


Special Edition Part 2: Highlights of the 36th European Cystic Fibrosis Conference



Welcome to Part 2 of this eCysticFibrosis Review Special Edition, our two-part series reporting on some of the key information presented at the 36th European Cystic Fibrosis Conference (ECFS) in Lisbon, Portugal, June 12 – 15, 2013.

As a special feature, many of these reports include links to streaming video of eCysticFibrosis Review Program Director Peter Mogayzel, MD, discussing the new data with the presenters.

Look for the  to link to this feature.

In this Issue...

Patients with cystic fibrosis (CF) have higher susceptibilities to infection than the population without CF and an unmet need to combat these infections with antibiotics. Investigators at the 36th European Cystic Fibrosis Conference in Lisbon, Portugal presented talks on this key issue and many other current topics in CF research.

In this issue we report the presentations focusing on:

- **Inhalation therapy:** High concentrations of nitric oxide (NO) significantly decrease antibiotic-sensitive and -resistant bacteria and fungi, while increasing lung function in patients with CF.
- **Emerging pathogens:** Nontuberculous mycobacteria (NTM) pose an ever-increasing threat to patients with CF through patient aerosol transmission causing rapid spread in CF centers.
- **Plasma biomarkers:** Alpha-1-antitrypsin/ neutrophil elastase (AAT/NE) complexes in blood plasma correlate with disease severity, exacerbations, and response to therapy.
- **Clinic:** Cough swabs do not measure up to bronchoalveolar lavage (BAL) in identifying lower airway pathogens in newborn-screened patients with CF.
- **Targeting the basic defect:** Interim analysis of a Phase 2 study of the combined correcting and potentiating effects VX-809 and ivacaftor, shows statistically and clinically significant improvements in lung function.

Program Information

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Length of Activity

- 1 hour Physicians
- 1 contact hour Nurses

Launch Date

September 26, 2013

Expiration Date

September 25, 2015

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- Step 1.** Please read the newsletter.
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LEARNING OBJECTIVES

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

- Describe the effects and safe dosage of nitric oxide (NO) for cystic fibrosis (CF) pathogen reduction
- Identify risk factors for nontuberculous mycobacteria (NTM) infection
- Describe the relationship between alpha-1-antitrypsin/neutrophil elastase (AAT/NE) and CF lung disease
- Discuss bronchoscopy as an alternative to cough swabs for detecting lower lung infections
- Explain the positive effects of VX-809 combined with ivacaftor on patients with two F508del *CFTR* mutations

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▼ Program Begins Below

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STATEMENT OF NEED

Based on a review of the current literature, including national and regional measures, detailed conversations with expert educators at Johns Hopkins, and a survey of potential program participants, this program will address the following core patient care gaps:

Disease-Modifying Therapies

- Clinicians remain uncertain how CFTR genotypes relate to phenotypes in patients with CF.
- Clinicians may not understand how CFTR genotype affects CFTR processing and function in CF.
- Clinicians may be unfamiliar with recently introduced and emerging disease-modifying therapies for CF and their appropriate use for individual patients.

Treating CF Patients with Inhaled Antibiotics

- Clinicians lack knowledge about the use of existing and emerging inhaled ABX to treat chronic pulmonary infections.
- Clinicians need more information to make informed decisions about the use of inhaled ABX in combination.
- Clinicians lack information about best practices for scheduling ABX therapy to suppress chronic airway infections.
- Common clinician assumptions about treating pulmonary exacerbations lack supporting evidence.
- CF clinicians are not aware of and/or are not actively advocating inhaled ABX patient-adherence strategies.

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NITRIC OXIDE

Symposium 13: New Inhaled Therapies

Inhaled nitric oxide; Chris Miller MD

Talk from the 36th European Cystic Fibrosis Conference; June 12-15, 2013; Lisbon, Portugal

Although *Pseudomonas aeruginosa* (PA) is frequently the focus of concern in cystic fibrosis (CF) lung disease due to its virulence and high prevalence in the CF lung; pulmonary infections are not limited to one pathogen. In fact, it remains unclear in the complex microbiota of the CF airway which pathogens pose the greatest threat. With



existing antibiotics becoming increasingly ineffective because of the growing number of antibiotic-resistant microbial strains, the use of nitric oxide (NO) may offer a viable, highly effective, and safe antimicrobial alternative.

In a pilot study headed by the late Professor Gerd Döring MD of the University Clinic Tübingen, Tübingen, Germany, the use of inhaled NO was investigated for safety as a primary endpoint and antimicrobial efficacy and lung function as secondary endpoints, as reported by Dr. Chris Miller, Head of the Nitric Oxide Research Laboratory of the Vancouver Coastal Health Research Institute, Vancouver Canada, at the 36th European Cystic Fibrosis Congress during a symposium dedicated to *New Inhaled Therapies*. Inhaled NO sessions were incorporated into the antibiotic regimen of eight adult patients with CF, during the off-month of inhaled tobramycin treatment for PA infection. Inhaled NO was given at a dose of 160 ppm three times daily for 30 minutes, with at least 3.5 hours between treatments, for five days. The five-day NO regimen was repeated twice.

Two of the patients were female and six were male, aged 34.6 ± 7.5 years, with a mean weight 59.1 ± 8.3 kg, mean blood pressure $119 \pm 9/74 \pm 8$ mmHg, and a mean heart rate 77 ± 7.5 . At baseline, nonmucoid PA was noted in eight patients, mucoid PA in one, *Staphylococcus aureus* (SA) and *Candida albicans* in two, and one occurrence each of *Stenotrophomonas maltophilia*, *Aspergillus fumigatus*, and *Aspergillus flavus*. The patients were chronically ill and showed little response in bacterial load to tobramycin therapy.

The outcome of the pilot study revealed that blood pressure and heart rate remained steady in all eight of the study subjects over the treatment period. NO was zero before treatment, reaching 4.0 ± 0.8 ppm during treatment, and returned to 0 after treatment ($P < 0.001$). Methemoglobin (MetHb) was 0.6 ± 0.4 ppm before treatment, 2.7 ± 0.4 ppm during, and returned to 0 after treatment ($P < 0.001$). The maximum midexpiratory flow (MMEF) was $28.9\% \pm 16.2$ before and $28.5\% \pm 16.5$ during treatment ($P = 0.49$). Other safety parameters such as leukocytes, neutrophils, platelets, creatinine, AST, ALT, CRP, and IgG remained stable over the treatment period, showing no significant changes.

The investigation demonstrated that NO decreased the bacterial load in the airways of all eight patients with CF. Both PA and SA, which display resistance to various antibiotics and are therefore difficult to treat, decreased significantly ($P = 0.002$ PA; $P = 0.24$ SA). Nitric oxide also decreased the fungal load in six patients: *C albicans* ($P = 0.02$) and *Aspergillus* sp. ($P = 0.04$). In addition to reducing these pathogens, NO significantly increased forced expiratory volume in one second (FEV₁) both clinically and statistically by about 10% in this group.

One patient had a fall in FEV₁ max $< 10\%$. Other adverse events such as dry mouth occurred in four of the eight patients, viral infections in two, and gastroenteritis in one (not drug-related). Occurrences of elevated MetHb $> 3.0\%$, were noted twice. One patient weighing 50 kg reached MetHb 3.0%, necessitating a protocol change of reduced inhalation time to 20 – 25 minutes.

Patients with CF are at high risk for acquiring resistant microbial pathogens, which lead to increased morbidity and mortality. The unmet medical need for new antibiotics and the ever-present threat and rise of drug resistant bacteria now ubiquitous in hospital settings advocate the need for new solutions. Inhaled NO targets the lung directly, where the problem lies, reducing the PA load and improving lung function, at the dose of 160 ppm intermittent therapy.

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NTM EPIDEMIOLOGY

Special Symposium: ECFS/CFF Guidelines for the Management of Non-tuberculous Mycobacteria in CF; Epidemiology and Risk Factors for NTM; Andres Floto, MD

Talk held at the 36th European Cystic Fibrosis Conference; June 12-15, 2013; Lisbon, Portugal

Non-tuberculous mycobacteria (NTM) are the greatest emerging threat to individuals with cystic fibrosis (CF), and according to data from the CF Foundation Patient Registry, such infections have doubled in prevalence between 1995 and 2009, from 2.3% to 4.4%.



To spread, NTM require a substrate, defective immunity, and exposure. Thriving in a milieu of disrupted mucociliary clearance, a structurally damaged CF airway is the ideal environment for NTM to adhere to and grow, according to Andres Floto, MD, Research Director of the Cystic Fibrosis Unit at Papworth Hospital, Cambridge, UK.

Several characteristics of patients with CF suggest a predisposition to NTM infection. Low BMI seems to have a strong correlation with infection, which, as with *Mycobacterium tuberculosis*, is inversely related to infection reactivation. Another aspect that has been suggested is that the *CFTR* mutation itself may have an intrinsic defect in macrophages, making individuals with CF uniquely susceptible.

Once the host cells are infected with NTM, the mycobacteria interfere with phagosome/lysosome fusion, which is the cell's innate autophagic response. Autophagic killing is also impaired by azithromycin, a strong antimycobacterial agent used against NTM. Using this drug in patients harboring azithromycin-resistant NTM strains, therefore, exposes patients to its detrimental effects only.

Finally, researchers have speculated that using antibiotics for conventional bacteria may have allowed a niche to form in the lungs for NTM growth.

Nontuberculous mycobacteria can be acquired independently, from a dominant clone, or by recent transmission from another person with CF.

Since 2004, hospitals have developed strict rules to limit spread of pathogenic bacteria among individuals with CF, such as single rooms in the CF unit, limiting nurse interaction within the hospital, and separating outpatients so they never meet face to face. The CF Foundation and the ECFS recommend minimizing cross infections by following national infection control guidelines.

In his patients with NTM infections, Dr. Floto identified *M. abscessus* with inducible macrolide resistance, although many patients had never been exposed to macrolides. This strongly suggested spread from patients infected with resistant strains. *M. massiliense*, on the other hand, is sensitive to macrolides.

Genetic evidence linked Dr. Floto's patients infected with NTM to the same hospital, while those without infection had less outpatient interaction. He suspects indirect person-to-person transmission through infectious aerosol, since NTM is known to exist in humid air and has been cultured from mist in humid climates.

"Knowing the genome sequence allows us to work out a model for transmission, and then prove those in mouse models. We can correlate the clinical behavior with the *in vitro* phenotype and work out in theory whom to treat, who got the aggressive and nonaggressive bugs, and how to treat. We are able to see the evolution of all virulence factors — the evolution of the virulence genes — within patients during the course of an infection," he said.

In the UK, two current studies have focused on NTM. First, the National *M. abscessus* Genotype-Phenotype Study, currently with 900 UK isolates, seeks to give an idea about transmission in the UK. Also, the Global *M. abscessus* Sequencing Study has roughly 1000 isolates, which should give a global picture of diversity, population structure, and transmission.

Some key environmental exposures that are associated with developing NTM are hot tubs, running water, showers, gastroesophageal reflux, soils, and exposure to humidity.

"I would suggest, therefore, it is the responsibility of individual countries to consider this emerging information and work out how we are going to actually change infection control policies to address this very difficult issue."

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Symposium 27: Biomarkers of exacerbation of lung function decline

Plasma biomarkers to determine the severity of Lung function in CF; Andre Cantin, MD

Talk from the 36th European Cystic Fibrosis Conference; June 12-15, 2013;
Lisbon, Portugal

Blood biomarkers for cystic fibrosis (CF) have the advantage of being available, minimally invasive, and reflective of the entire lung, not just selected parts. Canadian investigator, Andre Cantin, MD of the University of Sherbrooke, Quebec, Canada, discussed his research on serum biomarkers and their value in predicting exacerbation and lung damage in individuals with CF, as part of an ECFS Conference symposium on *Biomarkers of exacerbation of lung function decline*.

Evidence suggests that blood neutrophil-derived products correspond to the rise and fall of C-reactive protein (CRP) in the blood, which many practitioners already use as a biomarker to help gauge disease state in individuals with CF. However, the high degree of variability and overlap of CRP and other blood biomarker levels, like sialic acid and IL-6, between people with CF and healthy control subjects undermine any associations and require more precise indicators.

Dr. Cantin's investigations focus on neutrophil-derived products, in particular plasma alpha-1-antitrypsin/ neutrophil elastase (AAT/NE) complexes, which, according to his work, showed more reliable predictive values. Neutrophil elastase forms a complex with AAT in the blood plasma, which is easy to measure.

In a study that included 47 controls and 28 patients with CF, Dr. Cantin implemented sandwich ELISA assays, which use an anti-elastase and an anti-alpha-1-antitrypsin antibody to test samples taken from individuals with CF during a stable phase, an exacerbation and after antibiotic treatment. He observed that AAT/NE was increased in the plasma of individuals with CF in stable-state, compared to non-CF controls. He observed a strong association between AAT/NE and respiratory exacerbations and response to antibiotic therapy in individuals with CF compared to controls. After 14 days of antibiotic treatment, the AAT/NE levels returned to low levels, which were no different than control levels. Further results showed a strong correlation between the plasma AAT/NE complexes and lung function, determined by FEV₁.

"Neutrophil-derived products seem to be the right place to look for plasma biomarkers. Of the plasma biomarkers we examined, AAT/NE complexes were best associated with disease severity, exacerbations and response to therapy. Furthermore, neutrophil derived products in plasma predicted advanced lung disease, such as bronchiectasis, which results from lung infection and the ensuing neutrophilic reaction. Recent evidence corroborates that free lung NE levels correlate strongly with the development of bronchiectasis, increasing the four-fold risk in newborns," Dr. Cantin said.

He elucidated that NE has many direct implications in the pathophysiology of inflammatory reactions associated with more severe disease, such as stimulating mucus secretion and expression of mucin genes; digesting tissue connective, which makes airways floppier; increasing the phagocytic defect, cleaving receptors on macrophages that will increase the inflammation; and finally also increasing IL-8, which increases the neutrophil response and potentiates a vicious cycle.

"AAT/NE complex appears to be one of the better and clinically meaningful blood biomarkers in CF. Our next step would be to relate these results to CT scans and to better indices of future lung disease. Since AAT/NE levels reflect structural damage of the whole lung, I would speculate that CT scans will be better to detect small areas of bronchiectasis, as we don't know if this marker will detect small bronchiectasis pockets. Furthermore, AAT/NE may help us determine high and low risk of patients to develop bronchiectasis. It would be interesting to compare CT scans from patients over time, to study variation."

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During the 36th Annual European Cystic Fibrosis Conference held in Lisbon, Drs. Peter Mogayzel and André Cantin, Professor at the University of Sherbrooke in Quebec, Canada, discuss the importance of identifying biomarkers for lung disease in CF.

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BRONCHOALVEOLAR LAVAGE DETECTS MORE LOWER AIRWAY BACTERIA

Workshop 1: Infection in the Clinic

Abstract: WS1.4: Significant bacterial infection missed using cough swabs compared to bronchoalveolar lavage in one-year old newborn screened CF infants. L.P. Thia, S. Rand, L. Hill, S.A. Prasad, A. Bush, L.M. Balfour-Lynn, C. Pao, G. Ruiz, J. Stocks, C. Wallis, R. Suri, London Cystic Fibrosis Collaboration (LCFC).

Talk from the 36th European Cystic Fibrosis Conference; June 12-15, 2013; Lisbon, Portugal

A strong focus of interest in cystic fibrosis (CF) research is discovering how best to preserve lung functional and anatomical integrity in infants with CF diagnosed by newborn screening (NBS). By employing regular lung surveillance at a young age, identifying and eradicating pathogens early in life may help stave off harsh disease progression.

Bronchoalveolar lavage (BAL) may provide an alternative and better diagnostic tool for reflecting lower airway pathogens of infants with CF diagnosed by NBS, according to a new study performed by the London Cystic Fibrosis Collaboration (LCFC) that showed a significant difference between BAL and cough swabs in the infectious agents identified.

“The surveillance and prompt eradication with antibiotics of lower airway pathogens are vital to preserve lung and digestive function and to prevent progression in infants with CF. However, obtaining lower airway samples from nonexpectorating infants is a challenge,” according to Lena Thia, MD of the Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, London, UK, on behalf of the LCFC, during a presentation she gave at a workshop entitled, *Infection in the Clinic*.

The study included 39 infants diagnosed with CF by NBS (87% F508del homozygous or heterozygous) aged one year (mean age at diagnosis was four weeks; range one-12 weeks) who underwent both BAL and paired cough swab sampling.

When asymptomatic, the newborns underwent elective flexible bronchoscopy and lavage using a 2.8 mm bronchoscope, under general anesthesia, using standard operating procedures for BAL based on European Respiratory Society guidelines. BAL was performed on both sides of the lungs using aliquots of saline (1ml/kg). Three aliquots were taken from the right lung (usually right middle lobe) and one from the left lung (usually lingua). The first samples from the right and left lungs were pooled and sent for routine microbiological culture analysis. The cough swabs were obtained on the day of bronchoscopy or ≤ 5 days before bronchoscopy.

Of 39 cough swabs, only three had bacterial growth (7%), while six of the BAL samples had bacterial growth (15%). Closer inspection revealed small numbers of the organisms: *P. aeruginosa* (PA), *S. Aureus*, and *H. influenzae*.

An individual case study revealed an infant testing positive for PA on BAL, but negative from cough swabs and from previously taken cough swab samples.

Dr. Thia reported that there was an overall low prevalence of infection in asymptomatic infants at one year (cough swab 7%; BAL 15%). She noted that although the cough swabs detected less lower airway infection than BAL, the small patient number may have limited the study results. Furthermore, lavages were carried out in only two lobes and may have underestimated the incidence of lower airway infection.



By comparison to previous studies that looked at infant cohorts, Dr. Thia noted a corroboration in findings that isolated PA from about 10% of the infants using BAL. When comparing the two techniques, BAL showed low sensitivity and positive predictive value, while cough swab had a higher specificity and negative predictive value. Translated, the results say that a negative throat culture can rule out lower airway PA infection, but positive cough swabs do not necessarily rule in a pulmonary infection, she noted.

Physicians at the LCFC believe they may not have adequate evidence to carry through a BAL protocol for newborns with persistent symptoms and negative cough swabs. Furthermore, annual or biannual BAL surveillance to test efficacy may prove difficult because of the high threshold for this procedure in infants and its cost implication. In practical terms, regular oropharyngeal cough swabs remain the better option.

“It would be exciting to develop a better method of lower airway surveillance using induced sputum or cough swabs with 7% hypertonic saline as a mucolytic, as an adjunct to physical therapy in infants,” she said.



[During the 36th Annual European Cystic Fibrosis Conference held in Lisbon, Drs. Peter Mogayzel and Jean-Marc Rolain, Professor of Microbiology at the University of the Mediterranean in Marseille, France, discuss the microbiome and its benefits.](#)

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BASIC DEFECT: CORRECTOR/ POTENTIATOR THERAPY

Workshop 7: Novel Therapies

Abstract WS7.4: Lumacaftor, an investigational CFTR corrector, in combination with ivacaftor, a CFTR potentiator, in CF patients with the F508del-*CFTR* mutation: Phase 2 interim analysis. M. Boyle, S.C. Bell, M. Konstan, S. McColley, P. Flume, L. Kang, Y. Wu, D. Waltz, N. Patel for the VX09-809-102 Study group.

Talk from the 36th European Cystic Fibrosis Conference; June 12-15, 2013; Lisbon, Portugal

Clinically significant improvements in lung function and high safety and tolerability standards were demonstrated by the combined effects of lumacaftor (VX-809) and ivacaftor in phase 2 and phase 3 clinical trials conducted in individuals with cystic fibrosis (CF) who are

homozygous for the F508del *CFTR* mutation, according to the interim analysis presented at the 36th European Cystic Fibrosis Conference.

Two study cohorts examined different doses of lumacaftor monotherapy and lumacaftor/ivacaftor combination therapy. Cohort 2 was a phase 2 trial that investigated the efficacy of lumacaftor monotherapy at 200 mg, 400 mg, and 600 mg once daily doses on days 1-28, and then from days 28-56 in combination with ivacaftor 200 mg. Cohort 3, which followed, was a phase 3 trial designed to determine the optimal dose of lumacaftor that would attain the desired effects of the drug without compromising safety. This study used lumacaftor 400 mg q12h from days 1-28, followed by combination therapy with ivacaftor 250 mg from days 28-56. The primary endpoints were safety and change in sweat chloride; the secondary endpoints were pharmacokinetic (PK) parameters and change in lung function measure by the forced expiratory volume in one second (FEV₁).

The investigation of cohort 2 revealed that lumacaftor at a dose of 600 mg qd demonstrated the greatest improvement of FEV₁ and chloride transport, in combination with ivacaftor. The combined therapy resulted in a 6.1% ($P = 0.001$) absolute improvement in FEV₁ and a 9.7% ($P = 0.001$) relative improvement in FEV₁, compared within the group, not to placebo.

In cohort 3, the FEV₁ pattern for subjects taking 400 mg every 12 hours monotherapy revealed no benefits. In combination with ivacaftor, however, the absolute change in FEV₁ was 6% from days 28-56 and the relative change was 9%, which mirrored the results obtained at a dose of 600 mg daily in cohort 2.



“The dosing strategy in cohort 3 did achieve some of the pharmacokinetic goals we hoped for. There was roughly a 25% increase in patient drug exposure,” said Michael Boyle MD, Director of the Adult Cystic Fibrosis Program at the Johns Hopkins Cystic Fibrosis Center, Baltimore, Maryland, USA, during his presentation of the trials at a conference workshop on *Novel Therapies*.

Dr. Boyle observed that lumacaftor 400mg q12h demonstrated an increase in the daily area under the curve (AUC) 1.24-fold compared to patients receiving lumacaftor 600 mg daily in cohort 2, which represented a 25% increase over the 600 mg/day dosage. The C_{max} was lower, 0.85-fold, but the C_{min} increased 2.14-fold compared to values obtained at 600 mg daily.

In cohort 3, the total sweat chloride change from day 1 to 56 of the trial was -11.8 mmol/L ($P = 0.002$), which was significant compared to placebo. Sweat chloride was also significantly reduced during both the monotherapy phase (days 1-28): -8.4 mmol/L ($P = 0.01$) and the combination therapy phase (day 28-56): -3.3 mmol/L ($P = NS$). A similar sweat chloride response was seen at 600 mg daily in cohort 2, Dr Boyle noted.

The same number of patients discontinued therapy in cohorts 2 and 3. There was no significant difference between the groups in the occurrence of serious adverse events. A subset of patients experienced dyspnea, chest tightness, and a decline in FEV₁ coincident with the initiation of lumacaftor monotherapy 600 mg once daily or 400 mg twice daily. These episodes were mild to moderate and transient, were not noted during combination therapy, and did not predict whether the patient would respond to therapy.

Pooling cohorts 2 and 3 revealed no effect on absolute change in FEV₁ percent predicted in patients receiving monotherapy. The pooled cohorts 2 and 3 confirmed the positive response in patients receiving combination therapy.

“Pulmonary function was statistically and clinically improved with the combination therapy of lumacaftor and ivacaftor in F508del homozygotes, at lumacaftor doses of 600 mg once daily or 400 mg twice daily. Lumacaftor in combination was generally well tolerated, and the safety profile was similar to that of placebo. Based on these findings, 2 Phase 3 confirmatory studies, TRAFFIC and TRANSPORT, have been initiated to evaluate the effects of lumacaftor in combination with ivacaftor in patients homozygous for F508del. These 24-week phase 3 studies include both lumacaftor 600 mg daily and 400 mg every 12 hours in combination with 250 mg ivacaftor,” Dr. Boyle said.



[During the 36th Annual European Cystic Fibrosis Conference held in Lisbon, Drs. Peter Mogayzel and Michael Boyle, Associate Professor of Medicine at the Johns Hopkins University in Baltimore, Maryland, discusses his findings for the VX-809 and ivacaftor trial for F508del mutation.](#)

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