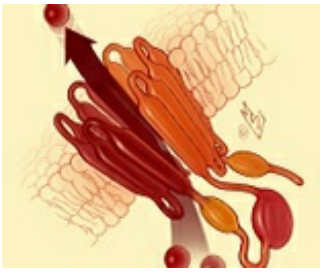
JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
Jointly provided by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
eCysticFibrosis Review
Vol 7: Supported by educational grants from Gilead Sciences, Inc., Vertex Pharmaceuticals Incorporated, AbbVie, Inc., and Chiesi USA, Inc.



VOLUME 7 - ISSUE 12

LISTEN TO PODCAST | DOWNLOAD PODCAST | PHYSICIAN POST-TEST | NURSE POST-TEST

CFTR Modulators: Clinical Insights

- Describe potential side effects that may occur with CFTR modulator treatment.
- Discuss which patients are candidates for CFTR modulators and what short- and long-term benefits might be seen.
- Summarize the potential disease modifying therapies in clinical development to treat cystic fibrosis.

Guest Faculty Disclosure
Dr. Clancy has disclosed that he has served on clinical trial contracts for Bayer, Concert, ProQR, and Vertex; clinical trial grant review contracts for Gilead; clinical ad board contracts for Nivalis; and an unbranded educational talk for Genzyme.

Unlabeled/Unapproved Uses
Dr. Clancy has indicated that there will be no references to the unlabeled/unapproved uses of any drugs or products in today's discussion.

MEET THE AUTHOR

John P. Clancy, MD
Professor, UC Department of Pediatrics
Gunnar Esiason/Cincinnati Bell Chair
Research Director, Division of Pulmonary Medicine
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio

Release Date:
February 03, 2018

Expiration Date:
February 02, 2020

LISTEN TO PODCAST NOW | DOWNLOAD PODCAST | SUBSCRIBE NOW | PHYSICIAN POST-TEST | NURSE POST-TEST

OTHER RESOURCES

Download the podcast transcript

NEWSLETTER ARCHIVE | SHARE WITH A COLLEAGUE

PROGRAM DIRECTORS

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

Noah Lechtzin, MD
Director, Adult Cystic Fibrosis Program
Associate Professor of Medicine
The Johns Hopkins University
Baltimore, Maryland

Suzanne Sullivan, RN, BSN
Senior Clinical Nurse
Johns Hopkins Hospital
Baltimore, Maryland

Podcast Transcript

BOB BUSKER: Welcome to this *e*CysticFibrosis Review podcast.

I'm Bob Busker, managing editor of *e*CysticFibrosis Review. Our guest today is Dr. John P. Clancy, professor in the University of Cincinnati Department of Pediatrics at Cincinnati Children's Hospital Medical Center. We're here to talk about the clinical aspects of the information in Dr. Clancy's recent newsletter issue on Emerging Disease-Modifying Therapies in Cystic Fibrosis.

***e*CysticFibrosis Review is jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from Gilead Sciences, Vertex Pharmaceuticals Incorporated, AbbVie, and Chiesi USA.**

Learning objectives for this audio program include:

- **Describe potential side effects that may occur with CFTR modulator treatment.**
- **Discuss which patients are candidates for CFTR modulators and what short- and long-term benefits might be seen.**
- **Summarize the potential disease modifying therapies in clinical development to treat cystic fibrosis.**

Dr. Clancy has disclosed that he has served on clinical trial contracts for Bayer, Concert, ProQR, and Vertex; clinical trial grant review contracts for Gilead; clinical ad board contracts for Nivalis; and an unbranded educational talk for Genzyme. He has indicated that there will be no references to the unlabeled/unapproved uses of any drugs or products in today's discussion.

MR. BUSKER: Dr. Clancy, thank you for joining us today.

DR. CLANCY: Thank you so much for the kind invitation and the opportunity to discuss some exciting new therapies that are coming to patiets with CF.

MR. BUSKER: In your newsletter issue, you reviewed some of the key literature about recent research in CFTR modulator therapy. **Today our focus is on how some of that new information can be applied in the clinic. So please start us out with a patient scenario.**

DR. CLANCY: Our first patient is an 11-year-old young lady with CF who has a genotype of F508del homozygous. This young lady has an FEV_1 of 80% predicted, and she is currently prescribed several routine CF therapies including twice daily airway clearance, once daily inhaled dornase alfa, twice daily inhaled hypertonic saline, azithromycin 250 mg taken orally three times a week, pancreatic enzyme replacement therapy with meals and with snacks, and fat soluble vitamin supplements.

Her body mass index is 35^{th} percentile and her oropharyngeal cultures are typically positive for methicillin-sensitive *Staphylococcus aureus* but not *Pseudomonas aeruginosa*. She was started on lumacaftor/ivacaftor therapy about three months ago, and in clinic today her parents have a number of questions about her being started on this CFTR modifying therapy.

MR. BUSKER: Let's assume that one of their first questions would be about the potential side effects of this treatment. What specifically should they be aware of?

DR. CLANCY: Whenever we start patients on new therapies, obviously we need to discuss the potential side effects that could be seen, 1) to make sure that patients are safe; and 2) if there are side effects that aren't dangerous, so the patients are not caught off guard.

The one that's probably been most commonly reported is some chest tightness that's observed in patients when they begin ivacaftor/lumacaftor. Somewhere around 10% to 15% of patients in the larger studies did describe some chest tightness that was prominent over the first one to two weeks that they were on ivacaftor/lumacaftor. Thankfully, this doesn't seem to be in and of itself a persistent problem, and usually we can manage it by using bronchodilators. Sometimes we have to reduce the dose briefly and then send it back up, but usually over the first one to two weeks those feelings of chest tightness resolve.

We follow other standard types of things for patients when we start them on modulators. One is liver function tests, which are recommended quarterly for the first year and then once a year, as we do for routine CF care.

Some potential drug/drug interactions also have to be thought about in patients treated with ivacaftor/lumacaftor. Specifically, one of the antibiotics we sometimes use to treat *S aureus* is rifampin, and that can certainly have interactions with ivacaftor/lumacaftor; and also antifungals. Some of the azole-type oral antifungals have the capacity to interact with these drugs. When those medications are used at the same time it's good to review the product insert to see how doses should be adjusted.

Finally, there's been some associations of ivacaftor and cataracts in younger patients. Most of this is based on animal studies; however, it has been recommended by the FDA that patients have yearly ophthalmologic examinations to ensure that cataracts are not observed, particularly in our younger CF population.

MR. BUSKER: Another question her family is likely to have is about the potential benefits of this therapy. Starting with the short-term benefits, what might be expected?

DR. CLANCY: Patients starting ivacaftor/lumacaftor can have some small improvements in lung function, it's on the order of about 3% FEV_1 predicted, which may be difficult for a patient to really notice because it's a relatively small effect in absolute change in lung function.

There is, however, a bigger effect on disease stability, particularly in risks of pulmonary exacerbation, and there is also generally a reduction in pulmonary symptoms such as cough or general respiratory feeling. In general, sweat chloride values will go down in patients who are treated with ivacaftor/lumacaftor, and this can be on the range of 20 to 25 points, depending on the patient's age. I'm not sure if a patient would necessarily feel that difference, but perhaps that would be relevant in a hot environment where sweat losses of sodium and chloride could be more important. But the biggest effects really seem to be on disease stability and respiratory symptoms that a patient might notice on a day-to-day basis.

MR. BUSKER: And the longer-term benefits this patient might anticipate?

DR. CLANCY: We've learned from longer term studies of ivacaftor/lumacaftor that the risk of pulmonary exacerbations, basically the risk of hospitalizations or need for IV antibiotics for pulmonary symptoms, is reduced by about a third. In addition, there are improvements in body mass index, so often over time patients will gain some weight if that's been a problem.

The most exciting thing I would note is that lung function decline is altered. That means when we look at lung function over time in patients with CF, there is certainly a tendency to lose lung function, and this typically becomes most pronounced during adolescence.

When we look at patients who are treated with ivacaftor/lumacaftor compared with controls, their loss of lung function is cut in half, and this change in the trajectory of lung function decline represents modification of the disease, meaning the disease course is fundamentally altered.

We're excited about that, because if we project that slowed loss of lung function over years and decades, we think that's going to amount to many, many years of added life and wellness and health for patients with CF.

MR. BUSKER: Thank you for that case and discussion. And we'll continue, with Dr. John Clancy from Cincinnati Children's Hospital Medical Center, in just a moment.

MR. BUSKER: Welcome back to this *e*CysticFibrosis Review podcast. We've been talking with Dr. John Clancy, from Cincinnati Children's Hospital Medical Center, about Current and Emerging Disease-Modifying Therapies in Cystic Fibrosis — and how some of the new information presented in his newsletter issue can affect clinical practice. So to continue in that vein, please bring us another patient scenario.

DR. CLANCY: Our next patient is a 6-year-old young lady with cystic fibrosis and a genotype of G551D/N1303K. This patient has an FEV_1 of 92% predicted and is currently prescribed several routine CF therapies including twice daily airway clearance, once daily inhaled dornase alfa, inhaled hypertonic saline with colds, pancreatic replacement enzymes with meals and snacks, and fat soluble vitamin supplements.

Her BMI is 45th percentile and her oropharyngeal cultures are typically positive for *H. influenzae*. She does not grow either MRSA or *Pseudomonas*.

MR. BUSKER: What's important for clinicians and families to know about starting ivacaftor in a patient like this?

DR. CLANCY: We've gained a fair amount of experience with ivacaftor over the last five years, and I think most of us in the CF-treating community feel quite comfortable starting this medication. Some things are recommended, for example, quarterly monitoring of liver function tests for the first year, and also to monitor for cataracts, as there were some studies, particularly in juvenile animals, that suggested a relationship between ivacaftor exposure and detection of cataracts. I don't know if we clearly have cause and effect demonstrated in people yet, but it is recommended at this time that eye exams be done annually for patients on ivacaftor, specifically the younger kids.

It is important to remember that medication works best if taken every 12 hours, and it also is really important that patients take this with some fat. It doesn't mean they have to eat a lot of fat, but usually something small such as cheese or crackers with peanut butter, or perhaps yogurt or something along those lines to help with the absorption, because this can really have a pretty profound effect on how much drug actually is available in the bloodstream to be able to do its thing, and it makes CFTR work better.

MR. BUSKER: What potential benefits of ivacaftor might the parents expect to see in their 6-year-old?

DR. CLANCY: Ivacaftor has been shown to be a profoundly effective medication in a number of mutations, and I would expect that this patient who has a gating mutation, G551D, would receive some significant benefits.

First, patients who start ivacaftor typically see an improvement in lung function very quickly, within the first several days to weeks, and depending on the baseline lung function it could be as much as 10% to 15%. This isn't universal but it's certainly something seen in the majority of patients.

In addition, weight gain and increase in BMI are also typically seen relatively quickly over the span of several weeks to a few months. There is a significant reduction in pulmonary symptoms, including cough and other respiratory symptoms, mucus production, and so forth. If we look over a little bit longer timeframe it's also been demonstrated that ivacaftor helps stabilize lung function and helps reduce the loss of lung function over time. In other words, it's helping to modify the disease course and changing the trajectory of lung function decline.

It can reduce sweat chloride values by about half, on average. And while a patient may not feel that on a day-to-day basis, it might be important in hot environments where sweat losses could be problematic.

Some evidence in younger patients indicates that there can be some measurable improvements in pancreatic function; specifically, the pancreatic enzyme levels can actually be increased in younger patients. This is an exciting possibility that modulators could help improve pancreatic function. It's a bit early to say whether that's universal and how well we can predict that, but certainly in younger patients there have been some reports of improvements in pancreatic activity.

Finally, in studies started in animal models and confirmed in human studies, the airway smooth muscle tone may actually be reduced by ivacaftor in patients with responsive mutations. There's some evidence that suggests that when CFTR is not working correctly, the bronchial muscles are a bit too tight, they're constricted, and ivacaftor may help relax them. One hypothesis is that some of the original early improvements in lung function on the span of hours to days may represent the reduction in airway smooth muscle tone.

MR. BUSKER: In your presentation of this patient, you described her current CF therapies — airway clearance, inhaled dornase alfa, inhaled hypertonic saline, PERT. What's the likely impact starting ivacaftor would have on these other therapies?

DR. CLANCY: That's usually the first question that a family will ask me: what else do I have to do, what do I not have to do anymore? Unfortunately, we don't have any studies yet that have examined whether other therapies can be discontinued. All the studies that have been reported so far have been looking at ivacaftor in addition to standard of care as opposed to replacing standard of care.

Our current recommendations are to continue these other established therapies, but we certainly acknowledge that there is a critical need for what I would call novel biomarkers, which are basically things that we could measure that could help us determine when and what is safe to discontinue without long-term risks.

These studies are not far away, and I think one of the most important questions we need to answer for the CF community is how many of the routine, established therapies are necessary when you have a highly effective modulator therapy. I don't have a clear answer to that one yet, but it's certainly very high on our priority list in the CF research community.

MR. BUSKER: Sweat chloride was one of the biomarkers you talked about in your newsletter issue. Should clinicians be assessing sweat chloride to monitor the benefits of ivacaftor?

DR. CLANCY: Sweat chloride has been an incredibly valuable test for diagnosing CF, and it's also been an incredibly valuable biomarker for trials to help demonstrate that these modulators are working the way we think they are — in other words, making the CFTR work better. When CFTR works better, sweat chloride values in patients with CF go down, and these have been shown in a number of studies with a number of CFTR modulators.

Unfortunately, this doesn't translate very well to the individual, meaning that a patient who starts a modulator may have a clinical benefit but may not have a dramatic change in their sweat chloride. So although in principle it seems we could use this, I think we've come to realize that there is a disconnect on a patient-by-patient basis between what happens with the sweat chloride and what happens with the clinical benefit. Therefore, we don't generally recommend doing this routinely and feel it's more important to monitor the patient's symptoms, lung function, and other aspects of CF symptomatology.

MR. BUSKER: Thank you. Please bring us another patient.

DR. CLANCY: The next patient is a 24-year-old young man with the genotype of G542X and F508del. He is on traditional CF therapies, including twice daily airway clearance, dornase alfa once daily, hypertonic saline twice daily, azithromycin three times a week, and pancreatic enzyme replacement with fat soluble vitamin supplements. He uses inhaled tobramycin twice daily for 28-day cycles on and off, and he routinely grows mucoid *Pseudomonas*. His lung function is about 58%.

MR. BUSKER: He has one copy of the F508del mutation. What does the research say about the effects of lumacaftor/ivacaftor in those patients?

DR. CLANCY: F or patients with one copy of F508del and a second mutation with minimal function, ivacaftor/lumacaftor does not desmonstrate clear benefits in lung function or weight. This study by Rowe and colleagues, which I reported in the accompanying newsletter, did suggest that there were some measurable reductions in sweat chloride and some improvements in pulmonary symptoms in patients with one copy of F508 and a second mutation with minimal function, but currently there are no approved modulator therapies for patients who have a single copy of F508del.

However, I would like to highlight that some of the studies with the next generation correctors combined with ivacaftor/tezacaftor did indeed show benefits for patients with one copy of F508del; these were some of the results reported at the 2017 North American CF Conference. We are excited about this possibility and envision these later phase 3 studies to begin in 2018.

MR. BUSKER: Dr. Clancy, I want to thank for giving me a perfect transition line. I was just going to ask you about you about NACFC — the recent North American Cystic Fibrosis Conference — and about the CFTR modifying therapies under development that were highlighted there.

DR. CLANCY: A number of exciting results were reported, and I'll give you some of the highlights from this year's conference. The first had to do with a different modulator combination called tezacaftor and ivacaftor. That is a combination of drugs that are felt to be effective to improve the function of F508del, the most common CF-causing mutation, and also some other partial function mutations.

Two studies were reported. One looked at the activity of that combination in patients who had two copies of the F508 mutation. It was a large phase 3 study, and the results indicated that compared with placebo, the combination of tezacaftor and ivacaftor improved the lung function on the order of 3% to 4% and also reduced the risk of pulmonary exacerbations. In many ways it looked similar to what was seen with ivacaftor/lumacaftor.

MR. BUSKER: Similar but not exceptionally better?

DR. CLANCY: I'd say the big difference was there were no differences in the report, pulmonary symptoms compared with placebo, when initiating that drug. I mentioned that there were some symptoms of chest tightness in some patients with CF starting ivacaftor/lumacaftor, but that didn't seem to be a problem with the combination of ivacaftor/tezacaftor.

Another result with that combination therapy was looking at patients who had one copy of F508 and a second mutation that was felt to be responsive to ivacaftor. In that study there was also benefit that was shown both with ivacaftor alone and even more with the combination of tezacaftor and ivacaftor.

That study was exciting because it's the first time that we've had one medication that targets both of the CF causing mutations when they're not the same. The tezacaftor/ivacaftor combination helps the F508del, while the ivacaftor is felt to help that second mutation that had some ivacaftor responsiveness.

That's an example where we're extending the available modulators into new populations, and that data has been submitted to the FDA and hopefully will be available to patients in the not too distant future.

Building on the success of the tezacaftor/ivacaftor studies were studies with a new generation of medications called next generation correctors. Specifically, we know that the F508 mutation is difficult to fix. It has problems with folding, it has

problems with opening, and it's not very stable when it's at the cell membranes.

So when we use drugs like tezacaftor and ivacaftor or lumacaftor and ivacaftor to improve the function of F508, we are still far away from normal levels. The next generation corrector drugs can be added on top of the background of tezacaftor and ivacaftor to boost the effectiveness and improve the function of F508 dramatically.

Three different next generation correctors were studied. I won't go into the details of their names because they're all numbers at this point, but the exciting thing is they showed similar trends across the different molecules. Specifically, the combination of next generation correctors on top of tezacaftor and ivacaftor helped improve the lung function of patients who had two copies of F508. Probably most important, it helped to improve the function of patients who had one copy of F508 and a second mutation that was not functional. That was exciting, and we think that if this approach is successful, we may be able to bring this type of therapy to all patients who have at least one copy of F508. That would mean that up to 90% of patients with CF would have an effective modulator-based therapy. Those studies are just in phase 2, but they're setting the stage for a very exciting 2018 as we begin to look at these combinations and phase 3 studies.

I just talked primarily about medications that are under development by Vertex, but other companies are also developing modulators that are well into clinical trials. These include Bayer, Galapagos in collaboration with AbbVie, Flatley Discovery Lab, and Novartis. Results were reported from many of these; they tended to be earlier phase studies but they provided evidence that we will have a variety of modulators available over time as these drugs continue to be worked through their studies.

Finally, I wanted to highlight one last approach that was a bit different. Modulators are basically pills taken by mouth that help improve the function in CFTR proteins. Another approach is using RNA antisense therapy — an inhaled therapy that helps make the RNA templates work more normally and produce a functional CFTR protein.

A company called ProQR has been looking at an RNA antisense therapy that is targeting F508. They provided data indicating that there was safety and a well-tolerated approach that was only taken three times a week. And when looking at different subgroups of patients treated with inhaled CFTR RNA antisense therapy, they were able to demonstrate some improvements in lung function and symptoms. These effects were exciting, but the caveat is that these are small studies. We look forward to them moving into phase 2, which will be more definitive to determine whether this approach can lead to clinical benefits.

We're excited about this because at least in principle this approach could be tailored to different CF causing mutations and therefore might be an option for patients who are not candidates for the modulators that are in development.

MR. BUSKER: So all in all, what do you see happening over the next, let's say three to five years, in the development of CFTR modulator drugs?

DR. CLANCY: I hope you can appreciate from some of the studies I've highlighted that there is an awful lot of research going on seeking to improve current modulator therapies or extend them to new populations. I would predict that over the next few years the CF community will be seeing several CFTR modulator options becoming available, including some novel correctors of F508del, additional potentiators that may be chosen or added to background therapies, and potentially other therapies such as agents that improve the function of *CFTR* mutations caused by premature termination codons or stop mutation, and agents called amplifiers may actually increase the amount of available CFTR that modulators can then act on.

These last two approaches are earlier in development. The studies of premature stop mutations are mostly in the laboratory right now, while the studies of amplifiers have begun to get into early phase 1 studies in patients with CF. Because of the complexity of the F508del mutation, it looks like optimal benefits will require the addition of add-on correctors such as next generation correctors which were discussed earlier. Finally, next generation correctors may also be effective for patients who only have one copy of F508.

Therefore, putting this altogether I think there is a very good chance we'll have highly effective modulator therapies available for well over 90% of patients with CF.

MR. BUSKER: And a follow-up question, Dr. Clancy. It looks like we're entering a world where all different kinds of CFTR modulators will be available. How can a clinician determine what's the best option for any given patient?

DR. CLANCY: I think that's going to be one of our more exciting opportunities and challenges in the coming years. We'll definitely see a need to better assign appropriate therapies to patients when given a variety of different choices. Possibly we test samples from patients combining these novel biomarkers to demonstrate some benefit.

It's clear that connecting benefits to the best therapies will require working with regulators and third party payers so we can ensure that all patients have access to the best treatments for their form of CF, and acknowledging these are lifelong treatment decisions. Having clear guidance for selecting agents will have long-term critical impact.

Finally, treatment regimens, like all therapies, are best determined by a shared decision making approach between the

patient and the CF care team. That will continue to be critical for CFTR modulators, in addition to the maintenance therapies that modulators are added to.

MR. BUSKER: Thank you for sharing those insights and for today's cases and discussion. Let's wrap things up now by reviewing what we've talked about today in light of our learning objectives. Our first learning objective: the potential side effects that may occur with CFTR modulator therapy.

DR. CLANCY: The things to pay attention to when starting CFTR modulator therapies include the potential for drug/drug interaction, specifically those when modulators are used with rifampin or antifungals. There is a need to monitor liver function tests and to monitor for cataracts in younger patients, particularly those who are on ivacaftor. Chest tightness has been reported with patients starting ivacaftor/lumacaftor, but that typically resolves over one to two weeks.

MR. BUSKER: And our second learning objective: how to determine which patients are candidates for modulator therapy, and what short-term and long-term benefits might be seen?

DR. CLANCY: Ivacaftor is FDA approved for approximately 35 *CFTR* mutations. These include gating mutations; the R117H mutation, which is a mixed gating and conduction mutation; and several rare mutations that have recently been shown to be responsive to ivacaftor in laboratory testing. Ivacaftor approval for these different populations and these patients with different genetic causes of CF goes down to the age of two years. Ivacaftor/lumacaftor is approved for patients with two copies of F508del and are over the age of six years.

Short-term benefits can be seen in lung function and symptoms, and this is most effectively seen in patients who are candidates for ivacaftor. Longer-term benefits include disease stability, improvement in weight, and change in lung function decline over time. This has been shown for both ivacaftor-treated patients, specifically those with a G551D *CFTR* mutation, and also for patients with two copies of F508 treated with ivacaftor and lumacaftor combination therapy.

MR. BUSKER: Finally: the potential disease modifying therapies that are currently in in clinical development to treat cystic fibrosis.

DR. CLANCY: The first is that the available modulators will continue to be extended into new populations. This includes younger patients or patients with less established disease. There also is the potential to extend it into new CFTR causing mutations.

There are numerous drugs and modulators specifically that are in development by several different companies. These include new correctors of F508, new potentiators, next generation correctors, and drugs that work differently such as suppressors of premature stop mutations and amplifiers which will increase the amount of available CFTR substrate for subsequent modulation by other drugs.

MR. BUSKER: From the Cincinnati Children's Hospital Medical Center, Dr. John Clancy, thank you for participating in this *e*CysticFibrosis Review Podcast.

DR. CLANCY: No, I want to say thank you. This has been a lot of fun. I've enjoyed being able to give you these updates and I look forward to what next year brings. We're very excited in the CF research community. Thank you again.

MR. BUSKER: To receive CME credit for this activity, please take the post-test at www.ecysticfibrosisreview.org/test.

This podcast is presented in conjunction with *e*CysticFibrosis Review, a peer-reviewed CME/CE credit publication that is emailed monthly to clinicians treating patients with cystic fibrosis.

This activity has been developed for the CF care team, including pulmonologists, pediatric pulmonologists, gastroenterologists, pediatricians, infectious disease specialists, respiratory therapists, dietitians, nutritionists, pharmacists, nurses and nurse practitioners, physical therapists, and others involved in the care of patients with cystic fibrosis.

There are no fees or prerequisites for this activity.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education, through the joint sponsorship of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing.

The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians. The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 credit*.™ Physicians should claim only the credit commensurate with the extent of their participation in this activity.

The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

For nurses, this 0.5 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour.

This educational resource is provided without charge, but registration is required. To register to receive *e*CysticFibrosis Review by email, please go to our website: www.ecysticfibrosisreview.org.

The opinions and recommendations expressed by faculty and other experts whose input is included in this program are their own. This enduring material is produced for educational purposes only.

Use of the names of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing implies review of educational format, design, and approach.

Please review the complete prescribing information for specific drugs, combinations of drugs, or use of medical equipment, including indication, contraindications, warnings, and adverse effects, before administering therapy to patients.

*e*CysticFibrosis Review is supported by educational grants from Gilead Sciences Inc., Vertex Pharmaceuticals Incorporated, AbbVie Inc., and Chiesi USA, Inc.

CME/CE INFORMATION

ACCREDITATION STATEMENT
Physicians
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses
The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CREDIT DESIGNATION STATEMENT
Physicians
Podcast: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 0.5 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
Podcast: These paired 0.5 contact hour Educational Activities are provided by the Institute for Johns Hopkins Nursing. Each podcast carries a maximum of 0.5 contact hour, or a total of 3 contact hours for the 6 podcasts in this program.

POLICY ON SPEAKER AND PROVIDER DISCLOSURE
It is the policy of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing that the speaker and provider globally disclose conflicts of interest. The Johns Hopkins University School of Medicine OCME has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Detailed disclosure will be made in the instructional materials.

INTERNET CME/CE POLICY

DISCLAIMER STATEMENT

STATEMENT OF RESPONSIBILITY

STATEMENT OF NEED

INTENDED AUDIENCE

CONFIDENTIALITY DISCLAIMER FOR CME ACTIVITY PARTICIPANTS

HARDWARE & SOFTWARE REQUIREMENTS

COMPLETE CME INFORMATION

This activity was developed in collaboration with DKBmed.