



June 24, 2014

Two 24-Week Phase 3 Studies of Lumacaftor in Combination with Ivacaftor Met Primary Endpoint with Statistically Significant Improvements in Lung Function (FEV1) in People with Cystic Fibrosis who have Two Copies of the F508del Mutation

-Combination of lumacaftor and ivacaftor is the first regimen designed to treat the underlying cause of CF in people with two copies of the F508del mutation, the most common form of the disease-

-All four 24-week treatment arms achieved primary endpoint of mean absolute improvement in FEV₁, compared to placebo, with a range of 2.6 to 4.0 percentage points ($p \leq 0.0004$); mean relative improvement of 4.3% to 6.7% ($p \leq 0.0007$)-

-Pooled analysis of Phase 3 studies showed statistically significant reductions of 30 and 39 percent in rate of pulmonary exacerbations for those who received the combination regimens compared to those who received placebo ($p \leq 0.0014$)-

-The combination regimens were generally well tolerated; 4.2 percent of patients receiving the combination regimens discontinued treatment due to adverse events compared to 1.6 percent of patients who received placebo; more than 1,000 patients have entered the rollover study to receive a combination regimen-

BOSTON--(BUSINESS WIRE)-- [Vertex Pharmaceuticals Incorporated](#) (Nasdaq: VRTX) today announced results from two Phase 3 studies of lumacaftor in combination with ivacaftor that showed statistically significant improvements in lung function (percent predicted forced expiratory volume in one second, or ppFEV₁) in people ages 12 and older with cystic fibrosis (CF) who have two copies (homozygous) of the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. All four 24-week combination treatment arms in the studies, known as TRAFFIC and TRANSPORT, met their primary endpoint of mean absolute improvement in ppFEV₁ from baseline compared to placebo at the end of treatment. Mean absolute improvements in ppFEV₁ of between 2.6 and 4.0 percentage points from baseline compared to placebo were observed across the studies ($p \leq 0.0004$), with mean relative improvements of 4.3 percent to 6.7 percent ($p \leq 0.0007$).

The combination regimens were generally well tolerated. The most common adverse events, regardless of treatment group, were infective pulmonary exacerbation, cough, headache and increased sputum. 4.2 percent of patients who received the combination regimens discontinued treatment because of adverse events compared to 1.6 percent of those who received placebo. More than 1,000 patients have entered a rollover study to receive a combination regimen.

Data from a pre-specified pooled analysis showed improvements in multiple key secondary endpoints. For patients who received the combination regimens compared to those who received placebo, there were statistically significant reductions in the rates of pulmonary exacerbations and statistically significant improvements in both body mass index and the proportion of patients with at least a 5 percent relative improvement in ppFEV₁. Statistically significant changes were not consistently observed for patient-reported respiratory symptoms as reported in the CF questionnaire-revised (CFQ-R).

Based on these data, Vertex plans to submit regulatory applications for approval in multiple countries, including a New Drug Application (NDA) in the United States and Marketing Authorisation Application (MAA) in Europe, in the fourth quarter of 2014 for people with CF ages 12 and older who have two copies of the F508del mutation.

"On average, people with CF who have two copies of the F508del mutation lose nearly two percent of their lung function each year, underscoring the urgent need for new medicines that address the underlying cause of this disease," said Bonnie Ramsey, M.D., Professor of Pediatrics, University of Washington School of Medicine, Director of the Center for Clinical and Translational Research at Seattle Children's Research Institute and a lead Principal Investigator for TRANSPORT. "These data showed consistent evidence of clinical benefit in lung function and other measures of the disease. The significant improvements in pulmonary exacerbations are particularly important given the potential for these events to result in hospitalizations, permanent lung damage and the need for additional treatment with antibiotics and other medicines."

"The combination of lumacaftor and ivacaftor is the first regimen designed to address the underlying cause of CF for people with the most common form of the disease, and based on these data, we plan to move as fast as possible to submit applications for approval of this combination regimen in countries around the world," said Jeffrey Chodakewitz, M.D., Senior

Vice President and Chief Medical Officer at Vertex. "I would like to thank the more than 1,100 people who took part in these studies worldwide, as well as their families, friends and caregivers."

"These data mark an exciting day for the CF community and validate our more than 30-year commitment to develop medicines that target the underlying basic defect of cystic fibrosis for all people with this devastating disease," said Robert J. Beall, Ph.D., President and CEO, Cystic Fibrosis Foundation. "While we await the FDA's review of these data, we're grateful to the many people with CF, families and volunteers who have committed their time and resources to help accelerate our efforts to bring effective therapies to all people living with the disease."

Cystic fibrosis is a rare genetic disease for which there is no cure. CF is caused by defective or missing CFTR proteins at the cell surface that result from mutations in the *CFTR* gene. The defective function or absence of CFTR proteins in people with CF results in poor flow of salt and water into and out of the cell in a number of organs, including the lungs. In people with two copies of the F508del mutation, the CFTR protein is not processed, or folded, normally within the cell and generally does not reach the cell surface. Lumacaftor 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, there are more than 22,000 people ages 12 and older who have two copies of the F508del mutation.

About the Study:

TRAFFIC and TRANSPORT were two global Phase 3, randomized, double-blind, placebo-controlled studies designed to evaluate the efficacy and safety of lumacaftor in combination with ivacaftor in people with CF ages 12 and older who have two copies of the F508del mutation. Each study included two combination treatment groups and one placebo group. The combination treatment groups evaluated lumacaftor dosed at either 600 mg once daily or 400 mg every 12 hours (q12h) in combination with ivacaftor dosed at 250 mg q12h. 1,108 people enrolled and received at least one dose of study drug in the two studies (549 in TRAFFIC; 559 in TRANSPORT) at approximately 200 clinical trial sites throughout North America, Europe and Australia. The primary endpoint of TRAFFIC and TRANSPORT was the mean absolute change from baseline in percent predicted FEV₁ at the end of the 24-week treatment period as assessed by the average change in lung function at Week 16 and at Week 24 analyzed using a Mixed Model for Repeated Measures (MMRM). Based on the design of the study, which included multiple treatment arms within each study, statistical significance for each arm versus placebo was based on a p-value of less than or equal to 0.0250.

In addition to the primary endpoint analysis for each study, a pre-specified pooled analysis evaluated the two combination treatment groups by dose from each study (two dose arms of lumacaftor 600 mg once daily in combination with ivacaftor 250 mg q12h combined; two dose arms of lumacaftor 400 mg q12h in combination with ivacaftor 250 mg q12h combined; two placebo arms combined).

Efficacy Results - Lung Function (ppFEV₁):

All four treatment arms within the studies met their primary endpoint. Additionally, statistically significant mean absolute and relative improvements in lung function were observed for all four treatment groups, both within group and versus placebo, at all time points within the study (Weeks 2, 4, 8, 16 and 24). As patients in the study continued to be treated with their standard CF medicines, improvements observed for patients in the combination treatment arms were in addition to any benefits experienced with the use of other CF medicines. The mean baseline lung function of patients was approximately 61 percent predicted FEV₁ for patients who received the combination regimen and for patients who received placebo. Detailed data from each arm of the study are provided below:

| Change in ppFEV ₁ * | TRAFFIC Study | | | | TRANSPORT Study | |
|--|----------------------|---|---|----------------------------------|---|---|
| | Placebo (n=184) | Lumacaftor (600 mg once daily) + Ivacaftor (250 mg q12h) (n=183) | Lumacaftor (400 mg q12h) + Ivacaftor (250 mg q12h) (n=182) | Placebo (n=187) | Lumacaftor (600 mg once daily) + (400 mg q12h) + Ivacaftor (250 mg q12h) (n=185) | Lumacaftor (400 mg q12h) + Ivacaftor (250 mg q12h) (n=187) |
| Mean Absolute Change (percentage points) | N/A | 4.0 (p < 0.0001 [^]) | 2.6 (p=0.0003 [^]) | N/A | 2.6 (p=0.0004 [^]) | 3.0 (p < 0.0001 [^]) |
| Treatment Difference | Within Group | -0.44 (p=0.4002) | 3.6 (p < 0.0001) | 2.2 (p < 0.0001) | -0.15 (p=0.7744) | 2.5 (p < 0.0001) |
| Mean Relative Change (%) | Treatment Difference | N/A | 6.7% (p < 0.0001 [^]) | 4.3% (p=0.0006 [^]) | N/A | 4.4% (p=0.0007 [^]) |
| | Within Group | -0.34% (p=0.7113) | 6.4% (p < 0.0001) | 4.0% (p < 0.0001) | 0.0% (p=0.9983) | 4.4% (p < 0.0001) |
| | | | | | | 5.3% (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≤0.0250 required for statistical significance

^Statistical significance was confirmed in the hierarchical testing procedure

Efficacy Results - Key Secondary Endpoints:

Within the individual studies, people who received the combination regimens experienced a 28 to 43 percent decrease in the rate of pulmonary exacerbations (events of worsening signs and symptoms of the disease requiring treatment with antibiotics) over the 24-week treatment period compared to placebo. Detailed data for all key secondary endpoints from each arm of the study are provided below:

| Key Secondary Endpoints* | TRAFFIC Study | | | TRANSPORT Study | | |
|--|---|---|--|-----------------------|---|---|
| | Placebo (n=184) | Lumacaftor (600 mg once daily) + Ivacaftor (250 mg q12h) (n=183) | Lumacaftor (400 mg q12h) + Ivacaftor (250 mg q12h) (n=182) | Placebo (n=187) | Lumacaftor (600 mg once daily) + Ivacaftor (250 mg q12h) (n=185) | Lumacaftor (400mg q12h) + Ivacaftor (250 mg q12h) (n=187) |
| Change in Body Mass Index | Treatment Difference | +0.16 (p=0.1122) | +0.13 (p=0.1938) | N/A | +0.41 (p < 0.0001^) | +0.36 (p=0.0001^) |
| | Within Group | +0.19 (p=0.0065) | +0.35 (p < 0.0001) | +0.32 (p < 0.0001) | +0.07 (p=0.2892) | +0.48 (p < 0.0001) |
| Change in CFQ-R | Treatment Difference | +3.9 (p=0.0168) | +1.5 (p=0.3569) | N/A | +2.2 (p=0.1651) | +2.9 (p=0.0736) |
| | Within Group | +1.1 (p=0.3423) | +5.0 (p < 0.0001) | +2.6 (p=0.0295) | +2.8 (p=0.0152) | +5.0 (p < 0.0001) |
| Patients with 5% or Greater Relative Improvement in ppFEV₁ | % | 22% | 46% | 37% | 23% | 46% |
| | Odds Ratio | | 2.94 (p < 0.0001) | 2.06 (p=0.0023) | N/A | 2.96 (p < 0.0001) |
| Number of Pulmonary Exacerbations | Number of Events (rate per 48 weeks) | 112 (1.07) | 79 (0.77) | 73 (0.71) | 139 (1.18) | 94 (0.82) |
| | Rate Ratio | N/A | 0.72 (p=0.0491) | 0.66 (p=0.0169) | N/A | 0.69 (p=0.0116) |

*A hierarchical testing procedure was performed for the primary and key secondary endpoints versus placebo, noted strictly in the order above; p≤0.0250 required for statistical significance

^Statistical significance was confirmed in the hierarchical testing procedure

Pooled Analysis:

In the pre-specified pooled analysis, statistically significant improvements in lung function were observed across each combination dose group compared to placebo, as outlined below:

| Pooled TRAFFIC and TRANSPORT | | | |
|---|-----------------------------|---|--|
| Change in ppFEV ₁ | Placebo (n=371) | Lumacaftor (600 mg once daily) + Ivacaftor (250 mg q12h) (n=368) | Lumacaftor (400 mg q12h) + Ivacaftor (250 mg q12h) (n=369) |
| Mean Absolute Change (percentage points) | Treatment Difference | N/A | 3.3 (p < 0.0001) |
| | Within Group | -0.32 (p=0.3983) | 3.0 (p < 0.0001) |
| Mean Relative Change (%) | Treatment Difference | N/A | 5.6% (p < 0.0001) |
| | Within Group | -0.17% (p=0.8030) | 5.4% (p < 0.0001) |

p≤ 0.0250 required for statistical significance (vs. placebo)

For patients who received the combination regimens, there were statistically significant decreases in the rates of pulmonary

exacerbations compared to those who received placebo of 30 and 39 percent. There were also statistically significant improvements in body mass index compared to placebo and in the proportion of patients with a 5 percent or greater relative improvement in ppFEV₁ compared to placebo. Detailed data on the pooled secondary endpoints are noted below:

| Key Secondary Endpoints | Pooled TRAFFIC and TRANSPORT | | |
|--|---|--|--|
| | Placebo (n=371) | Lumacaftor (600 mg once daily) + Ivacaftor (250 mg q12h) (n=368) | Lumacaftor (400 mg q12h) + Ivacaftor (250 mg q12h) (n=369) |
| Number of Pulmonary Exacerbations | Number of Events (rate per 48 weeks) | 251 (1.14) | 173 (0.80) |
| | Rate Ratio | N/A | 0.70 (p=0.0014) |
| Change in Body Mass Index | Treatment Difference | N/A | +0.28 (p < 0.0001) |
| | Within Group | +0.13 p=0.0066 | +0.41 (p < 0.0001) |
| Patients with 5% or Greater Relative Improvement in ppFEV₁ | % | 22% | 46% |
| | Odds Ratio | N/A | 2.95 (p < 0.0001) |
| Change in CFQ-R | Treatment Difference | N/A | +3.1 (p=0.0071) |
| | Within Group | +1.9 (p=0.0213) | +4.9 (p < 0.0001) |

p≤0.0250 required for statistical significance (vs. placebo)

Safety Results:

Safety results from these studies are being reported on a pooled basis for each dosing arm across the studies. The combination regimens were generally well tolerated. The most common adverse events, regardless of treatment group, were infective pulmonary exacerbation, cough, headache and increased sputum, and adverse events that occurred more frequently in patients who received the combination regimens than those who received placebo were generally respiratory in nature and included dyspnea and respiration abnormal. 4.2 percent of all patients who received combination therapy, regardless of dosing group, discontinued treatment because of adverse events compared to 1.6 percent of those who received placebo. Across the two studies, elevated liver enzymes (greater than three times the upper limit of normal) were observed in 5.2 percent of patients who received combination therapy compared to 5.1 percent of those who received placebo. Seven patients who received combination therapy experienced serious adverse events related to abnormal liver function tests, compared to zero patients who received placebo. Following discontinuation or interruption of the combination treatment, liver function tests returned to baseline for six of the seven patients and the seventh patient's liver function tests improved substantially. Detailed safety data from each arm of the study are provided below:

| Safety Data | Pooled TRAFFIC and TRANSPORT | | |
|--|------------------------------|---|---|
| | Placebo (n=370) | Lumacaftor (600mg once daily) + Ivacaftor (250 mg q12h) (n=369) | Lumacaftor (400mg q12h) + Ivacaftor (250 mg q12h) (n=369) |
| Number of Patients who Experienced Any Adverse Event | 355 (96%) | 356 (97%) | 351 (95%) |
| Number of Patients who Discontinued Treatment Due To Adverse Events | 6 (1.6%) | 14 (3.8%) | 17 (4.6%) |
| Number of Patients who Experienced a Serious Adverse Event | 106 (29%) | 84 (23%) | 64 (17%) |
| Most Common Adverse Events | | | |
| ---Infective Pulmonary Exacerbation | 182 (49%) | 145 (39%) | 132 (36%) |
| ---Cough | 148 (40%) | 121 (33%) | 104 (28%) |
| ---Headache | 58 (16%) | 58 (16%) | 58 (16%) |
| ---Sputum Increased | 70 (19%) | 55 (15%) | 54 (15%) |
| Adverse Events that Occurred More Frequently in Patients who Received the Combination Regimens: | | | |
| ---Dyspnea | 29 (7.8%) | 55 (15%) | 48 (13%) |
| ---Respiration Abnormal | 22 (5.9%) | 40 (11%) | 32 (8.7%) |

All patients who completed the 24-week study, regardless of treatment assignment, were given the opportunity to enroll in a rollover study. Following the end of the 24-week dosing period, more than 1,000 patients chose to enter the rollover study to receive a combination regimen.

Planned Regulatory Submissions:

Based on these data, Vertex plans to submit a New Drug Application (NDA) in the U.S. and Marketing Authorisation Application (MAA) in Europe in the fourth quarter of 2014. In the U.S., the combination of lumacaftor and ivacaftor received Breakthrough Therapy Designation in late 2012.

Compassionate Use Program:

Vertex recognizes that there are people with CF who have very severe disease and who are in immediate need of new CF medicines. Based on the data from these studies, Vertex will work with the CF community, doctors and regulators to explore options to make the combination of lumacaftor and ivacaftor available to certain patients who have two copies of the F508del mutation while we are seeking approval of this regimen from regulatory agencies around the world.

About Cystic Fibrosis

Cystic fibrosis is a rare, life-threatening genetic disease affecting approximately 75,000 people in North America, Europe and Australia. Today, the median predicted age of survival for a person with CF is between 34 and 47 years, but the median age of death remains in the mid-20s.

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 more than 1,900 known mutations in the CFTR gene. Some of these mutations, which can be determined by a genetic, 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 proteins in people with CF results in poor flow of salt and water into and out of the cell in a number of organs, including the lungs. This leads to the buildup of abnormally thick, sticky mucus that can cause chronic lung infections and progressive lung damage.

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

Vertex initiated its CF research program in 1998 as part of a collaboration with CFFT, the nonprofit drug discovery and development affiliate of the Cystic Fibrosis Foundation. This collaboration was expanded to support the accelerated discovery and development of Vertex's CFTR modulators.

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 four 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.

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, the statements in the fifth through seventh paragraphs of the press release, and the information provided regarding Vertex's plans to submit regulatory applications for the approval of lumacaftor in combination with ivacaftor in multiple countries, including a New Drug Application (NDA) in the United States and Marketing Authorisation Application (MAA) in Europe, in the fourth quarter of 2014 for people ages 12 and older who have two copies of the F508del mutation. 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, lumacaftor in combination with ivacaftor 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. 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 today at 8:00 a.m. ET to discuss the TRAFFIC and TRANSPORT 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 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 until July 24, 2014.

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