April 12, 2019

Via EDGAR

Orrick, Herrington & Sutcliffe LLP
1000 Marsh Road
Menlo Park, CA 94025-1015

+1 650 614 7400

orrick.com

Suzanne Hayes
Assistant Director, Office of Healthcare & Insurance
Division of Corporation Finance
United States Securities and Exchange Commission
100 F Street, N.E.
Washington, DC 20549

Re: Cortexyme, Inc.
Draft Registration Statement on Form S-1
Submitted March 4, 2019
CIK No. 0001662774

Dear Ms. Hayes:

On behalf of our client, Cortexyme, Inc. (the "Company"), we submit this letter to the Staff of the Securities and Exchange Commission (the "Commission") with respect to the above referenced Draft Registration Statement on Form S-1 (the "Draft Registration Statement"). Set forth below are the Company's responses to the comments contained in the Staff's letter dated April 2, 2019. The Staff's comments are repeated below in bold face type and followed by the Company's responses in regular type. Concurrent with this letter, the Company is filing its Registration Statement on Form S-1 (the "Registration Statement"), which incorporates the Company's responses to the Staff's comments. The page references set forth in the Company's responses below are to the Registration Statement. For the Staff's reference, we have included both a clean copy of the Registration Statement and a copy marked to show all changes from the version confidentially submitted on March 4, 2019.

Draft Registration Statement on Form S-1
Prospectus Summary, page 1

1. **We refer to the first paragraph of your Summary, which highlights that Alzheimer's patients treated with COR388 showed "positive trends of improvement" across "several" exploratory cognitive tests commonly used in Alzheimer's trials. Please revise your Summary here and on page 2 to balance your presentation concerning the significance of the efficacy results demonstrated from testing nine patients. In this regard, we note that your CEO's October 24-27 presentation, concluded, "There was a trend of improvement in some of the cognitive tests...; however, these results should be interpreted with caution due to the small sample size." In addition, we note that your disclosure on page 94 indicates that two of the three conducted tests did not produce statistically significant results.**

Response:

In response to the Staff's comment, the Company has revised the prospectus Summary and throughout the Business Section to include the requested disclosure. In addition, we amended the pertinent risk factor on pages 15 and 16 of the prospectus.

Management's Discussion and Analysis of Financial Condition and Results of Operations
Critical Accounting Policies and Significant Judgments and Estimates
Stock-Based Compensation
Common Stock Valuations, page 74

2. Once you have an estimated offering price or range, please explain to us how you determined the fair value of the common stock underlying your equity issuances and the reasons for any differences between the recent valuations of your common stock leading up to the IPO and the estimated offering price. This information will help facilitate our review of your accounting for equity issuances including stock compensation and beneficial conversion features.

Response:

The Company confirms that once an estimated IPO price is available, it will provide the Staff an explanation to progressively bridge the fair value per share determination in each valuation to the estimated IPO price per share.

Results of Operations
Research and Development Expenses, page 76

3. Please revise the disclosure to disaggregate research and development expenses by nature or type of expense for each period presented.

Response:

In response to the Staff's comment, the Company has revised page 78 of the prospectus to include the requested disclosure.

Business, page 83

4. Given the large number of preclinical tests discussed or referenced in your prospectus, please consider whether a table briefly identifying these studies and their purpose would assist investors in understanding your preclinical work and statements, including those concerning:

- **the presence of *P. gingivalis* in the brain;**
- **the causal link between *P. gingivalis* and Alzheimer's; and**
- **successful treatment of Alzheimer's disease pathology with gingipain inhibitors, including with your COR388 inhibitor**.

Response:

In response to the Staff's comment, the Company has revised pages 87 and 88 of the prospectus to include the requested disclosure.

5. Please revise to discuss in greater detail the following preclinical testing:

- **the human observational study showing that 100% of 50 mild to moderate Alzheimer's patients tested positive using your proprietary test for *P. gingivalis* DNA fragments in cerebral spinal fluid (CSF) (pages 2 and 89) and**
- **your detection of the presence of *P. gingivalis* DNA from multiple genes, confirming the presence of bacteria (page 89)**.

Response:

In response to the Staff's comment, the Company has revised pages 3 and 92 of the prospectus to include the requested disclosure.

6. At first use, please describe the following terms employed concerning your testing results:

- **"demonstrated effects";**
- **"positive trends of improvement";**
- **"clinically significant trends";**
- **"clinically meaningful changes"; and**
- **"numerical trends of improvement".**

Also, revise your discussions of testing results, where necessary for context, to present p-values and to clarify whether the results are or are not statistically significant. For instance, we note your discussions on pages 94-95 concerning MMSE and CANTAB results do not provide p-values or address statistical significance.

Response:

The Company respectfully acknowledges the Staff's comment, and advises the Staff that the Company has elected to remove the terms "demonstrated effects," "positive trends of improvement," "clinically meaningful" and "numerical trends of improvement," and the disclosure on pages 2, 15, 85, 86, 95, 96, 97 and 99 have been modified accordingly. In addition, the phrase "clinically significant trends" was eliminated on pages 2, 15, 16, 85, 86 and 96, and the Company added more specificity on the clinical results from its Phase 1a and 1b clinical trials under the section entitled "*Our COR388 Clinical Results*."

7. We note your disclosures on pages 89 and 93 indicating that you have developed proprietary technology to test for the presence of *P. gingivalis* DNA fragments in the CSF. Please tell us, and revise, as applicable, to discuss whether there are challenges or uncertainties with respect to testing for the presence of *P. gingivalis* in the human brain.

Response:

The Company respectfully advises the Staff that it has developed a method to assess the presence of *P. gingivalis* DNA in human cerebral spinal fluid, or CSF, because there are no currently available methods to sample human brain tissue for bacterial DNA from live subjects and no imaging technology currently available for the detection of the bacteria in the brain of live subjects. The detection of multiple bacterial genes in human brain tissue using quantitative polymerase chain reaction, or qPCR, as well as the detection of gingipain proteins by immunohistochemical, or IHC, analysis was all completed on available postmortem brain tissue samples. In the process of developing this method of detection in CSF, which can be obtained using a lumbar puncture from subjects under a clinical protocol, the Company identified that the bacterial DNA found in CSF was fragmented and was not composed of intact bacterial genomic DNA. The Company also identified that levels were low enough to require a highly sensitive PCR methodology.

Challenges inherent in the detection of CSF and unique from the detection in postmortem brain tissue include: The DNA found is fragmented and represents a fraction of the genomic bacterial DNA present in the whole brain; because the DNA is fragmented it is a qualitative measure of the presence of a central nervous system infection and, while specific amounts of DNA can be identified in a specified volume of CSF, the Company cannot currently correlate it to a specific amount of bacteria present in whole brain tissue; the level of fragmented DNA is small and isolation of small amounts of DNA is subject to high variability; CSF is a biofluid that turns over regularly and will contain DNA that has been released or shed with a recent known timeframe. However, CSF has an advantage in that it circulates throughout the entire brain and, as such, represents not just a small sampling of one area of the brain, but a representation of bacterial DNA present throughout the brain tissue. CSF is also readily available with a significant volume that can be sampled from subjects in a clinical trial setting before and after treatment.

In response to the Staff's comment, the Company has revised pages 92 and 98 of the prospectus to include the requested disclosure.

***P. gingivalis* and the Role of Gingipains, page 88**

8. Please reconcile your disclosure on page 88, which appears to attribute the work to your collaborators at the University of Auckland, and the second sentence of the prospectus summary, which highlights "your seminal discovery" observed across multiple studies to date. Please note that we may have additional comment after reviewing your response.

Response:

In response to the Staff's comment, while the Company believes that it was the first to discover *P. gingivalis* and gingipains in the brain, other researchers have also identified *P. gingivalis* in the brain, and published their findings. As such, the Company has revised pages 1, 72 and 85 of the prospectus to change all references to "our" seminal discovery to "the" seminal discovery.

The Company respectfully advises the Staff that certain researchers at the University of Auckland are referenced as co-authors, together with the Company, of the paper published in the peer reviewed journal, *Science Advances*, that was cited in the prospectus. In response to the Staff's comment, the Company has revised page 91 of the prospectus to clarify that the statements from that paper are attributable to the Company. The prospectus refers to two other independently conducted academic studies that were published in peer reviewed journals that are publicly available without a subscription.[1]

***P. gingivalis* Infection Causes Alzheimer's Disease Pathology in Mice, page 89**

9. We note your statement indicating that the ability to reproduce disease in an infected animal is an important criterion for demonstrating causation. Please revise to identify briefly other criteria typically used to demonstrate causation, or advise.

Response:

In response to the Staff's comment, the Company has revised page 92 of the prospectus to include disclosure of the criteria that supports a causal relationship between *P. gingivalis* and Alzheimer's disease.

10. We refer to your disclosure on page 1 highlighting that you have "observed that *P. gingivalis* infection causes Alzheimer's pathology in animal models." We note; however, that your discussion under the heading on page 89 appears limited to discussion of a single animal model. In revising this section, please be sure to identify and explain the work that your team conducted. Also, identify any other studies or factors that form the basis for your conclusions concerning causation.

Response:

In response to the Staff's comment, the Company has revised pages 92 and 93 of the prospectus to include the requested disclosure.

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1 Illievski, V., Zuchowska, P., Green, S., Toth, P., Ragozzino, M., et al. "Chronic oral application of a periodontal pathogen results in brain inflammation, neurodegeneration and amyloid beta production in wild type mice." *PLoS ONE*. October 2018; Poole, S., Singhrao, S., Kesavalu, L., Curtis, M., Crean, S. "Determining the Presence of Periodontopathic Virulence Factors in Short-Term Postmortem Alzheimer's Disease Brain Tissue." *Journal of Alzheimer's Disease*. Volume 36, Number 4, August 2013.

Exploratory Cognitive Testing, page 94

11. We note your disclosure on page 2 and elsewhere noting that the study was not "designed to be powered for significance" on cognitive tests. Accordingly, please tell us, and revise the discussion of your cognitive testing on Alzheimer's patients, as applicable, to explain the implications of conducting testing and presenting efficacy results where the study was not designed to be powered for significance. With reference to your disclosure on page 100 concerning the IND and IRB processes, please tell us whether this exploratory testing was conducted pursuant to an FDA-authorized IND and whether you submitted the testing protocols to FDA. Similarly, please tell us whether an IRB reviewed and approved the study plan and protocols.

Response:

The Company respectfully acknowledges the Staff's comment. The Company respectfully advises the Staff that standard Phase 1 studies have a primary goal of assessing for any safety signals, and, because the safety is not known *a priori*, Phase 1 studies are not constructed or designed to be powered to assess statistical significance for any endpoints. The Company further advises the Staff that, despite safety being the primary analysis for a Phase 1 study, it is also standard practice in the industry to include and examine other measures (often referred to "exploratory endpoints") whose result does not bear on the primary safety measure, to assess activity of the product candidate being evaluated. The assessments of the cognitive endpoints in the Company's Phase 1a/1b study were exploratory in nature, and, as customary, were designed to assess for potential signals of efficacy, and their approximate magnitude, to guide the design of future, more definitive studies. All non-primary outcome measures (e.g., non-safety related) are conducted, assessed and communicated in standard practice. There was an open IND ("FDA-authorized") for COR388, the protocols were submitted to the FDA, and they were reviewed and approved by IRBs, all of which are standard practice.

12. Please explain why you chose to test using three measures (MMSE, CANTAB, WLA) but did not test using ADAS-Cog 11. In this regard, we refer to your disclosure on page 1 that ADAS-Cog 11 has served as a key endpoint in supporting regulatory approval of drugs for Alzheimer's disease as well as your disclosure on page 95 that you have selected mean change in ADAS-Cog 11 as the primary endpoint for your planned Phase 2/3 GAIN clinical trial.

Response:

The Company respectfully advises the Staff's that it did not select ADAS-Cog in the Phase I exploratory cognitive testing because ADAS-Cog is inherently highly variable and, as such, typically requires large numbers of patients to provide reliable data. Accordingly, ADAS-Cog would not be an appropriate measure in Phase I exploratory testing. MMSE is typically used as a screening tool to categorize Alzheimer's disease patients as mild, moderate or severe and therefore this test was necessarily included at baseline and therefore used at study endpoints. CANTAB and WLA were selected because they are thought to be more sensitive to changes in smaller studies, in part because they are computerized and thus less variable.

13. Please revise your discussion of each of the three measures (MMSE, CANTAB, WLA) to explain the results in Figure 7 and to demonstrate the numerical trend of improvements or statistically significant improvement cited.

Response:

The Company respectfully notes the Staff's comment. In response to the Staff's comment, the Company has revised pages 99 and 100 of the prospectus to include the requested disclosure.

14. Please revise your discussion of the Winterlight speech-based cognitive assessment (WLA) to address the following:

- **Revise to present the endpoints and results for each of the three WLA measurements that you highlight. Here, we note that Figure 7 appears to depict results for only one measurement, or possibly a portion thereof (i.e., use of prepositions).**
- **Indicate whether WLA analysis was limited to the three measurements you present.**
- **Discuss whether FDA has accepted WLA testing as the basis for review and/or approval of drugs for Alzheimer's treatment or any drugs treating other diseases, disorders or conditions that impact cognitive function. Here, we note your risk factor disclosure on page 11.**

Response:

The Company respectfully advises the Staff as follows:

- There were a total of 35 markers in the exploratory test assessed statistically in the Winterlight Speech-Based Cognitive assessment. The Company included three of these measurements because the subjects treated with COR388 showed improvements from baseline. Two of the measurements (object units, and prepositions/subordinating conjunctions) showed improvement that was statistically significantly greater for subjects treated with COR388 versus subjects dosed with placebos, with the prepositions/subordinating conjunctions parameter remaining significant even after adjustment using a conservative Bonferroni correction. The Company also focused on these three measurements because they have been shown to be indicative of the presence and severity of Alzheimer's disease, with these speech content measurement ranking as the most important measurements in speech associated with disease severity.[2]
- The FDA has not accepted WLA testing as a basis for review or approval of drugs for the treatment of Alzheimer's disease or any related cognitive conditions, although to the best of the Company's knowledge, no company has submitted a drug for approval using WLA. The measurements collected by WLA have been shown in multiple studies to be indicative of the presence and severity of Alzheimer's disease, so they may be reasonably interpreted to be predictive of accepted measurements such as the ADAS-Cog11.

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2 Fraser, K., Meltzer, J., Rudzicz, F. "Linguistic features identify Alzheimer's disease in narrative speech." *Journal of Alzheimer's Disease*. Volume 49, Number 2, 2016

In response to the Staff's comment, the Company has revised pages 100 and 101 of the prospectus to include additional disclosure about the WLA.

Our Planned Phase 2/3 GAIN Clinical Trial of COR388, page 95

15. We note that your discussion on page 102 concerning human clinical studies in support of an NDA indicates that Phase 2 and Phase 3 are typically conducted in sequential phases. Please revise to discuss your decision to combine these two phases, including any attendant challenges. Also, revise to discuss the current regulatory status of the proposed GAIN trial. In this regard, your disclosure on page 11 suggests that FDA acceptance of your GAIN trial remains pending.

Response:

In response to the Staff's comment, the Company has revised pages 102 and 109 of the prospectus to include the requested disclosure.

Intellectual Property, page 98

16. Please revise your disclosure regarding your intellectual property to clarify the jurisdiction in which you hold issued patents and pending applications.

Response:

In response to the Staff's comment, the Company has revised pages 2, 86 and 104 of the prospectus to include the requested disclosure.

17. We refer to your disclosure on page F-25 concerning a research grant and license agreement with an unidentified stockholder. Please revise your intellectual property section to add disclosure concerning this agreement. Identify the counterparty, discuss the subject of the license, and clarify whether the $1.05 million is an annual limitation. Also, file the agreement as an Exhibit to the registration statement or explain why it is not required to be filed pursuant to Item 601(b) (10) of Regulation S-K.

Response:

The Company respectfully advises the Staff that it does not believe the research grant and license agreement to be a material agreement that is required to be discussed in the prospectus or filed pursuant to Item 601(b)(10). The agreement was entered into in June 2014, and was

amended in November 2015 (in each case, more than two years before the filing of the Registration Statement). The agreement provided for a small research grant of less than $500,000, which was fully paid in 2014 and the issuance of a warrant to purchase 76,002 shares of common stock. The parties recently amended the agreement to remove the royalty provisions, and thus there will be no future payments under the agreement. The license granted to the counterparty is a limited, non-exclusive license for non-commercial uses related to (i) academic research carried out by a nonprofit educational, research or scientific institution or (ii) a nonprofit humanitarian organization. In addition, the non-commercial license is not permitted to be used in the field of the diagnosis, treatment or prevention of Alzheimer's disease or other neurodegenerative disorders through the inhibition of bacterial gingipains or in a manner that is otherwise competitive with the commercial use of the Company's intellectual property.

Description of Capital Stock, page 139

18. We note that your current certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the sole and exclusive forum for any derivative action or proceeding brought on your behalf. Please tell us whether the amended and restated certificate of incorporation that is to be in effect upon closing of the offering will contain a similar or a modified provision.

Response:

The Company respectfully advises the Staff that it plans to include exclusive forum provisions in the Company's Amended and Restated Certificate of Incorporation that will be effective upon the closing of this offering. The provision will not designate the Court of Chancery as the exclusive forum for any derivative action arising under the Securities Exchange Act of 1934, as amended since there is exclusive federal jurisdiction for such an action, and instead will designate the federal district court for the District of Delaware in such instance. However, it will apply to Securities Act of 1933 claims, although there is uncertainty as to whether a court would enforce such provision.

In response to the Staff's comment, the Company has revised pages 58, 59, 152 and 153 of the prospectus to include this disclosure.

General

19. Please provide us proofs of all graphics, visual, or photographic information you will provide in the printed prospectus prior to its use, for example in a preliminary prospectus. Please note that we may have comments regarding this material.

Response:

If the Company uses graphics, visual, or photographic information in the printed prospectus, the Company will supplementally provide the Staff with proofs under cover of a separate letter.

20. Please supplementally provide us with copies of all written communications, as defined in Rule 405 under the Securities Act, that you, or anyone authorized to do so on your behalf, present to potential investors in reliance on Section 5(d) of the Securities Act, whether or not they retain copies of the communications.

Response:

The Company will supplementally provide the Staff with copies of its written communications that are used in Testing the Waters meetings pursuant to Section 5(d) of the Securities Act under cover of a separate letter.

We appreciate your time and attention to the Company's responses to the Staff's comments. Should you have any additional questions or concerns, please call me at (415) 773-5970.

Very truly yours,

/s/ Andrew D. Thorpe
Andrew D. Thorpe

cc: Casey C. Lynch, Cortexyme, Inc.
Christopher Lowe, Cortexyme, Inc.
Kristin Gafric, Esq., Cortexyme, Inc.
Scott Iyama, Esq., Orrick, Herrington & Sutcliffe LLP
Peter Lamb, Esq., Orrick, Herrington & Sutcliffe LLP
Brian J. Cuneo, Esq., Latham & Watkins LLP
B. Shayne Kennedy, Esq., Latham & Watkins LLP
Ross McAloon, Esq., Latham & Watkins LLP
Jeffrey Gabor, Esq., Securities & Exchange Commission
Joseph McCann, Esq., Securities & Exchange Commission