LOI DECISION LETTER

DDTBMQ000057

August 12, 2019

COPD Foundation
3300 Ponce de Leon Blvd.
Miami, FL 33134

Dear Ms. Merrill,

We are issuing this Letter of Intent (LOI) response letter to notify you of our decision on your proposed qualification project submitted to the Center for Drug Evaluation and Research (CDER) Biomarker Qualification Program (BQP) on March 25th, 2019. We have completed our review of your LOI submission and have concluded to **Not Accept** it into the CDER BQP. You have proposed qualification of blood eosinophil count as a predictive biomarker in COPD clinical trials to further stratify patients who have a clinical history of exacerbations. Please note that the 21st Century Cures Act was signed into law in December 2016 and adds the 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:

Drug Development Need Considerations

> ***Requestors drug development need statement:*** *Blood eosinophil counts are proposed as a predictive biomarker that will be used in clinical trials of novel anti-inflammatory treatments to identify patients with a distinct inflammatory profile that is likely associated with a higher response to the specific pharmacological intervention. This strategy is expected to enhance identification of the "right" population with greatest response, thus increasing the power in a clinical trial and decreasing the number of patients needed for enrollment. Current standards for such studies involve enrichment of the trial population by enrolling subjects with a clinical history of exacerbation(s) in the previous year; we propose that blood eosinophil counts will be used as an additional biomarker to enable further enrichment and stratification of the population.*

The drug development need for qualification is insufficient based on the following:

- Peripheral blood eosinophil counts are already being used as a predictive biomarker on an ad

hoc basis in recent clinical trials of anti-inflammatory drugs. Therefore, qualifying this biomarker would not address a drug development need that cannot be addressed in an individual clinical development program.

- Even if the ultimate goal of qualification is to establish a standardized eosinophil threshold cut-off that would better establish which patients are more likely to respond, you have proposed a literature-based approach and retrospective analyses that are unlikely to be sufficient for biomarker qualification given that the available data on this biomarker are derived from different study designs, eosinophil thresholds, and drugs tested. With so much uncertainty, it is not clear how you can determine the threshold that consistently predicts efficacy for "current and novel therapeutics" retrospectively.

Context of Use (COU) Considerations

> ***Requestor's COU statement:*** *Blood eosinophil count is a predictive biomarker to enrich for populations more likely to respond to current and novel pharmacological interventions in clinical trials. The population of interest is "high risk" COPD patients with a history of exacerbation(s) in the previous year. This history enriches the population for individuals more likely to experience future exacerbations. Use of blood eosinophils will stratify these high-risk patients based on the level of potential eosinophilic inflammation.*

The context of use for blood eosinophil counts to be used for "current and novel pharmacological interventions" for COPD is an overly broad classification of the mechanism of action of the therapeutic products for which the COU would apply based on the following:

- Recent data from randomized controlled clinical trials of anti-interleukin 5 (IL-5) biologic products in COPD populations are not supportive of this context of use. Specifically, trials of both mepolizumab [1] and benralizumab [2] (which target eosinophils) do not support the utility of the peripheral blood eosinophil count biomarker in predicting the rate of exacerbation endpoints or lung function endpoints. Furthermore, while post-hoc analyses of one of two studies in the mepolizumab program (trial 106) suggested a potential relationship between exacerbation rate efficacy and higher baseline eosinophil count, both benralizumab trials and the second mepolizumab trial (trial 113) did not support this relationship. At this time, there is no rationale – from a mechanistic standpoint or from empiric data – that the efficacy of other "novel" therapies would be predicted by peripheral blood eosinophils.

- Even if restricted to a COPD patient population with exacerbations that are undergoing inhaled corticosteroid (ICS) treatment, the literature shows variability in outcomes for the use of blood eosinophil counts as a predictive biomarker. Some post hoc analyses suggest greater ICS efficacy at higher blood eosinophil counts, although a study by Bafadhel et al.

suggests that this predictive ability may be heavily influenced by smoking status [3]. The pre-specified analyses follow a similar trend, but with smaller differences at higher blood eosinophil counts. The effect of smoking, however, has not been evaluated in the pre-specified data. In the IMPACT trial [4], ignoring concerns about incident versus prevalent ICS use and ICS withdrawal at randomization, the efficacy difference with higher eosinophils is clinically small.

Biological Plausibility Considerations

Requestors statement: *We will supply information on the long and short term stability of blood eosinophil counts in COPD patients. While there is a minor degree of between day variation, the majority of COPD patients categorized above or below different blood eosinophil thresholds remain in the same category when sampled again after months or years.*

Retrospective studies do not adequately address the within-subject variability of peripheral blood eosinophils. The within-subject variability of peripheral blood eosinophil counts in COPD patients is not minor, but is high over time, and counts are influenced by factors such as season, hormonal state, time of day, fasting versus fed state, comorbid conditions, use of medications, and other factors. [5-10]. This within-subject variability represents a significant limitation to the reliability and interpretation of a single peripheral blood eosinophil count measurement as a predictive biomarker in COPD.

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.[1]

If you have questions or wish 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.

Christopher L. Leptak -S

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[1] https://www.fda.gov/drugs/cder-biomarker-qualification-program/biom - -

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2. Criner, G.J., et al., *Benralizumab for the Prevention of COPD Exacerbations.* N Engl J Med, 2019.
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4. Lipson, D.A., et al., *Once-Daily Single-Inhaler Triple versus Dual Therapy in Patients with COPD.* N Engl J Med, 2018. **378**(18): p. 1671-1680.
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10. Singh, D., et al., *Eosinophilic inflammation in COPD: prevalence and clinical characteristics.* Eur Respir J, 2014. **44**(6): p. 1697-700.