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: June 6, 2016

ATTN: Jan De Backer MSc, Ph. Chief Executive Officer
FLUIDDA nv
Groeningenlei 132
2550 Kontich
Belgium

Subject: Biomarker Letter of Support

Dear Dr. De Backer:

We are issuing this Letter of Support to FLUIDDA to encourage further study of Functional Respiratory Imaging (FRI) measurements of lung and airway structural and functional parameters measured by low-dose high-definition volumetric computerized tomography (HDCT) scans and quantitative imaging technology, as prognostic biomarkers of disease progression and pharmacodynamic response to therapeutic intervention in clinical trials for idiopathic pulmonary fibrosis (IPF).

IPF is characterized by the creation of fibrotic tissue in the lungs that progressively reduces the capacity to properly move oxygen into the bloodstream. Presently, there are no qualified biomarkers to measure disease progression or treatment benefit. Forced Vital Capacity (FVC) was used as the primary endpoint for two recent drug approvals; however FVC has not been validated as a surrogate for likelihood of death or other clinically meaningful efficacy variables in IPF. Sensitive biomarkers measuring disease stage and biological response to treatment would facilitate clinical development decisions and accelerate drug development.

We support FLUIDDA's proposed study of FRI biomarkers for the evaluation of disease progression and biological response to treatment. FRI measurements may provide regional information on anatomical and functional characteristics of the respiratory system. Such measurements have the potential to be more accurate and sensitive in evaluating disease state and progression, thereby also evaluating potential treatment effects when used as longitudinal measurements. Current evidence suggests that assessment of changes in airway radius and lung volumes may be the most promising FRI biomarker candidates. Greater experience with these imaging biomarkers in clinical trials would provide useful information to determine their clinical utility for drug development decisions and for demonstration of efficacy of treatment interventions.

We also refer FLUIDDA to the Qualification Process for Drug Development Tools Guidance to aid in understanding the different expectations for a pharmacodynamic biomarker intended to demonstrate a biological response to a therapeutic intervention compared to a surrogate endpoint which requires extensive experience using the biomarker in drug development and robust scientific evidence that treatment effect on the biomarker predicts treatment effect on a clinical endpoint (direct measure of how a patient functions,

feels, or survives). As mentioned previously, there are uncertainties using FVC as a surrogate endpoint for IPF. As such, validating future surrogate endpoints for IPF using FVC is problematic. To establish FRI as a surrogate endpoint, consider correlating FRI with more clinically meaningful outcomes such as disease exacerbations and/or mortality.

As FRI development progresses, we encourage FLUIDDA to choose one specific measure of FRI as a biomarker, in order to fully understand the variability and reliability of this specific FRI measurement.

No specific imaging technique or methodology is endorsed by this Letter of Support. Applying rigorous scientific and laboratory practices for quality control to analysis approaches for FRI is imperative. We recommend the use of standardized imaging acquisition protocols and calculation methodologies to facilitate analyses across studies and study sites.

We encourage exploration of the use of FRI biomarkers measured via HDCT scans and quantitative imaging technology in clinical trials to evaluate disease stage and progression, biological response to therapeutic intervention, provide quantifiable predictions about drug performance, and contribute to clinical development decisions. If sponsors intend to include FRI biomarkers to support regulatory decision making for a given Investigational New Drug (IND), they should prospectively discuss the approach with the relevant division at the Center of Drug Evaluation and Research (CDER).

Any groups (academia, industry, government) that would like to join in this effort or have information or data that may be useful can contact Jan De Backer (Jan.DeBacker@fluidda.com), the FLUIDDA point of contact for this project.

Sincerely,

Janet Woodcock, M.D.
Director, CDER
U.S. Food and Drug Administration