Breakthrough Drug is a Breath of Fresh Air for Cystic Fibrosis Patients

Anna Freitas

Thirty years after the discovery of cystic fibrosis, researchers have developed a new therapy that is expected to improve the condition of 90 percent of the cystic fibrosis population. Last October, the U.S. Food and Drug Administration expedited the approval of Trikafta (elexacaftor/ivacaftor/tezacaftor), a triple combination therapy licensed by Vertex Pharmaceuticals

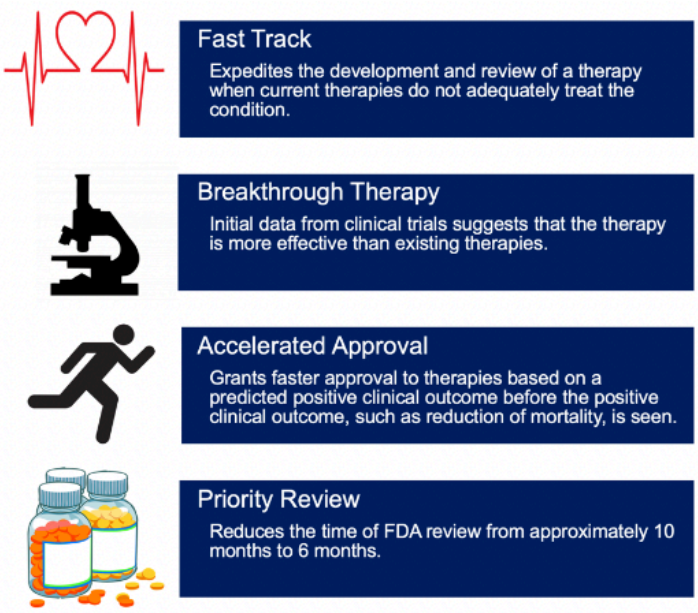
What is cystic fibrosis?

Cystic fibrosis is a genetic disease: one that is caused by mutations in DNA. This disorder typically presents as a lung disease, in which patients suffer from a persistent, shortness of breath, and frequent respiratory infections. Those who have cystic fibrosis can also experience issues with digestion and are more prone to liver disease.

In a seminal paper, Riordan et al. (1989) found that cystic fibrosis is caused by a mutation in the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR facilitates the flow of chloride ions to flow out of cells. These chloride ions are accompanied by sodium ions and water to maintain charge neutrality. Without the proper concentration of chloride ions on the surface of the cell, excessive water and sodium ions are absorbed, leading to the build-up of thick mucus on organs including the lungs, pancreas, and liver. In the lungs, the accumulation of thick mucus increases the risk of respiratory infections, which may result in progressive lung damage. Additionally, the mucus blocks release of digestive enzymes from the pancreas and bile from the liver, resulting in a reduction of nutrient absorption and liver damage, respectively.

How does Trikafta work?

Trikafta belongs to a class of cystic fibrosis therapies known as CFTR modulators, which specifically target CFTR defects. This CFTR modulator is effective for patients with at least one copy of the ΔF508 mutation: an in-frame deletion that results in the loss of phenylalanine at the 508th position. As a result of the deletion, the mutant CFTR proteins fold more slowly than their wild type counterparts and become degraded before the CFTR is transported to the plasma membrane. Two components of Trikafta, Elexacaftor and Tezacaftor, act as chaperones to facilitate folding of the mutant CFTR protein. The third component of the triple combination therapy, Ivacaftor, helps open CFTR for the transport of chloride ions, such that the properly-folded CFTR proteins that are transported to the membrane are more effective in transporting ions.



Infographic describing different designations for expedited drug review, adapted from the U.S. Food and Drug Administration.

As explained in Vertex Pharmaceuticals press release, the efficacy of Trikafta was tested in two randomized, Phase 3 clinical trials, which looked at increases in the percent predicted forced expiratory volume in one second (ppFEV1). An established marker of lung function, and therefore cystic fibrosis lung disease progression, ppFEV1 is the amount of air that is exhaled in one second divided by the expected amount given factors such as their sex and height. A 24-week, placebo-controlled trial was performed with 403 patients who had one copy of the ΔF508 mutation. The mean ppFEV1 increased by 13.8 percent in patients taking Trikafta compared to the placebo. The second trial was four-weeks long and active-controlled with 107 patients who had two identical ΔF508 mutations. In this trial, the mean ppFEV1 increased 10 percent in patients taking Trikafta compared to tezacaftor/ivacaftor alone.

According to Reshma Kewalramani, M.D., Executive Vice President, Global Medicines Development and Medical Affairs and Chief Medical Officer at Vertex, in a Vertex press release, the results of the clinical trials are unprecedented: “The results of the TRIKAFTA studies published in

both The Lancet and NEJM are impressive and represent a historic moment in CF care, with the medicine demonstrating improvements in multiple CF outcome measures in clinical trials, while being generally well tolerated."

How has the FDA facilitated the approval of Trikafta?

The FDA expedited the process of approving Trikafta by designating the drug under Priority Review, Fast Track, and Breakthrough Therapy. They also classified Trikafta as an orphan drug—one that targets diseases that affects less than 200,000 people in the United States. As a result, the FDA approved Trikafta in approximately three months, about five months ahead of its target date in March of 2020.

"At the FDA, we're consistently looking for ways to help speed the development of new therapies for complex diseases, while maintaining our high standards of review" said the acting FDA Commissioner Ned Sharpless, M.D in a press release. "Today's landmark approval is a testament to these efforts, making a novel treatment available to most cystic fibrosis patients, including adolescents, who previously had no options and giving others in the cystic fibrosis community access to an additional effective therapy."

What about cystic fibrosis patients who do not have the ΔF508 mutation?

According to the Cystic Fibrosis Foundation, approximately 7 percent of people with cystic fibrosis are unable to respond to CFTR modulators. These patients typically have a nonsense mutation, which cause a premature end to protein synthesis, on both copies of the gene encoding for CFTR. Another class of rare mutations that cannot be treated by CFTR modulators are mutations that cause splicing variants. In this case, the mutation causes a portion of the messenger RNA—the information used by the protein synthesis machinery to generate the correct sequence of protein building blocks—to be cut out before the protein is produced.

For people with nonsense or splicing mutations, CFTR modulators are ineffective because the mutation causes an issue with protein production rather than protein folding. Treatments for people with these rare cystic fibrosis mutations are currently in development and include replacing the nonsense messenger ribonucleic acid or deoxyribonucleic acid that encodes the CFTR protein.

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