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Afferent's P2X3 inhibitor shows 75 percent reduction in chronic cough frequency

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Afferent Pharmaceuticals today announced publication of results from a Phase 2 clinical trial demonstrating that the company's novel drug candidate, AF-219, reduced daytime cough frequency by 75% compared to placebo in patients with treatment-refractory chronic cough.

These data are featured in an article titled, "P2X3 Receptor Antagonist (AF-219) in Refractory Chronic Cough: A Randomised, Double-Blind, Placebo-Controlled Phase 2 Study," which is appearing online in *The Lancet*. These results support Afferent's current development strategy to initiate a Phase 2b clinical trial early in 2015. AF-219 is a selective, non-narcotic and orally administered agent that targets the mechanism by which certain nerve fibers become hyper-sensitized and lead to chronic and debilitating symptoms such as cough.

"Patients with refractory cough suffer from debilitating coughing and need new treatment options. Current therapies are largely ineffective, or can have significant side effects or potential for abuse, since most contain opioids or opiate-derivatives," commented Jacky Smith, M.B., Ch.B., MRCP, Ph.D., lead author of the Lancet article, and professor and honorary consultant in Respiratory Medicine, University of Manchester and University Hospital Manchester NHS Foundation Trust. "This is the first published study showing clear clinical benefit of a treatment for refractory cough. I am excited by these clinical results and believe that AF-219 represents a promising new antitussive."

Kathleen Sereda Glaub, Afferent's chief executive officer, stated, "The

remarkable findings in cough, as published in *The Lancet*, provide the first evidence that AF-219 may be able to reduce chronic coughing in patients whose nerve fibers have been hyper-sensitized. As a selective, oral and non-narcotic agent, we hope that AF-219 will enhance patients' treatment options. With approximately two-thirds of responders to AF-219 treatment showing more than a 50% reduction in cough frequency, we plan to advance the development of AF-219 by initiating a Phase 2b study in patients with chronic cough early next year and to initiate other studies in preparation for registration studies."

Results Show Significant Objective and Subjective Improvements with AF-219 Treatment

In the 24-patient randomized, placebo-controlled Phase 2 clinical trial, data showed:

- 75% reduction in daytime cough frequency compared to placebo (p=0.0003) in the intent-to-treat population and 84% reduction (p=0.0005) in cough frequency in the per protocol analysis.
- Statistically significant improvements over placebo in secondary endpoints, including severity and urge to cough, as well as quality of life and global ratings of change.
- All adverse events were either mild or moderate in severity; there were no serious adverse events in the study.
- Patients enrolled in the study were, on average, coughing approximately 40 times per hour and for over 10 years.

According to the trial's crossover design, patients with refractory chronic cough of at least eight weeks' duration were randomly assigned initially to either AF-219 or placebo treatment twice daily for two weeks, followed by a washout period, and further followed by crossover to the alternative treatment arm (AF-219 or placebo) for an additional two

weeks. The study's primary endpoint was reduction in daytime cough frequency as measured objectively using an ambulatory cough recorder. Secondary endpoints included cough severity, urge to cough, quality of life, and global ratings of change, as measured by patient-reported outcomes. A responder analysis of this study shows that approximately one-third of patients demonstrated more than a 90% reduction in cough frequency, and this analysis was consistent with patient-reported assessments of reduction in cough severity. Further, the analysis shows that approximately two-thirds of patients demonstrated more than a 50% reduction in cough frequency, also consistent with patient assessment of the reduction in cough severity.

Treatment-Refractory Chronic Cough Significant Unmet Need

Cough is the symptom for which patients most often seek medical attention, and chronic cough due to any cause affects an estimated 5-18% of the general population. A significant set of these patients (as many as approximately 40% of chronic coughers) is estimated to have cough refractory to treatment of associated conditions, such as gastroesophageal reflux or post-nasal drip.

Individuals with treatment-refractory chronic cough often report being distressed, depressed, angry and/or anxious. Nearly 80% feel cough interferes with social activities. In Afferent's Phase 2 study in chronic cough, patients enrolled were, on average, coughing approximately 40 times per hour and for over 10 years.

The last new cough therapy to be approved was dextromethorphan more than 50 years ago. There is little evidence suggesting that currently available antitussive drugs are effective for cough in any disorder. Further, safety and abuse liability concerns have restricted use of certain

antitussives.

More information: *The Lancet*, www.thelancet.com/journals/lan … (14)61255-1/abstract

Provided by Afferent Pharmaceuticals