DEPARTMENT OF HEALTH & HUMAN SERVICES PUBLIC HEALTH SERVICE

Food and Drug Administration
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: November 19, 2015

ATTN: Donn M. Dennis, M.D., F.A.H.A.
Chief Science Officer
Xhale, Inc.
3630 SW 47th Ave. - Suite 100
Gainesville, FL 32608

Subject: Biomarker Letter of Support

Dear Dr. Dennis,

We are issuing this Letter of Support to Xhale, Inc. to encourage the development of 2-butanone in human breath as a potential monitoring biomarker for use in clinical trials to evaluate drug dosing compliance on a dose-by-dose basis. This approach was outlined in your submission to the FDA Biomarker Qualification Program.

Determination of drug compliance in clinical trials, unless directly observed, is a challenging area as lack of compliance may result in inaccurate conclusions about an investigational drug product's safety or efficacy. Poor compliance with drug regimens in clinical trials can represent a significant barrier to acquiring a clear understanding of the human pharmacology (e.g., pharmacokinetics, pharmacodynamics) of an investigational drug. In addition, poor compliance may result in loss of study power, suboptimal dosing, and incomplete data for safety and efficacy assessments. The overarching goal of monitoring 2-butanone in human breath following ingestion of an investigational drug in a clinical trial setting is to provide drug developers and regulatory authorities with a greater understanding of how adherence to investigational drugs impacts a drug development program.

We support Xhale, Inc.'s development of 2-butanone in human breath as a monitoring biomarker for use in clinical trials. Your submitted preliminary findings support the potential value of 2-butanone in human breath as a means of monitoring drug compliance. Your proposal for including 2-butanol as part of a clinical trial's oral dose formulations (e.g., new active pharmaceutical ingredient, placebo, or active control drug) may allow for the detection of 2-butanone in human breath following metabolism of 2-butanol to 2-butanone. Some considerations for further development of this biomarker include: the evaluation of how food affects 2-butanol pharmacokinetics and the optimal breath sampling time, and considerations of how cognitive impairment or other conditions that alter a patient's mental status may impact the utility of this biomarker's use in clinical trials enrolling such patients.

No specific human breath monitoring system of 2-butanone is endorsed by this letter. Applying rigorous scientific and laboratory practices for quality control of reagents as well as device detection and interpretation is imperative. The analytical validity of a device and the reagents used in support of specific clinical performance characteristics for 2-butanone in human breath should be established prior to use of the system in clinical trials.

If sponsors intend to use 2-butanone in human breath as a biomarker to monitor medication compliance in their clinical drug development programs to support regulatory decision making, they should consult with the appropriate CDER regulatory review division.

Any groups (academia, industry, government) that would like additional information can contact Dr. Dennis (ddennis@xhale.com), the Xhale, Inc. point of contact for the project.

Sincerely,

Janet Woodcock, M.D.

Director, CDER

U.S. Food and Drug Administration