CYSTIC FIBROSIS FOUNDATION
ADDING TOMORROWS

April 27, 2015

Pulmonary-Allergy Drugs Advisory Committee
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993

Re: New Drug Application (NDA) 206038, lumacaftor/ivacaftor combination tablets for oral use, submitted by Vertex Pharmaceuticals, proposed for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

Dear Members of the Pulmonary-Allergy Drugs Advisory Committee:

I write today to express the Cystic Fibrosis Foundation's strong support for the application of lumacaftor and ivacaftor for treatment of individuals with F508del homozygous cystic fibrosis (CF). As you are aware, CF is an orphan disease that affects approximately 30,000 individuals in the United States. While improvements in care and new therapies have resulted in increased survival, the chronic progressive lung disease associated with CF continues to be a significant and life-shortening problem. Even with optimal therapy, over 90 percent of deaths in CF are due to progressive lung disease, and the median age of death from CF in 2013 was 27.5 years.[1] [2] For those living with CF, the pulmonary exacerbations associated with the disease significantly affect quality of life as well as the rate of lung function decline.

Most currently available therapies target the increased mucous, infection, and inflammation that are present in the lungs of these patients, and there are currently no therapies that address the underlying CFTR dysfunction that causes CF for individuals with the most common F508del/F508del genotype. Nearly 50 percent of individuals with CF in the United States carry the F508del/F508del genotype. Recent clinical trial data, as well as results from ongoing therapy with CFTR modulators in other CF genotypes, have

[1] Cystic Fibrosis Foundation Patient Registry 2013 Annual Data Report to the Center Directors Bethesda, Maryland ©2014 Cystic Fibrosis Foundation
[2] Cystic Fibrosis Foundation Patient Registry 2013 Annual Data Report Bethesda, Maryland ©2014 Cystic Fibrosis Foundation

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demonstrated that treatment of the underlying CFTR dysfunction results in significant improvement in multiple aspects of cystic fibrosis when added to standard care. These benefits include improvement in lung function as measured by FEV1, decrease in the rate of decline in lung function over time, increase in weight as measured by BMI, and decrease in the prevalence of chronic airway *P. aeruginosa* infection.[3] [4]

Recently, Vertex Pharmaceuticals has completed a series of trials examining the effect of the CFTR corrector lumacaftor in combination with CFTR potentiator ivacaftor in individuals homozygous for the F508del mutation. These trials were based on research conducted in multiple laboratories across the country that have repeatedly demonstrated in respiratory cells homozygous for the F508del mutation the necessity of corrector compounds to traffic F508del-CFTR to the cell surface, and the additional benefit of adding potentiator compounds to improve channel open time and chloride conductance once the corrector has moved F508del-CFTR to the cell surface. After extensive phase II trials were completed, over 1,000 patients were enrolled in two phase III trials and followed for six months.[5] The results of these trials clearly demonstrated that the combination of lumacaftor and ivacaftor is beneficial in multiple ways for F508del homozygous patients. First, patients treated with the lumacaftor/ivacaftor combination demonstrated a rapid (within two weeks) improvement in FEV1. While modest in size, this FEV1 improvement was remarkably consistent across study groups, and included individuals with a full spectrum of baseline characteristics. This benefit did not vary by gender, age, baseline severity of disease, or by microbiologic profile. Demonstrating the clinical significance of this benefit, patients also had a dramatic decrease in the frequency of exacerbations. Patients receiving the proposed 400 mg q12 of lumacaftor combined with 250 mg qd of ivacaftor demonstrated a 39 percent reduction in exacerbations during the six months of the trial. This decrease in exacerbations also resulted in a significant decrease in requirement for antibiotics and hospitalizations. Finally, these patients also demonstrated a significant increase in weight as measured by BMI.

The CF Foundation is writing to highlight both the importance of these findings in the lives of individuals with CF and the desperate need for additional therapies for this genotype group. It is important to realize that these benefits were observed on top of maximal current medical therapy, and the lumacaftor/ivacaftor combination offers hope to

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[3] Rowe SM, Heltshe SL, Gonska T, Donaldson SH, Borowitz D, Gelfond D, Sagel SD, Khan U, Mayer-Hamblett N, Van Dalfsen JM, Joseloff E, Ramsey BW; GOAL Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network. Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. Am J Respir Crit Care Med. 2014 Jul 15;190(2):175-84.

[4] Heltshe SL, Mayer-Hamblett N, Burns JL, Khan U, Baines A, Ramsey BW, Rowe SM; GOAL (the G551D Observation-AL) Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network. Pseudomonas aeruginosa in cystic fibrosis patients with G551D-CFTR treated with ivacaftor. Clin Infect Dis. 2015 Mar 1;60(5):703-12.

[5] Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, Colombo C, Davies JC, De Boeck K, Flume PA, Konstan MW, McColley SA, McCoy K, McKone EF, Munck A, Ratjen F, Rowe SM, Waltz D, Boyle MP. Lumacaftor with Ivacaftor in CF Patients Homozygous for Phe508del-CFTR. NEJM. 2015 May, in press.

a patient group that continues to experience decline in lung function even when utilizing all currently available therapies.

One particular aspect of the results that has the potential to dramatically affect lung health and quality of life in this patient group is the striking effect observed in reduction in frequency of exacerbation. Pulmonary exacerbations are the driving force behind progressive lung disease in CF and associated with both permanent reductions in lung function and an increase in the subsequent rate of decline in FEV1.[6] We also know from studies that 25 percent of exacerbations result in a decrease in baseline lung function of 10 percent or more, highlighting the impact of exacerbations on long-term lung health.[7] Finally, exacerbations are associated with prolonged episodes of missed work and school, affecting patients' ability to maintain their responsibilities and make significant contributions to society. The nearly 40 percent reduction in frequency of exacerbations demonstrated with treatment with lumacaftor/ivacaftor offers patients the opportunity to maintain a job, keep up in school, and avoid the side effects associated with repeated courses of IV antibiotics.

An additional key factor to appreciate is that experience with CFTR modulators in other genotypes demonstrates that treatments that correct underlying CFTR dysfunction result in long term benefits that accumulate over time. This is particularly evident when looking at rate of lung function decline. Beyond the initial immediate FEV1 improvement seen with the start of therapy, correcting CFTR function results in an ongoing change in rate of decline which results in increasing benefit in subsequent years as lung function in preserved and structural lung disease is prevented. [8]

It is clear from the clinical trial data that the lumacaftor/ivacaftor combination represents an important breakthrough and the first step in treating the underlying cause of the most common type of CF. For the thousands of F508del/F508del CF patients with significant progressive lung disease, the clock is ticking: if we are not able to start them now on therapy that will decrease their frequency of illness and stabilize their disease course, they will never be able to benefit from the even stronger therapies that are to come in the future. For young adolescents whose lung disease is currently moderate, the clock is also ticking: if they are not able to start CFTR modulator therapy now, they will march on untreated into late adolescence, which is the time of the most significant lung function loss in CF.

The results from the clinical trials suggest that lumacaftor/ivacaftor will improve lung function, stabilize progressive lung disease characterized by recurrent exacerbations, and potentially transform the CF experience for the largest patient group in CF.

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[6] Collaco JM et al. Am J Resp Crit Care Med 2010; Waters V et al. Eur Respir J. 2012.
[7] Sanders DB et al. Am J Resp Crit Care Med 2010.
[8] Sawicki GS, McKone E, Pasta DJ, Wagener J, Johnson C, Konstan MW. Journal of Cystic Fibrosis 2014 13(2):S6.

We ask that you recommend that patients throughout the United States have access to this therapy so that they can work with their physician to optimize their care today, and give them hope that they will be able to benefit from the new therapies of tomorrow.

Sincerely,

Robert J. Beall, Ph.D.
President and Chief Executive Officer