Vertex Receives European CHMP Positive Opinion for KALYDECO® (ivacaftor) to Treat Patients With Cystic Fibrosis Aged 12 to <24 months With Certain Mutations in the CFTR Gene

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If approved, ivacaftor will be the first and only medicine to treat the underlying cause of cystic fibrosis for these young children

LONDON--(BUSINESS WIRE)--Oct. 19, 2018-- Vertex Pharmaceuticals (Europe) Limited today announces that the European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion for KALYDECO® (ivacaftor) to include the treatment of people with cystic fibrosis (CF) aged 12 to <24 months who have at least one of the following nine mutations in their cystic fibrosis transmembrane conductance regulator (*CFTR*) gene: *G551D*, *G1244E*, *G1349D*, *G178R*, *G551S*, *S1251N*, *S1255P*, *S549N* or *S549R*.

If the European Commission issues a favorable adoption of the EMA CHMP opinion for the extension of indication, ivacaftor will be the first and only medicine approved in Europe to treat the underlying cause of CF in patients aged 12 to <24 months, who have specific mutations in the *CFTR* gene.

"Cystic fibrosis is a chronic, progressive disease that is present at birth, with symptoms often occurring in infancy, so early treatment is crucial to deliver the best possible outcomes for patients," said Reshma Kewalramani, MD, Executive Vice President, Global Medicines Development and Medical Affairs and Chief Medical Officer at Vertex. "Today's announcement marks an important step towards allowing young CF patients to benefit from treatment at an early stage of their disease, and brings us one step closer to our goal of treating all people living with CF."

The submission was supported by data from the ongoing Phase 3 open-label safety study (ARRIVAL) of children with CF aged 12 to <24 months who have one of 10 mutations in the *CFTR* gene that demonstrated a safety profile consistent with that observed in previous Phase 3 studies of older children and adults, and improvements in sweat chloride, a key secondary efficacy endpoint.

Ivacaftor is already approved in Europe for the treatment of CF in patients aged two years and older who have one of the nine following mutations in the *CFTR* gene: *G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N or S549R.* It is also approved for the treatment of CF in patients aged 18 years and older who have an *R117H* mutation in the *CFTR* gene.

About CF

Cystic fibrosis 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 proteins 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 build-up 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.

About the ARRIVAL Study

The ARRIVAL study is an ongoing Phase 3 open-label safety study of 25 children with CF aged 12 to <24 months who have one of 10 mutations in the *CFTR* gene (*G551D*, *G178R*, *S549N*, *S549R*, *G551S*, *G1244E*, *S1251N*, *S1255P*, *G1349D* or *R117H*; patients with the *R117H* mutation were eligible to enroll in regions where ivacaftor is approved for use in patients 2 through 5 years of age with an *R117H* mutation). The study demonstrated a safety profile consistent with that observed in previous Phase 3 studies of older children and adults; most adverse events were mild or moderate in severity, and no patient discontinued due to adverse events. Treatment was interrupted in two patients who had elevated liver enzymes greater than eight times the upper limit of normal, but continued to receive ivacaftor after a dose interruption. The most common adverse events (≥30%) were cough (74%), pyrexia (37%), elevated aspartate aminotransferase (37%), elevated alanine aminotransferase (32%) and runny nose (32%). Four serious adverse events were observed in two patients.

Mean baseline sweat chloride for the children in this study was 104.1 mmol/L (n=14). Following 24 weeks of treatment with ivacaftor, the mean sweat chloride level was 33.8 mmol/L (n=14). In the 10 subjects with paired sweat chloride samples at baseline and week 24, there was a mean absolute change of -73.5 mmol/L. Sweat chloride is used as a tool to diagnose infants with CF, where levels greater than or equal to 60 mmol/L indicate that CF is likely, levels of 30-59 mmol/L indicate CF is possible and levels less than 30 indicate that CF is unlikely. These data were presented at the 41st European Cystic Fibrosis Society (ECFS) Conference in June 2018 and published in *The Lancet Respiratory Medicine* (Volume 6, No 7, July 2018).

About KALYDECO® (ivacaftor)

KALYDECO® (ivacaftor) is the first medicine to treat the underlying cause of CF in people with specific mutations in the *CFTR* gene. Known as a CFTR potentiator, ivacaftor is an oral medicine designed to keep CFTR proteins at the cell surface open longer to improve the transport of salt and water across the cell membrane, which helps hydrate and clear mucus from the airways.

People with CF who have specific mutations in the *CFTR* gene are currently benefiting from ivacaftor in countries across North America, Europe and in Australia.

About Vertex

Vertex is a global biotechnology company that invests in scientific innovation to create transformative medicines for people with serious and

life-threatening diseases. In addition to clinical development programs in CF, Vertex has more than a dozen ongoing research programs focused on the underlying mechanisms of other serious diseases.

Founded in 1989 in Cambridge, Mass., Vertex's headquarters is now located in Boston'sInnovation District. Today, the company has research and development sites and commercial offices in the United States, Europe, Canada, Australia and Latin America. Vertex is consistently recognized as one of the industry's top places to work, including being named to *Science* magazine's Top Employers in the life sciences ranking for eight years in a row.

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. Kewalramani's statement in the third paragraph of this press release. While Vertex believes the forward-looking statements contained in this press release are accurate, 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 obtaining marketing approval from the European Commission and the other risks listed under Risk Factors in Vertex's annual report and quarterly reports filed with the Securities and Exchange Commission. Vertex disclaims any obligation to update the information contained in this press release as new information becomes available.

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