Cortexyme Reports GAIN Trial Data Demonstrated Relationship Between Reduction of P. gingivalis Infection and Slowing of Alzheimer's Disease Progression

October 26, 2021

In overall population, co-primary endpoints of ADAS-Cog11 and ADCS-ADL were not met

Pre-specified subgroups representing up to half of the participants based on P. gingivalis infection level showed approximately 50% slowing of cognitive decline

Clinical data validated upstream mechanism of action and benefits of targeting P. gingivalis

Additional top-line GAIN Trial results to be presented at CTAD 2021 on November 11th

Cortexyme to host investor conference call today Tuesday, October 26th at 4:30 p.m. Eastern Time

SOUTH SAN FRANCISCO, Calif.--(BUSINESS WIRE)--Oct. 26, 2021-- Cortexyme, Inc. (Nasdaq: CRTX) today reported top-line results from its Phase 2/3 GAIN Trial, a double-blind, placebo-controlled study evaluating the efficacy of atuzaginstat (COR388), an investigational orally administered small-molecule that targets gingipain proteases from the bacterium *Porphyromonas gingivalis* (*P. gingivalis*). The 643-participant study in mild to moderate patients with Alzheimer's disease did not meet statistical significance in its co-primary cognitive and functional endpoints as measured by ADAS-Cog11 and ADCS-ADL at end of the treatment period in the overall cohort.

The pre-specified subgroup of participants with *P. gingivalis* DNA detectable in saliva at baseline (PG-DS; n=242) showed a dose response, with a 57% slowing of cognitive decline as measured by ADAS-Cog11 in the 80 mg BID arm (p=0.02) and a 42% slowing in the 40 mg BID arm (p=0.07) vs. placebo. Significant benefits in this subgroup were not seen on the other co-primary, ADCS-ADL. The cognitive benefit of atuzaginstat in patients with high *P. gingivalis* infection was reinforced by similar results in multiple pre-specified infection related subgroups and with multiple methods of analysis. Additionally, reductions in *P. gingivalis* in saliva at week 24 were significantly correlated with improved outcomes at the end of the treatment period as measured by ADAS-Cog11 (p=0.0007), Clinical Dementia Rating–Sum of Boxes (CDR) (p=0.004), Mini-Mental State Exam (MMSE) (p=0.007), and a beneficial trend on ADCS-ADL (p=0.08).

The sub-study in periodontal disease demonstrated a trend to benefit on the primary clinical endpoint of pocket depth in the same pre-specified sub-group with *P. gingivalis* DNA detectable in saliva. Further results will inform the next stage of development in periodontitis and will be presented at a future scientific conference.

"Today marks a major milestone toward a comprehensive understanding of Alzheimer's and slowing of disease progression. The evidence from the GAIN Trial advances our ability to identify the right patients, impact an upstream target, and improve patient outcomes," said Casey Lynch, Cortexyme's chief executive officer, co-founder, and chair. "We are focused on next steps to advance this breakthrough treatment for the benefit of patients and their families."

Most adverse events were mild to moderate in severity. The most common were gastrointestinal, such as diarrhea in up to 16% and nausea in 6% of participants treated with atuzaginstat vs. 3% and 2% of placebo participants, respectively. Atuzaginstat was associated with dose-related liver enzyme elevations >3X the upper limit of normal: 2% on placebo, 7% on 40 mg BID, and 15% on 80 mg BID. These elevations alone were not clinically significant, and virtually all participants were asymptomatic. Two participants in the 80 mg BID arm had concomitant bilirubin elevations without alternative explanation. Lab changes resolved while participants remained on drug or after withdrawal without any known long-term adverse effects. Atuzaginstat treated groups showed no increase in ARIA (amyloid-related imaging abnormalities), including microhemorrhage and edema, or superficial siderosis.

"The first large clinical study of a gingipain inhibitor confirmed the benefits of treatment in the appropriate population at doses that reduce *P. gingivalis*. Disease modification and preservation of cognition as demonstrated in the GAIN Trial provides the foundation for altering the course of Alzheimer's," said Michael Detke, MD, PhD, Cortexyme's chief medical officer. "The *P. gingivalis*-infected participant population was easily identified with saliva or simple blood tests and was highly responsive to atuzaginstat treatment on multiple clinical measures, and we will be discussing next steps with global regulators promptly. We are grateful to the participants, caregivers, and investigators for their participation and dedication to this important study."

In light of the GAIN Trial results and the significant unmet medical need in Alzheimer's, Cortexyme is actively engaging with regulators, the medical community, patient advocacy groups, and other key stakeholders to advance development of atuzaginstat and the second-generation lysine-gingipain inhibitor COR588, which is differentiated by novel compound properties and once daily administration.

Additional Top-line GAIN Trial Results at CTAD 2021 on November 11th

Cortexyme will present the additional top-line results from the GAIN Trial at the upcoming 14th Clinical Trials on Alzheimer's Disease (CTAD 2021) conference on Thursday, November 11, 2021, at 11:35 a.m. Eastern Time in Boston, Massachusetts. Access to Cortexyme's CTAD 2021 presentation will be available on the company's Investor Relations website at ir.cortexyme.com.

Investor Call Today at 4:30 p.m. Eastern Time

Cortexyme management will discuss the GAIN Trial top-line results during an investor conference call beginning at 4:30 p.m. Eastern Time today, Tuesday, October 26, 2021. To join the call, participants may dial 877-451-6152 (domestic) or 201-389-0879 (international) and provide the conference ID: 13724711. To listen to a live webcast of the conference call, visit the Investor Calendar page under the News & Events heading of the Cortexyme's Investor Relations website at ir.cortexyme.com. A replay of the conference call will be made available and accessible on Cortexyme's Investor

Relations website shortly after the live call concludes.

About Cortexyme

Cortexyme, Inc. (Nasdaq: CRTX) is a clinical stage biopharmaceutical company pioneering upstream therapeutic approaches designed to improve the lives of patients diagnosed with Alzheimer's and other degenerative diseases. Cortexyme's lead program targets a specific, infectious pathogen called *P. gingivalis* found in the brain of Alzheimer's patients and other organs and tied to degeneration and inflammation in humans and animal models. The company's causation evidence for Alzheimer's disease and the mechanism of its novel therapeutic has been independently replicated and confirmed by multiple laboratories around the world, as well as published in peer-reviewed scientific journals. To learn more about Cortexyme, visit www.cortexyme.com or follow @Cortexyme on Twitter.

Forward-Looking Statements

Statements in this news release contain "forward-looking statements" that are subject to substantial risks and uncertainties. Forward-looking statements contained in this news release may be identified by the use of words such as "anticipate," "expect," "believe," "will," "may," "should," "estimate," "project," "outlook," "forecast," "potential" or other similar words. Examples of forward-looking statements include, among others, plans to present additional data from the GAIN Trial at CTAD 2021 and other medical meetings, the strategic development path for atuzaginstat, its business plans, strategy, planned clinical trials and timeline, prospects, and milestone expectations; the timing and success of the company's clinical trials and related data, including with respect to the GAIN Trial, as well as enabling and human studies of COR588; the potential of atuzaginstat to treat Alzheimer's disease, periodontal disease, and other potential indications; the timing of announcements and updates relating to its clinical trials and related data; the potential therapeutic benefits, safety and efficacy of the company's product candidate or library of compounds and statements about its ability to obtain, and the timing relating to, further development of atuzaginstat and COR588, regulatory submissions and related response and decisions, including with respect to the company's partial clinical hold, and approvals with respect to the company's drug product candidate. Forward-looking statements are based on Cortexyme's current expectations and are subject to inherent uncertainties, risks, and assumptions that are difficult to predict and could cause actual results to differ materially from what the company expects. Further, certain forward-looking statements are based on assumptions as to future events that may not prove to be accurate. Factors that could cause actual results to differ include, but are not limited to, the risks and uncertainties described in the section titled "Risk Factors" in Cortexyme's Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on March 1, 2021, its Quarterly Report on Form 10-Q filed with the SEC on August 6, 2021, and other reports as filed with the SEC. Forward-looking statements contained in this news release are made as of this date, and Cortexyme undertakes no duty to update such information except as required under applicable law.

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Source: Cortexyme, Inc.