LOI DECISION LETTER

DDTBMQ #000057

December, 18, 2017

COPD Foundation
3300 Ponce de Leon Boulevard
Miami, FL 33134

Dear Ms. Merrill:

We have completed our review of your Letter of Intent (LOI) submission of August 4, 2017 in support of blood eosinophil count and have decided to Not Accept it into the CDER Biomarker Qualification Program. Please note that the 21st Century Cures Act was signed into law and adds new section 507 to the Federal Food, Drug, Cosmetic Act (FD&C Act) concerning the qualification of drug development tools (DDTs). For this project, the FDA now operates its biomarker 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 may include scientific merit. In summary, our decision for your LOI was based on the following:

- The proposed Context of Use (COU) is unclear and the supportive information, describing blood eosinophil count as either a predictive or prognostic biomarker may not adequately address uncertainty in the literature surrounding the utility of this measure.
    - As a predictive COU, it is unclear how generalizable blood eosinophil count may be for anti-inflammatory therapeutics which do not target eosinophils directly.
    - As a prognostic COU, there is uncertainty in the added value of blood eosinophil count to enrich for more frequent exacerbations beyond other existing enrichment factors already used in COPD clinical trials, e.g., recent history of exacerbations. Also, it is unclear if blood eosinophil count would be prognostic of exacerbations in all COPD patients.
- Conflicting information is given about which type of blood eosinophil count assay or methodology will be used to support the COU.

The comments and questions in this letter represent CDER's scientific concerns related to the proposed biomarker and context of use. If you chose to further develop this tool for regulatory use, we recommend that you fully address these concerns prior to resubmission.

Biomarker Considerations

Requestor's Biomarker Description: Blood eosinophil count

- We agree with your proposed biomarker description.
- Please provide an analysis or additional information that supports blood eosinophil count's correlation with COPD exacerbation rates or response to therapy. If there are conflicting reports, please address your interpretation of the differing opinions or conclusions regarding the role of blood eosinophil count in COPD.

Context of Use (COU) Considerations

Requestor's COU: *"Blood eosinophil count is qualified as a predictive biomarker to improve the selection of subjects for enrollment into dose finding and/or pivotal efficacy studies in COPD, who are more likely to exhibit COPD exacerbations and thus can enrich studies investigating interventions to reduce the risk of COPD exacerbations."*

Insufficient information is provided in the LOI to support the use of blood eosinophil count as a biomarker to enrich subject populations enrolled in COPD clinical studies. Your COU statement is unclear because it indicates that blood eosinophil count is proposed as both a predictive biomarker (e.g., patients more likely to respond to therapy) and as a prognostic biomarker (e.g., enrichment with subjects who are more likely to exhibit exacerbations). Although a biomarker may have both predictive and prognostic properties, an LOI should focus specifically on a single COU because the information necessary to support different COUs would be substantially different. Once you have refined your COU, data that are supportive of that COU should be provided in support for that COU.

Considerations for a prognostic COU:

- As described in the BEST (Biomarkers, Endpoints, and other Tools) Resources(1), a prognostic biomarker's association with outcome is present without reference to different interventions and the presence or strength of a prognostic association may vary depending on the specific clinical setting (e.g., background therapy, stage of disease). Information demonstrating the added value of blood eosinophil count for prognostic enrichment, when used in addition to currently-employed criteria (e.g., history of prior exacerbations), is needed to adequately support the proposed COU.
- Please provide information to support that blood eosinophil count is prognostic of COPD exacerbations in all COPD patients, regardless of their underlying pathophysiology. If you intend to restrict the prognostic claim to only patients who have eosinophil-mediated exacerbations, the biomarker would have much less regulatory impact and value.
- While retrospective studies and post-hoc analyses of randomized trials may provide support, differences across studies (e.g., differences in inclusion/exclusion criteria, blood eosinophil cutoffs, definitions of exacerbation, and eosinophil measurement devices) may make it difficult to compare published literature reports. Please address how you will

manage these concerns if additional new data collection, analyses or studies are not planned.

Considerations for a predictive COU,

- Your LOI acknowledges that blood eosinophil count may not be a useful enrichment tool for novel drugs that target other aspects of the inflammatory cascade (i.e., non-eosinophil associated inflammation). Note that if you develop blood eosinophil count as a predictive biomarker and the biomarker is subsequently used in studies for classes of drugs where it is not predictive of response, then there is a risk of unnecessarily excluding patients from the study. This could hinder study recruitment and generalizability of the results. Because of these exclusions, the investigational drug's approval could be limited to the specific population that was studied in clinical trials. For example, the drug's approvability may be limited only to specific COPD populations (i.e., those with higher blood eosinophil count) for which it was demonstrated to be effective. We recommend that you carefully consider the patient population and the class of therapeutics for which the COU is developed.
- As described in BEST, randomization to treatment and control groups is important when qualifying a predictive biomarker because supportive evidence includes the demonstration that individuals who are positive for a biomarker and receive an investigational therapy experience a better outcome than those who receive the same therapy but are negative for the biomarker.
- The COU indicates that blood eosinophil count will be broadly qualified to improve selection of subjects for studies in COPD. However, statements throughout the LOI refer more specifically to "novel treatments targeting eosinophil associated inflammation", "targeted novel drugs", and "anti-inflammatory drugs". Please specify the class or classes of COPD treatments for which blood eosinophils will be qualified. Note that if all available data to support blood eosinophil count as a predictive biomarker are for a single class of drug, then it will be difficult to extrapolate the data to other drug classes in the absence of a scientific rationale.

Analytical Considerations

1. You identify specific analyzers which can be used for blood eosinophil counts, stating that these analyzers are FDA cleared. Elsewhere in the LOI, it appears that non-FDA cleared hematology analyzers (e.g., laboratory developed tests) will be used. The different technical parameters of each device could affect the acceptable range for determination of elevated blood eosinophil count. In addition, it is unclear if these devices can measure or count the blood eosinophil. A white blood cell count and granulocyte count may not give the correct parameters for the proposed COU.

    - Please clarify which measurement method(s) will be used to obtain blood eosinophil count. Please indicate if the above devices were specifically developed to assess eosinophil count. Please provide a brief description of the device limitations and how these limitations may affect the COU for this biomarker.

- Please provide a 510K number or PMA number for the intended use of the devices if they were cleared or approved by the FDA. This information is needed to ensure the devices were cleared by the FDA for blood eosinophil count and can consistently provide correct eosinophil count to support the COU. If you are not proposing to use FDA cleared devices with the same indication for use as you propose additional data will be necessary to validate and provide supportive evidence of the precision, sensitivity, and specificity of the methodology.

2. Post-hoc and retrospective analyses are proposed to support the COU by studying blood eosinophil count in COPD patients. It is unclear if the data for these analyses were collected and analyzed in the same manner, and if the processes were validated. Since this variability across studies could affect our ability to accurately interpret the strength of the evidence, please share how these concerns will be addressed.

Clinical Considerations

3. Please clarify the clinical trial patient population for whom your COU will apply.

   - We presume that you intend to use the same definition of moderate to severe exacerbations commonly used in clinical trials, building off the work of Anthonisen et al.(2). Please clarify and provide a detailed definition of moderate to severe pulmonary exacerbations in COPD patients in your submission.
   - Do you intend to restrict your COU to only COPD patients with a history of moderate and severe exacerbations? Please clarify if this is your intent and ensure the data that will be provided in support of the COU used this definition.
   - Please further define the discrete patient subgroup that you plan to target and provide more detail on how a specific blood eosinophil count threshold would improve identification of these clinical trial subjects. Please define and describe the distinct inflammatory profile of this subgroup, and provide any evidence that supports the utility of this blood eosinophil count threshold to discriminate between these subjects and those with other inflammatory profiles (i.e., primarily neutrophilic inflammation).

4. Please provide a description of how drug development trials would differ should this biomarker be qualified. If other biomarkers or criteria are currently used for this purpose, please briefly provide the added value of blood eosinophil count compared with currently used clinical trial design methods.

5. You state that a standard operating procedure (SOP) will not be used to collect blood for blood eosinophil count because the blood samples are collected by standard venipuncture. If an SOP is not used to collect blood samples, it is unclear how you will mitigate the influence of variables (e.g., timing and chronicity of inhaled or systemic corticosteroid use, concomitant asthma, parasitic infections, timing of exposure to other environmental allergens, etc.) that may have an impact on blood eosinophil count.

- Provide information for the blood collection method used in your studies and comparability across studies. If you plan to conduct prospective trials, please develop an SOP for collecting blood samples for the COPD subjects.
- The LOI states that inhaled corticosteroids (ICS) do not affect blood eosinophil count. The literature is unclear on whether there is any statistically significant effect (3-5) of ICS on blood eosinophil levels over time, although the magnitude of the effect is consistently thought to be clinically insignificant. Please address the potential impact of ICS on your measurement of blood eosinophils count.

6. In describing the mechanistic rationale in support of the proposed biomarker, you state that airway eosinophils are increased in a subset of COPD patients experiencing increased frequency of exacerbations. You also state that it is technically challenging to measure eosinophils in sputum and there is a correlation between sputum eosinophil count and blood eosinophil count. While there is a body of literature that favors the idea that sputum eosinophilia may be linked to COPD exacerbations, the prognostic value of the sputum measure is unclear (6). Retrospective data may suggest that sputum eosinophilia may have some utility in identifying patients that will respond to corticosteroids with respect to exacerbations or other measures; however, prospective, well-designed trials are limited (7, 8). In addition, the ability of blood eosinophil count to predict sputum eosinophilia appears to vary widely in its test characteristics when measured in different contexts(9)(10). Note, it may not be necessary to prove this link within the COU if the case can be adequately supported using blood eosinophil count alone.

7. Lack of consensus in the literature (see Appendix) highlights the need for additional information, analyses, or prospective studies to adequately address the outstanding questions about the role of blood eosinophil count as a biomarker without confounding factors. The two papers cited in the LOI (Siddiqui et al and Pavord et al) both conclude that further prospective studies are needed to clearly evaluate blood eosinophil count's role in the treatment of COPD subjects.

    - Please briefly discuss your interpretation of the available literature, and your plan to provide additional information or analyses that address this uncertainty.
    - In the setting of the totality of literature addressing this topic, the summary of post-hoc analysis data provided in the LOI may not be sufficient to support the COU

Statistical Considerations

8. You plan to pool post-hoc analyses of multiple clinical trials to establish cut-off / threshold values above which blood eosinophil counts predict a greater reduction in exacerbation rates. Establishing cut-off values generally requires independent data sets for discovery and validation of the cut-point. In addition, the device(s) used to measure the biomarker should be analytically validated around the proposed blood eosinophil count threshold (e.g., cutoff value) to be used to connate elevated eosinophil count.

- Please revise the COU to describe the specific blood eosinophil count threshold that defines the subgroup of COPD subjects of interest (i.e., severity and frequency of exacerbations or response to therapies).

We want to emphasize that this decision not to accept blood eosinophil counts into CDER's Biomarker Qualification Program (BQP) is not a final decision about that biomarker. You may submit a new LOI for review that contains the requested clarification of the COU and additional supportive scientific data and information recommended herein.

Sincerely,

Christopher Leptak, MD/PhD
Director, CDER Biomarker Qualification Program
CDER/Office of New Drugs, Immediate Office

Badrul Chowdhury, MD
Director, Division of Pulmonary, Allergy, and Rheumatology Products
CDER/Office of New Drugs

Appendix: Additional Considerations

1. Interpretation of existing literature. Summaries of two peer-reviewed journal articles examining patients with COPD and higher blood eosinophil counts were provided in the LOI. We summarize our interpretation of these studies and a sample of additional literature we reviewed:
    - In a retrospective analysis of the prospectively collected Copenhagen General Population Study, Vedel-Krogh et al reported a modest association of empirically determined blood eosinophil count cutpoints with moderate exacerbations and severe exacerbations separately, but did not provide data on the association with moderate and severe exacerbations as a combined endpoint. The association of moderate exacerbations with the empirically determined eosinophil percentage cutpoint was not statistically significant. These data are difficult to interpret in the setting of the COU, especially given the designations of "COPD" versus "clinical COPD" used within the study.
    - Siddiqui et al(11) claimed, in a post-hoc subgroup analysis of the FORWARD trial population, that the exacerbation rate reduction between the ICS/LABA and LABA treatment arms was 46% among subjects in the highest quartile of blood eosinophils at baseline, while the rate reduction among subjects in the lowest quartile was 22%. However, in the supplementary materials, it is shown that this same highest quartile of subjects had a higher number of COPD exacerbations in the last year, and that stratification by percentage eosinophils rather than number does not show this same progression of risk reduction, which confounds the proposed conclusion.
    - Similarly, Pascoe et al (12) reports, in a post-hoc subgroup analysis of pooled trials examining vilanterol vs vilanterol/fluticasone furoate, that the exacerbation rate reduction between the ICS/LABA and LABA treatment arms was 42% among subjects with blood eosinophils >6%, 32% among subjects with blood eosinophils 4-<6%, 24% among subjects with blood eosinophils 2-<4%, and 10% among subjects with blood eosinophils <2%. A response article(13) notes that these results "present the differences between treatments within each eosinophil count stratum, rather than the difference in response rates between strata, and hence, do not directly test this hypothesis".
    - The LOI also describes that a post hoc analysis of other clinical trials with different active comparators has also shown a greater effect of ICS on patients with higher blood eosinophil counts, but does not provide a reference. This may refer to the similar post-hoc meta-analysis of trial data by Pavord et al (14), which showed similar effects in only two out of three included trials. However, analysis of the third included trial in this manuscript showed discordant results.
    - There is additional conflicting evidence. A post-hoc analysis by Barnes et al(5) of the ISOLDE trial data showed that the association with exacerbation rate reduction (of the fluticasone propionate treatment arm versus placebo) was statistically significant in the low blood eosinophil group (<2%

eosinophils, rate reduction of 19%) compared to a non-significant association in the high blood eosinophil group (≥2% eosinophils, rate reduction of 12%).

- A recent prospective analysis of the FLAME trial data (which compared ICS/LABA to LABA/LAMA) authored by Roche et al(4) showed that indacaterol/glycopyrronium was superior to salmeterol/fluticasone in the prevention of COPD exacerbations in all categories of baseline eosinophil count tested. While the analysis by Roche et al analyzed data from a trial with a different design than the previous ICS/LABA versus LABA trials, the prospective trial data presented still prompt questions about the utility of blood eosinophils as a predictive biomarker to identify a clinically meaningful subgroup that would respond to treatment. In addition, while baseline eosinophilia of ≥2% was associated with a slightly higher baseline rate of exacerbations in the year prior to the trial, there was no difference in the rate of exacerbations collected prospectively during the trial period among those patients with ≥2% blood eosinophils, which is an important finding for evaluating the utility of blood eosinophils as a prognostic biomarker.
- A small, single center, consecutively recruited, randomized-by-minimization, placebo-controlled trial by Bafadhel et al(15) randomized 164 participants to treatment arms of "biomarker-directed" therapy for COPD exacerbations versus standard of care therapy for COPD exacerbations. In this study, blood eosinophil percentage was measured at presentation during a COPD exacerbation. In the biomarker-directed arm, any participant with blood eosinophilia ≥2% at exacerbation was given systemic corticosteroids (in addition to standard of care antibiotics); in the standard of care arm, all participants received systemic corticosteroids and standard of care antibiotics for their COPD exacerbations regardless of eosinophil percentage. The trial analyzed 166 exacerbation events among 109 COPD patients, and showed noninferiority of the biomarker-directed approach in the primary endpoint of health status as measured by the Chronic Respiratory Questionnaire.
- Two recent randomized, double-blind, placebo-controlled, multicenter trials of the anti-IL5 monoclonal antibody mepolizumab were recently reported by Pavord et al(16). A commentary on this article(17) stated that "blood eosinophil count is an imperfect biomarker", and called for further prospective trials to better clarify the role of blood eosinophils in COPD while also examining alternative or complementary ways to stratify these patients.

Bibliography

1. FDA-NIH_Biomarker_Working_Group. BEST (Biomarkers, EndpointS, and other Tools) Resource (https://www.ncbi.nlm.nih.gov/pubmed/27010052). Silver Spring (MD); 2016.
2. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. *Ann Intern Med* 1987; 106: 196-204.
3. Kreindler JL, Watkins ML, Lettis S, Tal-Singer R, Locantore N. Effect of inhaled corticosteroids on blood eosinophil count in steroid-naive patients with COPD. *BMJ Open Respir Res* 2016; 3: e000151.
4. Roche N, Chapman KR, Vogelmeier CF, Herth FJF, Thach C, Fogel R, Olsson P, Patalano F, Banerji D, Wedzicha JA. Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. *Am J Respir Crit Care Med* 2017; 195: 1189-1197.
5. Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur Respir J* 2016; 47: 1374-1382.
6. Siva R, Green RH, Brightling CE, Shelley M, Hargadon B, McKenna S, Monteiro W, Berry M, Parker D, Wardlaw AJ, Pavord ID. Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. *Eur Respir J* 2007; 29: 906-913.
7. Brightling CE, Monteiro W, Ward R, Parker D, Morgan MD, Wardlaw AJ, Pavord ID. Sputum eosinophilia and short-term response to prednisolone in chronic obstructive pulmonary disease: a randomised controlled trial. *Lancet* 2000; 356: 1480-1485.
8. Pizzichini E, Pizzichini MM, Gibson P, Parameswaran K, Gleich GJ, Berman L, Dolovich J, Hargreave FE. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. *Am J Respir Crit Care Med* 1998; 158: 1511-1517.
9. Schleich F, Corhay JL, Louis R. Blood eosinophil count to predict bronchial eosinophilic inflammation in COPD. *Eur Respir J* 2016; 47: 1562-1564.
10. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, McCormick M, Haldar K, Kebadze T, Duvoix A, Lindblad K, Patel H, Rugman P, Dodson P, Jenkins M, Saunders M, Newbold P, Green RH, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, Brightling CE. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184: 662-671.
11. Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agusti A, Paggiaro P, Wedzicha JA, Singh D. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; 192: 523-525.
12. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015; 3: 435-442.
13. Groenke L, Disse B. Blood eosinophil counts as markers of response to inhaled corticosteroids in COPD? *Lancet Respir Med* 2015; 3: e26.
14. Pavord ID, Lettis S, Locantore N, Pascoe S, Jones PW, Wedzicha JA, Barnes NC. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. *Thorax* 2016; 71: 118-125.
15. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, Brightling CE. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012; 186: 48-55.
16. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, Martinot JB, Sagara H, Albers FC, Bradford ES, Harris SS, Mayer B, Rubin DB, Yancey SW, Sciurba FC. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2017; 377: 1613-1629.
17. McDonald CF. Eosinophil Biology in COPD. *N Engl J Med* 2017; 377: 1680-1682.