying the information to patient scenarios. Our October author, Scott Donaldson, MD and Robert Busker, eCysticFibrosis Review's Managing Editor discuss case presentations on the topic: New Inhalation Therapies.

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## COMMENTARY

Lung disease is the major cause of morbidity and mortality in cystic fibrosis (CF), and inhaled therapies, which directly target the affected organ while minimizing systemic toxicities, have long been the mainstay of treatment. Currently, we are in the midst of an exciting explosion of new therapies – both inhaled and oral – that individually target many aspects of CF lung disease. Novel inhaled therapies are now showing promise against chronic *Pseudomonas aeruginosa* (PA) infection and the underlying physiologic processes that lead to defective mucus clearance.

A major advancement in the treatment of CF lung disease was the development of inhaled tobramycin solution (TOBI®; Novartis) as a suppressive therapy for patients with chronic PA infection.<sup>(1)</sup> The addition of other inhaled antibiotics to the armamentarium for the treatment of CF pathogens is clearly desirable. Reviewed here are recent articles by



Retsch-Bogart et al<sup>(2)</sup> and Oermann et al<sup>(3)</sup> that support the safety and efficacy of a new and recently approved antibiotic formulation, aztreonam lysine for inhalation (AZLI; Cayston®; Gilead Sciences). Both studies showed that AZLI significantly improved respiratory symptoms, lung function, and reduced PA density in sputum over 1 and 18 months of treatment.<sup>2,3</sup> Generally speaking, improvement in lung function and symptoms was observed with each treatment cycle even after 18 months (9 alternate month cycles) of use<sup>(3)</sup>. The main deficiency of these studies, however, is the absence of an extended comparison between AZLI and placebo (ie >28 days). Although no major safety signals were identified in these studies, the lack of a long-term comparison to placebo prevents us from formally assessing the frequency of treatment-related adverse events and the impact that this antibiotic may have on exacerbation frequency.

In the second cassette of reviews, we look at trial results with inhaled dry powder mannitol, a hyperosmotic agent, designed to improve the hydration of airway secretions and rate of mucociliary clearance. Two relatively small studies by Jaques et al<sup>(4)</sup> and Minasian et al<sup>(5)</sup> reported that mannitol improved FEV<sub>1</sub> by ~7% after 2 or 12 weeks of use, respectively. No other major effects on other clinical outcomes were observed in these relatively short-term studies. Interestingly, the effect of mannitol on lung function was compared to that measured with rhDNase (2.5 mg daily) given during a separate phase of the crossover study by Minasian et al, and yielded a very similar result. However, the combination of mannitol and rhDNase, in a third treatment period, appeared not to be effective.<sup>(5)</sup> Importantly, data is now beginning to emerge from a large phase III study of mannitol, which again confirms similar lung function improvement.<sup>(6)</sup> In contrast to the findings of Minasian et al, FEV<sub>1</sub> improvement was seen in the subgroup of patients also using rhDNase as well. Although the cause of these discrepant findings is not obvious, the simpler study design and larger sample size of the phase III study provides a greater weight of evidence on this issue, and suggests that the negative interaction seen between rhDNase and mannitol in the Minasian study may have been a chance event. Notably absent in early presentations of the phase III study data are the effects on exacerbation frequency and patient reported outcomes—data that will need to be examined carefully once they are published. Of equal importance are the data that examine the tolerability of dry powder mannitol. In each of the reviewed studies, tolerability tests were performed prior to randomization, and 20-25% of those tested were immediately withdrawn due to an acute drop in FEV<sub>1</sub>, excessive cough, or nausea.<sup>4,5</sup> A significant number of patients in the Minasian study also withdrew later because of troublesome cough. Although acute decreases in FEV<sub>1</sub> during a tolerability test (measured 60 seconds after each dose escalation) accounted for the majority of tolerability test “failures”, it is unclear if these events actually predict problems with safety or tolerability. It is certainly conceivable that these lung function changes may in part relate to the drug's mechanism of action (i.e. drawing fluid into the airway lumen), and/or would have been transient and clinically unimportant. One also wonders how tolerability will ultimately be assessed clinically if this drug is approved, and whether clinical assessments of tolerability (i.e. without formal bronchoprovocation testing) will lead to more patients being prescribed mannitol and, in turn, different safety/efficacy outcomes as a result of treating these additional patients.

The third review cassette focuses on denufosal tetrasodium. Denufosal is a P2Y<sub>2</sub> receptor agonist that has been shown to stimulate chloride secretion through non-CFTR chloride channels. Conceptually, this mechanism provides a strategy to circumvent the CFTR defect. Like mannitol, denufosal is purported to increase airway hydration and mucociliary clearance. In the phase II study by Deterding et al,<sup>(7)</sup> no significant safety issues were encountered and a small but significant increase in lung function, compared to placebo, was observed after 28-days of dosing. Currently, preliminary results from the first phase III study of denufosal are emerging.<sup>(8-10)</sup> In this phase III study, 352 patients were randomized to denufosal or placebo, administered 3 times daily for 24 weeks. As in the study by Deterding et al, enrolled patients were relatively young (mean age 14.5 years; 80% of participants < 18 years of age) and had mild lung disease (mean FEV<sub>1</sub> 93% of predicted). Once again, a small (45 ml) but statistically significant improvement in FEV<sub>1</sub> was observed at the end of the treatment period (vs. placebo; p=0.047). All patients then began open-label use of denufosal for another 24 weeks, during which time both groups had continued gradual improvement in lung function (115 ml vs. baseline in patients receiving denufosal for 48 weeks).<sup>(8)</sup> Disappointingly, no differences in other endpoints, such as pulmonary exacerbation frequency, were observed. However, an interesting trend (p = 0.06) toward protection against loss of lung function was observed



in subjects who did experience an exacerbation during the study with denufosal treatment.<sup>(9)</sup> Further, in adolescents (12-18 years; N=123), who often have accelerated lung function, denufosal may have also reduced lung function deterioration (change in % predicted lung function -1.1% vs. -4.1% in denufosal and placebo groups, respectively; p = 0.055).<sup>(10)</sup> We anxiously await, therefore, the results from a second phase III study that uses a 1-year placebo-controlled treatment period. Because mildly affected patients are being targeted, it may be more difficult to detect improvements in exacerbation frequency and other classical endpoints unless even longer studies are conducted. The notion that this agent may forestall the progression of disease is certainly exciting, however, and the prospect of testing it even earlier in life (i.e. infants and toddlers) with adequately long study periods is very attractive.

We are now entering an age where multiple agents with related mechanisms of action may soon be available, and our challenge will be to learn which drug is appropriate for a given patient at a specific point in their life. Although this challenge will be sizeable, the prospect of having multiple new inhaled therapies to treat CF lung disease is an enormous accomplishment and brings significant new hope to our patients.

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## INHALED AZTREONAM LYSINE FOR CHRONIC PSEUDOMONAS AERUGINOSA INFECTION IN CF

Retsch-Bogart,G.Z., Quittner,A.L., Gibson,R.L., Oermann,C. et al. **Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis**. 2009. *Chest* **135**:1223-1232.

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The management of chronic *Pseudomonas aeruginosa* (PA) airway infection in CF is one of the major challenges facing clinicians who care for these patients. The use of inhaled antibiotics on a cycling schedule has become a key part of the management of CF lung disease, and until recently only one approved therapy was available: tobramycin inhalation solution (TOBI®; Novartis). However, an alternative inhaled antibiotic, aztreonam lysine (AZLI; Cayston®; Gilead Sciences), received FDA approval earlier this year. Reviewed here are 2 recently published studies that contributed to the approval of this new therapy. In the first study (AIR-CF1), Retsch-Bogart et al conducted a randomized, double-blind, placebo-controlled study of AZLI (75 mg, TID via eFlow® Electronic Nebulizer; PARI Innovative Manufacturers) for 28 days in patients with moderate to severe CF lung disease and chronic PA infection.<sup>(1)</sup> The 164 enrolled patients were cared for at 53 CF centers in Australia, Canada, New Zealand, and the United States. Subjects were >6 years of age and had an FEV<sub>1</sub> between 25-75% of predicted (inclusive). Important exclusion criteria included infection with *Burkholderia cepacia* complex and use of azithromycin, hypertonic saline, or other antipseudomonal antibiotics. The primary efficacy outcome of this study was the change in respiratory symptoms, as indicated by the CFQ-R Respiratory Symptom scale. In the second study (AIR-CF3), Oermann et al conducted an 18-month open-label extension study to evaluate the long-term safety and efficacy of AZLI.<sup>(2)</sup> The 274 patients entering into this study had previously been enrolled either in AIR-CF1<sup>(1)</sup> or an earlier study (AIR-CF2),<sup>(3)</sup> which demonstrated a delayed time to need additional antibiotic interventions after AZLI. In this open-label extension study, subjects continued with their previously assigned BID or TID dosing schedule during treatment months, with treatment occurring every other month. In contrast to AIR-CF1, azithromycin and hypertonic saline use was allowed in AIR-CF3. Although no formal hypothesis testing was performed, the longitudinal effects on lung function, CFQ-R Respiratory Symptom scale, sputum PA density, and other endpoints were described.

In AIR-CF1, mean subject age was 29.6 years (77.4% > 18 years) with a mean baseline FEV<sub>1</sub> of 54.6%. Baseline therapy use included rhDNase (65%) and ~1.7 courses of inhaled tobramycin solution in the prior year. With regard to the primary outcome, a 9.7 point difference in the CFQ-R Respiratory scale was noted between treatment groups. Of note, the magnitude of this difference is well above the minimal clinically important difference (MCID) of 4.<sup>(4)</sup> A similar treatment effect was noted in those with moderate (FEV<sub>1</sub> >50-75% of predicted) or severe (FEV<sub>1</sub> 25-50% of predicted) lung disease, though younger patients (<18 years) appeared to have a larger improvement in respiratory symptoms. A significant treatment difference for FEV<sub>1</sub> (10.3%; p<0.001) was also noted, with similar improvement in the young vs. older age strata, and amongst those with moderate and severely reduced lung function. Other positive trends included fewer hospitalizations (5% vs. 14%; p = 0.064); fewer hospitalization days (0.5 vs. 1.5 days; p = 0.049); improved weight (1.1 vs. 0.1%; p = 0.004); and improvements in other CFQ-R domains (Eating, Emotional Functioning; Health Perceptions; Physical Functioning, Role Limitation/School Performance; and Vitality). Comparison of adverse event (AE) rates revealed less "productive cough" in AZLI-treated patients, and no other concerning safety signals. In AIR-CF3, 71.2% of patients completed the study, with a similar discontinuation rate between BID and TID treated patients. Only a small percentage of patients discontinued due to drug intolerance, study-related AE's, or noncompliance. By examining changes in FEV<sub>1</sub> and the CFQ-R Respiratory Symptom scale, it is clear that improvements in both parameters occurred with each treatment cycle, but that the improvements rapidly waned by the end of each "off" cycle. A somewhat larger treatment effect was noted in the TID group than in the BID group, perhaps most notably with regard to the CFQ-R Respiratory Symptom scale. The relative improvement in FEV<sub>1</sub> (% predicted) was 4.2-8.0% in the TID group, and 1.2-5.1% in the BID group. The decrease in PA density was <1 log<sub>10</sub> cfu/g with each treatment cycle in both groups. Transient

increases in the MIC90, but not the MIC50, were noted in both treatment groups. Adherence, according to empty vial counts, was 88.0% and 92.0% in the TID and BID groups, respectively.

As the result of these (and other) studies, there is little doubt that AZLI can lead to meaningful improvements in respiratory symptoms and lung function, while extending the time before needing additional anti-pseudomonal therapies after 28 days of therapy<sup>(3)</sup>. Perhaps not surprisingly, patients receiving fewer therapies at baseline in AIR-CF1 had larger clinical responses than patients already receiving more aggressive care in the previously published AIR-CF2 trial. In AIR-CF3, we are left to interpret data without an accompanying control group. This is particularly problematic when examining AE data. However, the presented data in AIR-CF3 does support an ongoing benefit over 18 months from AZLI, and a retrospective comparison to case matched controls in the CFF Registry receiving standard of care therapy also revealed a 28% lower risk of hospitalization (p=0.020).<sup>(5)</sup> Reassuringly, only a relatively minor change in aztreonam resistance patterns was observed (transient increase in MIC90) during the 18 month period of study.

Given the availability of multiple treatment options, one would ideally like to be able to compare their safety and efficacy. However, given the influence that other therapies and care practices have on antibiotic responses, comparisons to results with inhaled tobramycin more than a decade earlier are extremely problematic. Further, even a head-to-head comparison would likely only be interpretable if both groups were naive to their assigned therapy or, at the very least, had a similar prior exposure. Therefore, it is likely that the choice clinicians and patients make when choosing between inhaled tobramycin and aztreonam will likely revolve around factors other than evidence of superior efficacy. Rather, if tolerability is similar in a given patient, factors such time of treatment, preference for the appropriate delivery device, cost, and concerns regarding cumulative toxicity and the development of resistance will likely drive decision making. Clearly, the short treatment times achieved with use of the eFlow® nebulizer will likely be very desirable to many patients, and may have contributed to the high adherence rate observed in the long-term AIR-CF3 study. A larger, unanswered question is how the use of inhaled antibiotics should be personalized for individual patients. Should every patient with chronic PA infection and abnormal FEV<sub>1</sub> values be treated chronically with inhaled antibiotics, likely for decades, or can other factors (e.g. exacerbation frequency, prior rate of lung function decline) be incorporated into a decision-making process that extracts the most benefit out of the antibiotic over the lifetime of the patient? Clearly, as the number of treatment options grows, the complexity of these decisions will continue to increase, as will the expectations for improved outcomes.

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## INHALED, DRY POWDER MANNITOL FOR CF LUNG DISEASE

Jaques,A., Daviskas,E., Turton,J.A., McKay,K., et al. **Inhaled mannitol improves lung function in cystic fibrosis**. 2008. *Chest* **133**:1388-1396.

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Minasian,C., Wallis,C., Metcalfe,C., and Bush,A. **Comparison of inhaled mannitol, daily rhDNase and a combination of both in children with cystic fibrosis: a randomised trial**. 2010. *Thorax* **65**:51-56.

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Dry powder mannitol, like hypertonic saline (HS), is a hyperosmotic agent that has been shown to increase the hydration of airway secretions<sup>(1)</sup> and speed mucociliary clearance in patients with cystic fibrosis.<sup>2</sup> Two studies were recently published that report on the efficacy and tolerability of inhaled mannitol (Bronchitol®; Pharmaxis), emphasizing effects on lung function.

In the first publication, Jaques et al reported on a phase II, randomized, double-blind, placebo-controlled, crossover trial conducted at 7 centers in Australia and New Zealand. Eligible participants were >8 years of age with an FEV<sub>1</sub> between 41% and 91% of predicted. Key exclusion criteria included active use of HS (within 2 weeks of screening), and infection with *Burkholderia cepacia* complex. Forty nine patients were enrolled and underwent a standardized bronchoprovocation protocol to exclude those with a >15% fall in FEV<sub>1</sub> from baseline, measured 60 seconds after each sequential, escalating mannitol dose. Those passing this “mannitol challenge test” went on to be randomized to 420 mg of dry-powder mannitol or placebo twice daily for 2 weeks, given after bronchodilator treatment. After a 2-week washout period, the reciprocal therapy was initiated. Of note, to deliver this mass of mannitol, subjects were required to inhale 14 individual capsules at each dose. Placebo consisted of mannitol delivered as non-respirable particles (40% vs. <2% fine particle fraction for active and placebo preparations, respectively). The primary outcome of this study was the change in FEV<sub>1</sub> from baseline.

In the second recently published study, Minasian et al reported on a trial comparing mannitol, rhDNase, and the combination of these 2 agents in children with CF. This study was a prospective, open-label, double crossover trial. Eligible children were between 8 and 18 years of age and had an FEV<sub>1</sub> between 40-70% of predicted. As in the Jaques trial, a mannitol bronchoprovocation test was performed to exclude intolerant subjects. Thereafter, subjects passing the challenge test were randomized to one of three treatment blocks. In each block, mannitol 400 mg twice daily (10 capsules), rhDNase 2.5 mg daily, or mannitol and rhDNase was prescribed for 12 weeks. Following 2-week washout periods, the patient crossed over into the second and third treatment assignments, sequentially. The primary outcome measure was the change in FEV<sub>1</sub> that occurred during each treatment period.

In both of these studies, a sizable fraction of enrolled subjects did not tolerate the mannitol challenge. In Jaques et al, 10 of 49 enrolled subjects either failed due to a >15% fall in FEV<sub>1</sub> (n=6) or withdrew after the challenge due to nausea (n=2) or cough (n=2), leaving N=39 in the analyzed group. In Minasian et al, 10 of 38 enrolled subjects were withdrawn after the mannitol challenge (9 due to fall in FEV<sub>1</sub>; 1 due to nausea); an additional 8 subjects were later withdrawn due to troublesome cough associated with mannitol, leaving only 20 subjects available for the full analysis. In the subjects who completed these studies, however, a significant improvement in the FEV<sub>1</sub> was observed after mannitol treatment (7% in Jacques et al, p<0.001; 6.7% in Minasian et al, p=0.055).

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This improvement quickly reverted back to baseline during the subsequent 2-week washout period in the study by Jacques. Generally speaking, little or no improvements in quality of life (CFQ-R) domain scores or other secondary outcome measures were seen in either trial, although in Jacques patients >14 years of age had a small, significant change in the CFQ-R Respiratory Symptom scale. Comparison of the mean FEV<sub>1</sub> change with mannitol to that observed with rhDNase was very similar in Minasian et al, though the individual responses to each agent were quite variable. Surprisingly, not only did the combination mannitol and rhDNase fail to yield additive effects, the combination did not lead to any significant improvement from baseline (1.9%; p = 0.67).

Taken together, these studies provide optimism that dry powder mannitol can improve lung function in patients with CF over relatively short time intervals. Missing, however, are data that address the long-term impact on outcomes other than lung function, including exacerbation frequency, patient reported outcomes, and long-term safety and tolerability. We expect these answers soon, with the completion of a phase III study. Other questions that are of interest relate to comparisons between mannitol and other “hydrators”, including hypertonic saline (HS). In particular, comparisons of data on exacerbation frequency, patient acceptance/adherence (given their different delivery mechanism), and tolerability will need to be carefully considered. Ideally these comparisons would be made through head-to-head comparison studies; such trials, however, are not likely to be undertaken for a number of reasons.

Finally, identification of the best time to initiate use of mannitol and related compounds will be an extremely important issue to address. Conceptually, these drugs address pathogenic steps that occur early in the CF disease cascade, and therefore could conceivably have the largest impact early in life by slowing the spread of disease into unaffected lung regions and thus preventing disease progression. An ongoing study in CF infants is testing this concept with HS (“Infant Study of Inhaled Saline in Cystic Fibrosis”; ClinicalTrials.gov Identifier: NCT00709280), and similar arguments for early “prophylactic” use of mannitol and other hydrators can be readily made. While much needs to be learned in order to answer these questions, the development of multiple agents with beneficial effects on CF lung disease is incredibly exciting and should continue to improve survival and quality of life during the foreseeable future.

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## INHALED DENUFOSOL TETRASODIUM FOR CYSTIC FIBROSIS LUNG DISEASE

Deterding,R.R., Lavange,L.M., Engels,J.M., Mathews,D.W., et al. **Phase 2 randomized safety and efficacy trial of nebulized denufosal tetrasodium in cystic fibrosis**. 2007. *Am J. Respir. Crit Care Med.* **176**:362-369.

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Denufosal tetrasodium is an inhaled P2Y<sub>2</sub> agonist engineered to be more metabolically stable than natural receptor agonists. Activation of these receptors stimulates calcium-activated chloride channels,<sup>(1)</sup> inhibits sodium hyperabsorption,<sup>(2)</sup> increases cilia beat

frequency,<sup>(3)</sup> and has been shown to speed mucociliary clearance in healthy volunteers and smokers.<sup>(4)</sup> In this study, the safety and short-term efficacy of denufosal was tested in CF patients (age 8-50 yrs) with mild lung disease (FEV<sub>1</sub> > 75% of predicted). Randomized patients received either placebo or one of three denufosal doses (20 mg, 40 mg, or 60 mg), 3 times daily via a Pari LC® STAR nebulizer. During the study, patients could not use hypertonic saline, oral macrolide antibiotics, or any inhaled or intravenous antibiotics (e.g. TOBI®). Safety parameters, lung function, high resolution CT (HRCT) scans, and respiratory symptoms were assessed.

Eighty nine subjects were randomized, and 94% completed the study. Patients were relatively young (median age, 14.0 years) and had mild lung disease (mean FEV<sub>1</sub>, 93% of predicted). Thirty-six percent of patients had *P. aeruginosa* infection, 20% had been hospitalized for an exacerbation in the prior year, and 53% utilized rhDNase. After 28 days of study medication, no worrisome trends in adverse events or other laboratory safety parameters were observed. Measurement of lung function after the first dose of denufosal revealed a significant decline from baseline at 2 hours in the 40mg and 60 mg dose cohort. This had recovered by 5 hours post-dose. Lung function, when compared to the placebo group, was significantly improved in the 20 mg and 60 mg group, but not the 40 mg group. The adjusted FEV<sub>1</sub> difference from placebo in the combined denufosal group was 140 mL p = 0.006, largely reflecting a drop in lung function in the placebo group that did not occur in the denufosal group. No effect on HRCT scans were observed during this short study interval. Denufosal treated patients had more nocturnal cough at the end of the treatment period (29% vs. 0%), but also had more cough at baseline (37% vs. 8%).

These short term study results provide evidence that denufosal is safe, well tolerated, and leads to a small improvement in lung function in mildly affected patients. Now needed are longer term studies to confirm the apparent effects on lung function, and to assess effects on other important outcomes like exacerbation frequency and patient reported outcomes. While the recently completed phase III study<sup>(5)</sup> provides additional evidence for lung function improvement (as discussed in the Commentary section of this issue), other benefits have not yet been demonstrated. Perhaps key to the further development of this therapy is a better understanding of how to measure improvements in mildly affected patients who have good baseline lung function and infrequent exacerbations, while also exploring its utility in older and more severely affected patients where these traditional outcome measures might be more useful. Finally, if approved, clinicians will need to know how denufosal and other agents aimed at improving airway hydration and mucus clearance (e.g. hypertonic saline, mannitol, ENaC inhibitors, and CFTR rescue therapies) compare and interact.

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