LOI DECISION LETTER

DDTBMQ000074

January 29, 2019

Jan De Backer, M.Sc., Ph.D., M.B.A.
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Suite 9E
New York, NY 10017

Dear Dr. De Backer:

We are issuing this Letter of Intent (LOI) Decision Letter to notify you of our decision on your proposed qualification project. We have completed our review of your LOI submission of August 9, 2018, and have concluded to **Not Accept** it into the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP). Please note that the 21st Century Cures Act was signed into law in December, 2016, and adds new section 507 to the Federal Food, Drug, and Cosmetic Act (FD&C Act) concerning the qualification of drug development tools (DDTs). FDA now operates its DDT program under the section 507 provisions. As stated in section 507(a)(2)(B), an LOI submission may not be accepted based upon factors which include scientific merit.

In summary, our decision was based on the following;

- You propose to apply both continuous and categorical representations of the biomarker, $V_{LLL\%p}$. Continuous and categorical representations have different meanings, require very different approaches to development, and may have different applications in drug development. One representation of a biomarker is permitted per submission so that we may provide focused recommendations that will help support your qualification efforts.

- The proposed Context of Use (COU) is unclear and adequate supporting information for how the monitoring biomarker will be used in drug development in studies of Idiopathic Pulmonary Fibrosis (IPF) has not been provided.

- In the development of a categorical COU related to disease severity, due to the lack of a widely accepted disease staging criteria for IPF and that common clinical parameters do not accurately predict disease progression[1] or distinguish between progression and acute exacerbation(s), you would have to demonstrate that $V_{LLL\%p}$ based staging and the cut-offs proposed were linked to clinically meaningful outcomes. Linking $V_{LLL\%p}$ to FVC alone would likely be insufficient to support $V_{LLL\%p}$ use as a biomarker for disease staging.

[1] Ley B et al. Predictors of Mortality Poorly Predict Common Measures of Disease Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2016;194(6): 711. doi: 10.1164/rccm.201508-1546OC.

- The elements and the method of measurement, the application of and approach to validation of the analytics are not adequately described.

The data you have provided are encouraging, however, more information is needed to better understand how the use of volume of the lower lobes of the lungs (V_{LLL}) at maximal inspiration may be used as a monitoring biomarker for disease staging for patients with IPF. We encourage and support your further study of this biomarker including the validation to clinical or disease staging and collection of specified exploratory information from the proposed clinical trials. The comments and questions in this letter represent CDER's scientific concerns related to the proposed biomarker and COU, however, these may not be a comprehensive list of considerations for the final biomarker and COU.

If you choose to further develop this tool for regulatory use, we recommend that you refine the biomarker and COU and fully address the concerns relevant to the selected biomarker, COU and submission stage, should you resubmit the LOI.

Biomarker Considerations

***Requestor's Biomarker Description*:** Volume of the lower lung lobes (sum of the volumes of the right and left lower lobes) of the lungs (V_{LLL}) at maximal inspiration, as measured by High Resolution Computed tomography (HRCT).

The V_{LLL} measurement in the IPF population will be used as a percentage of the predicted normal $V_{LLL\text{-}\%p}$ (as determined for normal population subgroups based on sex, age and height).

$$V_{LLL\text{-}\%p} = \frac{V_{LLL\ IPF}}{V_{LLL\text{-}NORMAL\ (sex,\ age\ height)}}$$

You propose two representations of the same biomarker measurement, $V_{LLL\text{-}\%p}$, as the amount of change in the continuous value and using $V_{LLL\text{-}\%p}$ to categorize IPF patients (using cutpoints), indicating Stages 1 through 3 with increasing severity of disease.

To better understand the benefits of the proposed biomarker as a DDT, and to continue to refine the COU, please address the factors listed above and provide the following information where relevant to your selected biomarker and revised COU.

FDA's questions for continued development of the biomarker description:

1. Please evaluate the advantages and disadvantage of the two formats of the biomarker, as described above, namely continuous or categorical when monitoring for change or severity/stage of disease.

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Please indicate which format is most robust and provide a rationale for your proposed use in clinical studies. Please note that you will need to select one of the two approaches for the qualification effort as the data supporting each approach will be different and as such would need to be demonstrated using different types of clinical data in separate submissions.

Context of Use (COU) Considerations

Requestor's COU: Volume of the lower lobes of the lungs (V_{LLL}) at maximal inspiration is a monitoring biomarker for disease staging in patients with Idiopathic Pulmonary Fibrosis (IPF) for use in IPF treatment studies.

2. The proposed COU is not clear. Please describe how you envision this monitoring biomarker to be applied in the context of a clinical trial. Without a clear, specific COU, the submission is incomplete and it is difficult to evaluate the proposed biomarker. Some of the lack of clarity stems from your proposal to use this measurement in both a continuous and categorical manner and omission of a specific use for the monitoring activity in studies. Use of this measurement in a continuous manner versus use of this measurement in a categorical manner for change in disease or disease staging suggests very distinct uses which would be evaluated differently. As such, we recommend that you revise your COU to be more specific and clearly state the biomarker and the purpose for the biomarker in a clinical trial for the intended population.

3. In the context of IPF drug development, below are some examples of how a biomarker may be useful:

    - As a monitoring or pharmacodynamic biomarker for IPF patients that detects a treatment response earlier or with more specificity/sensitivity than currently used measures (e.g. FVC),
    - a diagnostic biomarker to indicate patients with a subtype (including severity) of IPF to enrich trials or treatment arms,
    - a predictive biomarker to enrich trials with patients more likely to respond to a specific therapy or group of therapies,
    - a prognostic biomarker that identifies patients having greater likelihood of disease progression for enrichment of IPF trials, or
    - a safety biomarker for assessing radiation-induced pulmonary fibrosis in animal efficacy studies for products developed under the Animal Rule.

    Please note that these examples of uses do not constitute a complete COU construct. Please see the Biomarker Qualification Program Web site for information on the proper construction of a COU. Given the unclear proposed COU for V_{LLL}, we recommend revising your submission to focus on one of the aforementioned drug development needs. A pharmacodynamic/response biomarker may also be beneficial, however, the pathway to qualification may be more challenging depending upon how the biomarker would be used in a drug development program.

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If you choose to use this biomarker to make conclusions of change in disease stage or severity it would be important to state in the COU that the biomarker was used in conjunction with other functional or clinical tests/parameters that correlate with disease progression/stage/severity. A generic COU for use of $V_{LLL\%p}$ for disease progression/stage/severity would contain the following elements; [Biomarker category] for [categorizing severity of disease, disease stage, or alternatively, observing change in V_{LLL}] in IPF patients, to be used with other functional and clinical measures of IPF for [specify a use, i.e., assignment to new treatment arms, evaluation of treatment response, for enrichment of trials, for correlation with changes in function] in studies of IPF drugs.

Analytical Considerations

Sample Collection, Handling, Stability and Supporting Standard Operating Procedures

4. Please describe how you plan to assure maximal inspiration when collecting patient images at full inspiration to ensure consistency of the imaging process. Certain aspects related to imaging such as positional changes, and consistency in maximal inspiration may impact lobe volume measurements. Please describe how you will manage the variability introduced by these and other aspects of imaging measurement.

5. For any manual measurements or calculations, please describe how the measurements are performed, including steps/procedures used to reduce error, especially efforts to reduce intra- and inter-observer variability.

Validation: Calibration, Controls, and Verification of Repeat Measures (Variability) and Demonstration of Capability for Full Parameter Range (Performance)

6. You indicate that "V_{LLL} is assessed by mathematically processing a single low-dose high resolution CT scan (HRCT)." The term low-dose needs to be defined in terms of the range of $CTDI_{vol}$ (Computed Tomography Dose Index). At the same time, the term HRCT needs to be defined in terms of slice thickness, slice overlap, reconstruction algorithm (filtered back-projection, adaptive iterative reconstruction, model-based iterative reconstruction), and reconstruction kernel, since these parameters affect the spatial resolution and could potentially affect the performance of the lobe segmentation tool.

7. Please provide a description of how you plan to validate the image segmentation system. Note that you mention that "CT scans are segmented using Mimics, version 20, a segmentation *program that has been cleared by the FDA's Center for Devices and Radiological Health (CDRH) under the 510(k) process (Food and Drug Administration, K073468) and has been CE marked in Europe (Conformité Européenne certificate, BE 05/1191.CE.01)*." However, the segmentation tool (Mimics) was cleared under a different intended use, i.e. "*The Materialise Mimics product is intended for use as a software interface and image segmentation system for the transfer of imaging information from a medical scanner and as pre-operative software for simulating / evaluating surgical treatment options*" and was

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not validated for lung lobe segmentation. In the supporting manuscript by De Backer et al, the Mimics tool was used for segmenting the airway tree but not the lung lobes. As such, the performance of the version of the tool you plan to use needs to be validated against an acceptable reference standard.

a. In the absence of a gold standard, an acceptable reference standard could be the manual segmentation of lung lobes by a panel (≥3) of trained radiologists. The resulting lobe volume could be used as a metric of performance for which measures of bias and variance could be extracted.
b. If a different semi-automated segmentation tool was to be used for determining the reference standard, that tool should preferably be FDA cleared and all panelists should be trained prior to the study in its use. Performance assessment should be conducted using an adequately sampled dataset that would be representative of age, sex, and height, since those parameters were identified as important factors affecting the VLLL. Exploration of other factors impacting lung expansion, including body fat percentage may also help to improve the measure.

8. The CT scans of the validation dataset should match the intended population of scanners and imaging protocols. For general use in terms of scanners, the scans should be acquired with different scanners and comparable protocols in terms of dose, slice thickness/slice overlap, and reconstruction algorithms/kernels. Provide details on the imaging devices, make, model and regulatory Pre-Market Authorization or 510k information.

Statistical Assessment of Analytic: Impacts of Variability, Sensitivity, Specificity, Positive Predictive Value and Negative Predictive Value

9. For analytical validation purposes, please include the number of replicates for each image and measurements of each image, and how variability and error in replicates and measurements is handled.

10. Analyses should include measurements of bias (based on a pre-determined reference standard) and variance (across the different scanners and imaging protocols) of the V_{LLL} measurement derived from the lung lobe segmentation. The Quantitative Imaging Biomarker Alliance has established protocols for deriving such measurements, made available on its Web site, that may help to inform your effort. https://qibawiki.rsna.org/images/d/d8/QIBA_CTVol_TumorVolumeChangeProfile_Consensus-20180209.pdf.

11. Section 507 of the FD&C Act includes transparency provisions that apply to your submission. Certain information about the analytical measurement method may be publicly posted if the biomarker is successfully qualified by the Agency. Please confirm technical parameter and other pertinent information about the measurement method that may be made public to ensure the biomarker can be used as a drug development tool by any interested party. The biomarker qualification process does not endorse or qualify a specific measurement method for use with the biomarker.

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Safety Concerns

12. While the frequency of the $V_{LLL\%p}$ measurement during a study is not explicitly stated, a monitoring biomarker is typically measured serially to assess disease status. We assume that it would be measured multiple times during a clinical trial. Given the risks associated with radiation exposure, please provide the number of replicates planned for each measurement and the number of measurements per study. Also, please provide a rationale for the measurement frequency and number of images. Please provide a safety assessment and explanations for any risks associated with the calculated radiation exposure (each measurement and cumulative study dose) and how the risks are balanced by the benefits in information gained. Is there a particular timeframe or set of characteristics for disease progression for which minimum imaging intervals can be established?

Clinical Considerations

Application of Biomarker, Contextual Considerations:

13. The biomarker is a measurement of lung lobe volume as measured using an "outline" of the lobes (fissure lines). Alone it is not a diagnostic tool for the condition, IPF. Please specify how IPF patients are to be identified and what functional or other parameters of IPF will be monitored concurrently with measurement of V_{LLL} to identify severity/stage or change in disease status.

Considerations on the form of the biomarker proposed, inclusion of additional inputs and relevance to population or disease

14. Volume of the Lower Lung Lobes in Normal and IPF patients appears to be measured at maximal inspiration with one maneuver. Given the known difficulty in achieving sufficient reproducibility on spirometry and the spirometric standards set forth by ATS for determination of adequate quality of data (which require multiple maneuvers)[2], we have concerns whether a single maneuver would be sufficient to provide an accurate, reliable, reproducible measurement. Your program will need to sufficiently address this concern.

Interpretive Criteria (Cut-points/Thresholds/Boundaries), Application & Validation in population

15. Additionally, you will need to provide information on the degree of intra-subject and inter-subject variability for $V_{LLL\%p}$, how this was accounted for as well as how reference ranges were established.

Gaps and Proposed Studies

16. Any gaps in understanding or assumptions made in application of the biomarker, its measurement and COU will need to be identified and a plan for addressing these will be needed in a Qualification Plan stage submission.

[2] Miller MR et al. ATS/ERS TASK FORCE: STANDARDISATION OF LUNG FUNCTION TESTING. Eur Respir J 2005; 26: 319-338

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17. While loosely defined clinical parameters have been used to describe disease stage (e.g. "mild", "moderate", "severe", "early", "advanced"), there is no widely accepted disease staging criteria for IPF. Additionally, prognostic scales (e.g. the Gender, Age, and Physiology (GAP) Index) and common clinical parameters (e.g. FVC, dyspnea, 6 Minute Walk Distance) do not accurately predict disease progression[3] or distinguish between progression and acute exacerbation(s). Given this gap, in order to support use of $V_{LLL\%p}$ in a categorical manner as a biomarker for disease staging (presumably to be used for population enrichment in clinical trials), you would have to demonstrate that $V_{LLL\%p}$ based staging and the cut-offs proposed were linked to clinically meaningful outcomes (e.g., mortality, exacerbation, etc.) and/or likelihood of response to a treatment. Linking $V_{LLL\%p}$ to FVC alone would likely be insufficient to support $V_{LLL\%p}$ use as a biomarker for disease staging.

18. You have also proposed to use $V_{LLL\%p}$ in a continuous manner and state that it may be more sensitive than FVC to detect changes in volume as FVC is a measure of the whole lung versus just the lower lobe. While this is potentially true, and $V_{LLL\%p}$ may be more sensitive to detect change in IPF, it is unclear if such changes would represent evidence of disease progression, a drug effect or are due to fluctuations in volumes that occur due to variability in patient performance or the measurement error inherent in the calculation of volume. Your development program for $V_{LLL\%p}$ used in a continuous or categorical manner would have to address these considerations. One option would be to characterize this measurement's behavior over time in an IPF population in addition to data on clinical and functional parameters. Additionally, to assess its utility in the context of a clinical trial and drug development, your program should also determine if $V_{LLL\%p}$ could detect a response faster or with more specificity/sensitivity than currently used measures (e.g. FVC).

Statistical Considerations

Biomarker Validation for Population/Clinical Validation of Derivative Tool:

19. Please provide a description of the normal population from which you establishe d $V_{LLL\text{-}NORMAL}$. Include the total group and subgroup sizes, descriptive characteristics of the population and subgroups including BMI, the V_{LLL} and amount of variability by subgroup. Please provide a description of the factors examined for relevance to lung volume in a normal population and whether or not these factors similarly impact IPF populations. Please indicate the source of these data and any potential biases in the population selected.

20. LOI section 4.4 states that age, sex, and height have been validated by FLUIDDA as the dominant parameters for determining the predicted values for the volume of the individual lobes of the lungs. Provide a description of the predictive parameters tested and the summary results of the analysis. Please provide the full data and analyses in the Qualification Package (FQP) for review.

[3] Ley B et al. Predictors of Mortality Poorly Predict Common Measures of Disease Progression in Idiopathic Pulmonary Fibrosis. Am J Respir Crit Care Med 2016;194(6): 711. doi: 10.1164/rccm.201508-1546OC.

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Interpretive Criteria & Cut-point Validation

21. Please address the minimum detectable change in V_{LLL}, $V_{LLL\%p}$ and the measurement variability and error associated with each. Please describe the factors that are associated with variability and error in measurement. For $V_{LLL\%p}$ continuous or categorical biomarker please describe how the magnitude of the detectable error and variability correspond to change in clinical IPF.

22. For the LOI please provide a description of how cut-point(s) were established and how you plan to validate these cut-points.

Other: Please specify

23. In your current exploration of correlation between $V_{LLL\%p}$ vs. $FVC_{\%p}$, data from all patients (treatment and placebo) and all visits (baseline and post-baseline) were used to estimate the underlying correlation measure. However, factors such as the within-subject time pattern, the inter-subject variations, and the between treatment differences will work together to make the so found correlation measure un-interpretable. We recommend that you explore the relationship between $V_{LLL\%p}$ vs. $FVC_{\%p}$ by visit and by treatment.

Please note that section 507 of the FD&C Act includes transparency provisions that apply to your submissions. Certain information contained within your submissions may be made publicly available on our Internet site. For examples of transparency and prior submissions see the Biomarker Qualification Submissions webpage.[4]

If you have questions, please contact Chris Leptak (christopher.leptak@fda.hhs.gov) via email. Should you want to discuss any of the items in this letter please send a request for a teleconference to the Biomarker Qualification Program email address at: CDER-BiomarkerQualificationProgram@fda.hhs.gov to let us know your attendees and available dates.

[4] https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535881.htm

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Sincerely,

Christopher L. Leptak -S

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