



March 28, 2017

## Two Phase 3 Studies of the Tezacaftor/Ivacaftor Combination Treatment Met Primary Endpoints with Statistically Significant Improvements in Lung Function (FEV<sub>1</sub>) in People with Cystic Fibrosis

*-Study in people who have two copies of the F508del mutation demonstrated a mean absolute improvement in ppFEV<sub>1</sub> of 4.0 percentage points compared to placebo (p < 0.0001)-*

*-Study in people who have one mutation that results in residual CFTR function and one F508del mutation demonstrated a mean absolute improvement in ppFEV<sub>1</sub> of 6.8 percentage points with the tezacaftor/ivacaftor combination treatment compared to placebo (p < 0.0001)-*

*-Across both studies, the combination treatment was generally well tolerated-*

*-Vertex to host investor conference call tomorrow at 8:00 a.m. EDT-*

BOSTON--(BUSINESS WIRE)-- [Vertex Pharmaceuticals Incorporated](#) (Nasdaq: VRTX) today announced results from two Phase 3 studies of the tezacaftor (VX-661) / ivacaftor combination treatment that showed statistically significant improvements in lung function (percent predicted forced expiratory volume in one second, or ppFEV<sub>1</sub>) in people with cystic fibrosis (CF) ages 12 and older who have certain mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The 24-week EVOLVE study evaluated the combination treatment in people who have two copies of the F508del mutation. This study met its primary endpoint with a mean absolute improvement in ppFEV<sub>1</sub> through 24 weeks of 4.0 percentage points from baseline compared to placebo (p < 0.0001). The second study, EXPAND, was an 8-week crossover study that evaluated the combination treatment in people who have one mutation that results in residual CFTR function and one F508del mutation. This study met the primary endpoints of absolute change in ppFEV<sub>1</sub> from baseline to the average of the Week 4 and Week 8 measurements, with the tezacaftor/ivacaftor combination treatment demonstrating a mean absolute improvement of 6.8 percentage points compared to placebo (p < 0.0001) and the ivacaftor monotherapy group demonstrating a mean absolute improvement of 4.7 percentage points compared to placebo (p < 0.0001). Based on these results, Vertex plans to submit a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) and a Marketing Authorization Application (MAA) to the European Medicines Agency (EMA) in the third quarter of 2017 for the tezacaftor/ivacaftor combination treatment in people with CF ages 12 and older who have two copies of the F508del mutation and in people who have one mutation that results in residual CFTR function and F508del mutation. Vertex will host a conference call for investors tomorrow, March 29, 2017 at 8:00 a.m. EDT, to discuss these results.

Across both studies, the tezacaftor/ivacaftor combination treatment was generally well tolerated. The most common adverse events, regardless of treatment group, were infective pulmonary exacerbation and cough. In both studies, rates of discontinuations due to adverse events were low and similar between placebo and treatment groups (2.1% for placebo vs 1.7% for the tezacaftor/ivacaftor combination). Rates of respiratory adverse events were similar between placebo and treatment groups (15.0% for placebo vs 11.4% for the tezacaftor/ivacaftor combination).

"The tezacaftor/ivacaftor combination treatment demonstrated clinically meaningful benefits, with a favorable safety profile, across multiple patient groups," said Jeffrey Chodakewitz, M.D., Executive Vice President and Chief Medical Officer at Vertex. "This combination treatment may provide a promising new option for treating the underlying cause of CF in the future and brings us increasingly closer to our goal of developing new medicines for all people with the disease."

### About the EVOLVE Study:

EVOLVE was a global Phase 3, randomized, double-blind, placebo-controlled study designed to evaluate the efficacy and safety of tezacaftor/ivacaftor combination treatment in people with CF ages 12 and older who have two copies of the F508del mutation. The combination group received tezacaftor 100 mg once daily (QD) in combination with ivacaftor 150 mg every 12 hours (q12h). In the study, more than 500 people were treated at more than 90 trial sites in North America and

Europe. The primary endpoint was absolute change in ppFEV<sub>1</sub> from baseline through Week 24 for those treated with the tezacaftor/ivacaftor combination treatment compared to placebo. The mean ppFEV<sub>1</sub> at baseline was approximately 60 percent for each study arm. Of the 477 people who completed the 24-week study, 461 chose to enroll in a rollover study to receive the combination treatment.

## Efficacy Results

*Primary Endpoint:* Through 24 weeks of the study, the mean absolute improvement in ppFEV<sub>1</sub> was 4.0 percentage points from baseline for those treated with the tezacaftor/ivacaftor combination compared to placebo (p < 0.0001).

Detailed data for the primary endpoint in the study are provided below:

| Mean Absolute Change in ppFEV <sub>1</sub> (percentage points) | Placebo<br>(n=256) | Tezacaftor + Ivacaftor<br>(n=248) |
|--|--------------------|-----------------------------------|
| <b>Treatment Difference</b>                                    | N/A                | +4.0 (p < 0.0001)                 |
| <b>Within Group</b>  | -0.6 (p=0.0601)    | +3.4 (p < 0.0001)                 |

*Key Secondary Endpoints:* Statistically significant improvements were seen in multiple key secondary endpoints, including a 35 percent reduction in the annualized rate of pulmonary exacerbations with the tezacaftor/ivacaftor combination treatment compared to placebo.

Detailed data for key secondary endpoints in the study are provided below:

| Key Secondary Endpoints*  |   | Placebo<br>(n=256) | Tezacaftor +<br>Ivacaftor<br>(n=248) |
|---|---|--------------------|--------------------------------------|
| <b>Mean Relative Change in ppFEV<sub>1</sub> (%)<br/>Through 24 Weeks</b> | <b>Treatment Difference</b>                     | N/A                | +6.8 (p < 0.0001 <sup>^</sup> )      |
|   | <b>Within Group</b>                             | -0.5 (p=0.3823)    | +6.3 (p < 0.0001)                    |
| <b>Number of Pulmonary Exacerbations<br/>Through Week 24</b>              | <b>Number of Events (rate<br/>per 48 weeks)</b> | 122 (0.99)         | 78 (0.64)                            |
|   | <b>Rate Ratio</b>                               | N/A                | 0.65 (p=0.0054 <sup>^</sup> )        |
| <b>Change in Body Mass Index at Week<br/>24</b>                           | <b>Treatment Difference</b>                     | N/A                | +0.06 (p=0.4127)                     |
|   | <b>Within Group</b>                             | +0.12 (p=0.0134)   | +0.18 (p=0.0004)                     |
| <b>Change in CFQ-R Through Week 24</b>                                    | <b>Treatment Difference</b>                     | N/A                | +5.1 (p < 0.0001)                    |
|   | <b>Within Group</b>                             | -0.1 (p=0.8889)    | +5.0 (p < 0.0001)                    |

\*A hierarchical testing procedure was performed for the primary and key secondary endpoints versus placebo, noted strictly in the order above; p≤0.050 required for statistical significance

<sup>^</sup> Statistical significance was confirmed in the hierarchical testing procedure

## Safety Results

The tezacaftor/ivacaftor combination treatment was generally well tolerated. The majority of adverse events were mild or moderate. The most common adverse events (≥15%), regardless of treatment group, were infective pulmonary exacerbation, cough, headache, nasopharyngitis and sputum increased. The rate of discontinuations due to adverse events was low and similar between the placebo group and the combination treatment group. Rates of adverse events, serious adverse events and respiratory-related adverse events were similar between the placebo and the tezacaftor/ivacaftor combination treatment groups.

Selected safety data from the study are provided below:

| Safety Data  | Placebo<br>(n=258) | Tezacaftor + Ivacaftor<br>(n=251) |
|--|--------------------|-----------------------------------|
| <b>Number of Patients who Experienced Any Adverse Event</b>                    | 245 (95.0%)        | 227 (90.4%)                       |
| <b>Number of Patients who Experienced a Serious Adverse Event</b>              | 47 (18.2%)         | 31 (12.4%)                        |
| <b>Number of Patients who Discontinued Treatment Due To Adverse<br/>Events</b> | 8 (3.1%)           | 7 (2.8%)                          |
| <b>Respiratory Adverse Events*</b>   | 41 (15.9%)         | 33 (13.1%)                        |

\* Respiratory events included dyspnea, respiration abnormal, bronchospasm and other (wheezing, asthma, chest discomfort, and bronchial hyper-reactivity)

## About the EXPAND Study:

EXPAND was a global Phase 3, randomized, double-blind, placebo-controlled, crossover, multicenter study designed to evaluate the efficacy and safety of tezacaftor/ivacaftor combination treatment as well as ivacaftor monotherapy in people with CF ages 12 and older who have one mutation that results in residual CFTR function and one copy of the *F508del* mutation. Patients were randomized to one of six treatment groups to receive tezacaftor/ivacaftor, ivacaftor monotherapy or placebo for eight weeks, followed by an 8-week washout period. Following the washout period, patients switched to one of the other two treatment regimens for another eight weeks. The combination treatment group evaluated tezacaftor 100 mg once daily (QD) in combination with ivacaftor 150 mg every 12 hours (q12h), and the monotherapy group evaluated ivacaftor 150 mg every 12 hours (q12h). In the study, approximately 250 people were treated at more than 80 trial sites, mainly in North America and Europe. The primary endpoints were absolute change in ppFEV<sub>1</sub> from baseline to the average of the Week 4 and Week 8 measurements for each of the treatment groups (tezacaftor/ivacaftor combination treatment and ivacaftor monotherapy) compared to placebo. The mean ppFEV<sub>1</sub> at baseline was approximately 62 percent for each study arm. Of the 235 people who completed the study, 227 chose to enroll in a rollover study to receive tezacaftor/ivacaftor combination treatment.

## Efficacy Results

**Lung Function:** The mean absolute improvement in ppFEV<sub>1</sub> was 6.8 percentage points from baseline compared to placebo ( $p < 0.0001$ ) for those receiving the tezacaftor/ivacaftor combination and was 4.7 percentage points compared to placebo ( $p < 0.0001$ ) for those receiving ivacaftor alone. An additional pre-specified analysis of the combination group compared to the monotherapy group showed that the tezacaftor/ivacaftor combination treatment provided a statistically significant improvement in ppFEV<sub>1</sub> over the use of ivacaftor alone (2.1 percentage points,  $p < 0.0001$ ).

**CFQ-R:** The key secondary endpoint was absolute change in the Cystic Fibrosis Questionnaire-Revised (CFQ-R) respiratory domain score from baseline to the average of the Week 4 and Week 8 measurements for each of the treatment groups (tezacaftor/ivacaftor combination treatment and ivacaftor monotherapy) compared to placebo.

Detailed data from the study are provided below:

| Primary and Key Secondary Endpoints  |                      | Placebo<br>(n=161)  | Treatment Arm          |
|--|----------------------|---------------------|------------------------|
| <b>Primary Endpoint: Mean Absolute Change in ppFEV<sub>1</sub> (percentage points)</b> |                      |                     |                        |
| Tezacaftor + Ivacaftor<br>(n=161)  | Treatment Difference | N/A                 | +6.8 ( $p < 0.0001$ )  |
|  | Within Group         | -0.3 ( $p=0.5035$ ) | +6.5 ( $p < 0.0001$ )  |
| Ivacaftor<br>(n=156)   | Treatment Difference | N/A                 | +4.7 ( $p < 0.0001$ )  |
|  | Within Group         | -0.3 ( $p=0.5035$ ) | +4.4 ( $p < 0.0001$ )  |
| <b>Key Secondary Endpoint: Mean Absolute Change in CFQ-R</b>                           |                      |                     |                        |
| Tezacaftor + Ivacaftor<br>(n=161)  | Treatment Difference | N/A                 | +11.1 ( $p < 0.0001$ ) |
|  | Within Group         | -1.0 ( $p=0.3265$ ) | +10.1 ( $p < 0.0001$ ) |
| Ivacaftor<br>(n=156)   | Treatment Difference | N/A                 | +9.7 ( $p < 0.0001$ )  |
|  | Within Group         | -1.0 ( $p=0.3265$ ) | +8.7 ( $p < 0.0001$ )  |

## Safety Results

In the EXPAND study, the safety profile observed for the tezacaftor/ivacaftor combination treatment was favorable and similar to that seen in the EVOLVE study. The tezacaftor/ivacaftor combination treatment as well as ivacaftor monotherapy were both generally well tolerated. The majority of adverse events were mild or moderate. The most common adverse events ( $\geq 15\%$ ), regardless of treatment group, were cough and infective pulmonary exacerbation. There were no discontinuations due to adverse events in the combination treatment group. Discontinuations due to adverse events were low and similar between the placebo group and the ivacaftor monotherapy group. The incidence of adverse events, serious adverse events and respiratory-related adverse events was similar between the placebo, tezacaftor/ivacaftor combination and ivacaftor monotherapy groups.

**INDICATION AND IMPORTANT SAFETY INFORMATION FOR KALYDECO® (ivacaftor)**

KALYDECO® (ivacaftor) is a prescription medicine used for the treatment of cystic fibrosis (CF) in patients age 2 years and older who have one of the following mutations in their CF gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N*, *S549R*, or *R117H*. KALYDECO is not for use in people with CF due to other mutations in the CF gene. KALYDECO is not effective in patients with CF with two copies of the *F508del* mutation (*F508del/F508del*) in the CF gene. It is not known if KALYDECO is safe and effective in children under 2 years of age.

**Patients should not take KALYDECO if they are taking certain medicines or herbal supplements such as:** the antibiotics rifampin or rifabutin; seizure medications such as phenobarbital, carbamazepine, or phenytoin; or St. John's wort.

**Before taking KALYDECO, patients should tell their doctor if they:** have liver or kidney problems; drink grapefruit juice, or eat grapefruit or Seville oranges; are pregnant or plan to become pregnant because it is not known if KALYDECO will harm an unborn baby; and are breastfeeding or planning to breastfeed because it is not known if KALYDECO passes into breast milk.

**KALYDECO may affect the way other medicines work, and other medicines may affect how KALYDECO works.** Therefore the dose of KALYDECO may need to be adjusted when taken with certain medications. Patients should especially tell their doctor if they take antifungal medications such as ketoconazole, itraconazole, posaconazole, voriconazole, or fluconazole; or antibiotics such as telithromycin, clarithromycin, or erythromycin.

KALYDECO can cause dizziness in some people who take it. Patients should not drive a car, use machinery, or do anything that needs them to be alert until they know how KALYDECO affects them. Patients should avoid food containing grapefruit or Seville oranges while taking KALYDECO.

**KALYDECO can cause serious side effects including:**

**High liver enzymes in the blood have been reported in patients receiving KALYDECO.** The patient's doctor will do blood tests to check their liver before starting KALYDECO, every 3 months during the first year of taking KALYDECO, and every year while taking KALYDECO. For patients who have had high liver enzymes in the past, the doctor may do blood tests to check the liver more often. Patients should call their doctor right away if they have any of the following symptoms of liver problems: pain or discomfort in the upper right stomach (abdominal) area; yellowing of their skin or the white part of their eyes; loss of appetite; nausea or vomiting; or dark, amber-colored urine.

Abnormality of the eye lens (cataract) has been noted in some children and adolescents receiving KALYDECO. The patient's doctor should perform eye examinations prior to and during treatment with KALYDECO to look for cataracts. The most common side effects include headache; upper respiratory tract infection (common cold), which includes sore throat, nasal or sinus congestion, and runny nose; stomach (abdominal) pain; diarrhea; rash; nausea; and dizziness.

These are not all the possible side effects of KALYDECO. **Please click [here](#) to see the full Prescribing Information for KALYDECO (ivacaftor).**

## About CF

CF is a rare, life-shortening genetic disease affecting approximately 75,000 people in North America, Europe and Australia.

CF is caused by a defective or missing CFTR protein resulting from mutations in the *CFTR* gene. Children must inherit two defective *CFTR* genes — one from each parent — to have CF. There are approximately 2,000 known mutations in the *CFTR* gene. Some of these mutations, which can be determined by a genetic test, or genotyping test, lead to CF by creating non-working or too few CFTR protein at the cell surface. The defective function or absence of CFTR protein results in poor flow of salt and water into and out of the cell in a number of organs. In the lungs, this leads to the buildup of abnormally thick, sticky mucus that can cause chronic lung infections and progressive lung damage in many patients that eventually leads to death. The median age of death is in the mid-to-late 20s.

In people with the *F508del* mutation, the CFTR protein is not processed, or folded, normally within the cell and generally does not reach the cell surface. Tezacaftor is designed to address the processing defect of *F508del*-CFTR to enable it to reach the cell surface where ivacaftor can further enhance the protein's function.

In North America, Europe and Australia, we believe there are more than 22,000 people ages 12 and older who have two copies of the *F508del* mutation, and there are more than 1,500 people ages 12 and older who have one mutation that results in residual CFTR function and one copy of the *F508del* mutation.

## About Vertex

Vertex is a global biotechnology company that aims to discover, develop and commercialize innovative medicines so people with serious diseases can lead better lives. In addition to our clinical development programs focused on cystic fibrosis, Vertex has more than a dozen ongoing research programs aimed at other serious and life-threatening diseases.

Founded in 1989 in Cambridge, Mass., Vertex today has research and development sites and commercial offices in the United States, Europe, Canada and Australia. For seven years in a row, *Science* magazine has named Vertex one of its Top Employers in the life sciences. For additional information and the latest updates from the company, please visit [www.vrtx.com](http://www.vrtx.com).

### **Collaborative History with Cystic Fibrosis Foundation Therapeutics, Inc. (CFFT)**

Vertex initiated its CF research program in 2000 as part of a collaboration with CFFT, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation. KALYDECO<sup>®</sup> (ivacaftor), ORKAMBI<sup>®</sup> (lumacaftor/ivacaftor) and tezacaftor were discovered by Vertex as part of this collaboration.

### **Special Note Regarding Forward-looking Statements**

This press release contains forward-looking statements as defined in the Private Securities Litigation Reform Act of 1995, including, without limitation, Dr. Chodakewitz's statements in the third paragraph, and the information provided regarding Vertex's plans to submit regulatory applications for tezacaftor/ivacaftor combination treatment, including a New Drug Application (NDA) in the United States and Marketing Authorization Application (MAA) in Europe, in the third quarter of 2017. While Vertex believes the forward-looking statements contained in this press release are accurate, these forward-looking statements represent the company's beliefs only as of the date of this press release, and there are a number of factors that could cause actual events or results to differ materially from those indicated by such forward-looking statements. Those risks and uncertainties include, among other things, that Vertex could experience unforeseen delays in submitting regulatory filings, that regulatory authorities may not approve, or approve on a timely basis, tezacaftor/ivacaftor combination treatment due to safety, efficacy or other reasons, and other risks listed under Risk Factors in Vertex's annual report and quarterly reports filed with the Securities and Exchange Commission and available through the company's website at [www.vrtx.com](http://www.vrtx.com). Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

### **Conference Call and Webcast**

The company will host a conference call and webcast tomorrow at 8:00 a.m. EDT to discuss these results. To access the call, please dial (866) 501-1537 (U.S.) or +1 (720) 545-0001 (International). The conference call will be webcast live, and a link to the webcast may be accessed through Vertex's website at [www.vrtx.com](http://www.vrtx.com) in the "Investors" section under "Events and Presentations." To ensure a timely connection, it is recommended that users register at least 10 minutes prior to the scheduled webcast. An archived webcast will be available on the company's website.

(VRTX-GEN)

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