

BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

COMMENTS: The following information will be made publicly available as per the 21st Century Cures Act

Biomarker Project Information

Biomarker: Blood eosinophil count

Therapeutic area: Pulmonary disease, specifically Chronic Obstructive Pulmonary Disease (COPD)

Patient Population: Patients more likely to experience COPD exacerbations

Administrative Information

Name of Organization: COPD Foundation, 20 F Street NW, Suite 200-A, Washington, DC 20001

Website: www.copdfoundation.org

Primary Point of Contact: Debora D. Merrill, COPD Foundation, 20 F Street NW, Suite 200-A, Washington, DC 20001, Phone: 866-731-COPD (2673) x 410, Email: dmerrill@copdfoundation.org

Alternate Point of Contact: N/A

Submission Date: August 29, 2016 with a concurrent EMA biomarker submission

Drug Development Need

COPD is a complex and heterogeneous disease. The majority of drugs with novel mechanisms of action being developed for the future treatment of COPD are anti-inflammatory and immune modulator agents rather than bronchodilators. Studies of anti-inflammatory treatments in COPD patients usually evaluate exacerbation rates to investigate anti-inflammatory effects. However, patients with a history of exacerbations have heterogeneous inflammatory profiles and therefore targeted novel drugs are likely to show efficacy in only a sub-population of the exacerbating COPD study population. These sub-populations are not currently well-defined.

- **Additional improvement by the proposed biomarker upon currently used standards:** COPD is a complex and heterogeneous disease. Blood eosinophil counts are proposed as a biomarker that will be used in clinical trials to identify exacerbating patients with a distinct inflammatory profile that is likely associated with a higher response to anti-inflammatory drugs, (e.g. ICS and other novel mechanisms). This strategy is expected to help identify the “right” population and to decrease the number of patients needed for enrollment.
- **Description of limitations for use of the proposed biomarker**
In geographical areas where parasitic infection is common, blood eosinophil counts may be less useful as a biomarker due to parasite induced eosinophilia.

There is a minor degree of within-day diurnal variation in blood eosinophil counts(6), meaning that sampling at a similar time of day is desirable to reduce variability. The majority of COPD patients categorized as “eosinophilic” or “non-eosinophilic” using different thresholds, remain in the same category when sampled again after months or years.

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Oral corticosteroids can reduce blood eosinophil counts, but inhaled corticosteroids have no effect. We will supply information on the stability of blood eosinophil counts in COPD patients.

Blood eosinophil counts may not be a useful enrichment tool for novel drugs that target other aspects of the COPD inflammatory cascade (i.e. non-eosinophil associated inflammation), but could possibly be used to exclude individuals less likely to respond based on their inflammatory profile.

- **Is there potential use of the biomarker across multiple drug development programs?**
Yes. Potential for drugs likely to influence the eosinophils, specifically anti-inflammatory treatments.

Biomarker Information

- **Biomarker name (for molecular biomarkers, please provide a unique ID) and type**
(Molecular/Image/Anatomic, etc.): Blood Eosinophils -- Molecular
- **Biomarker description:** Elevated Blood eosinophil count.
- **Biomarker Category:** Predictive and Prognostic.
- **Biological rational** (underlying biological process) reflected on the measurement if available
There is evidence that airway eosinophil numbers are increased in a subset of COPD patients experiencing exacerbations. Some of these events occur in the absence of pathogen detection, implicating the increase in eosinophilic airway inflammation as a driver of these exacerbations. This provides a rationale for selective targeting of patients with eosinophilic inflammatory profiles to develop interventions that may prevent exacerbations associated with excessive eosinophilic inflammation.

A subgroup of COPD patients have eosinophilic airway inflammation, and prospective clinical trials have shown that higher sputum eosinophil counts in stable COPD patients predict a greater clinical response to ICS. This suggests that eosinophil measurements can be used to predict anti-inflammatory drug effects in COPD patients.

Measuring sputum eosinophils is technically challenging and time consuming; some patients are not able to provide adequate samples for analysis. Blood eosinophil measurements are widely available and less time-consuming. There is a correlation between sputum and blood eosinophil counts within the same individual, suggesting that blood eosinophil counts can be used to identify COPD patients with corticosteroid responsive eosinophilic airway inflammation.

- **Is this a composite biomarker?** No.

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Context of Use

- **Proposed Context of Use (COU) Statement:** 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.
- **Conditions for Qualified Use:** Blood eosinophils will be used as a biomarker in COPD patients with a history of moderate and severe exacerbations. The beneficial effects of targeted anti-inflammatory therapies in these patients are likely to be restricted to discrete subgroups with distinct inflammation profiles. Blood eosinophil measurements may optimize enrollment of appropriate subjects for novel treatments targeting eosinophil associated inflammation that results in exacerbations. This should limit exposure in patients who are less likely to benefit from a novel therapy, increase the efficiency and reduce the costs of COPD clinical trials by reducing number of subjects needed and study duration. This may also enable future targeting of therapies in the clinic to a more appropriate patient population.
- **Drug Development Space for Biomarker Use:**
Early-phase clinical trials (e.g., Phase I or II)
Late-phase clinical trials (Phase III or post-marketing)

Biomarker Measurement (Analytical)

- **General description of what aspect of the biomarker is being measured and by what methodology:**
Blood eosinophil counts; The primary analysis will be the predictive value of the baseline measurement.
- **The biomarker test/assay is available for public use?** Yes.
- **The biomarker test(s)/assay(s) used to generate the biomarker measurements is a:** Laboratory Developed Test.
- **The biomarker assay/test will be performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory?** Yes. Healthcare professionals performing CLIA-waived tests obtain a Certificate of Waiver.
- **The biomarker test is under review within the FDA Center for Devices and Radiological Health?** No.
- **A standard operating procedure (SOP) exists for sample collection, storage and test/assay methodology:** No. Blood eosinophil measurements are routinely obtained from blood samples obtained by standard venipuncture in clinical practice and research.
- **A laboratory SOP exists for the assay/methodology:** No.
- **Performance characteristics for the biomarker assay/tests (sensitivity, specificity, accuracy and precision):** Yes, the CBQC aims to provide assay validation documents for some of the studies

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included in the integrated database that used central laboratories to determine blood eosinophil counts.

- **Information about the specific technical platform:**

Analyzers in point-of-care outpatient clinics are covered by associated tests' waiver from CLIA regulatory oversight (Clinical Laboratory Improvement Amendments of 1988). Healthcare professionals performing CLIA-waived tests obtain a Certificate of Waiver (CoW); use of a hematology analyzer requires higher certification for moderate and high complexity testing.

There are a number of hospital automated hematology analyzers which are FDA-cleared and CLIA-classified as "moderately complex", such as the Medonic M-Series Autoloader Analyzer CDS-1400075 and the Beckman Coulter AC.T diff2 Analyzer BKM-ACTDIFF2. Vendors provide calibration kits and procedure standards to ensure assay performance; calibration samples are run at a pre-defined frequency and the instrument calculates the standard deviation and the coefficient of variation (%CV), and prints PASS or FAIL for the reproducibility test for clinical lab calibration records.

Vendors typically provide device performance data for different hematology analyzers. For example the Siemens Advia system, commonly used in US clinical trials, has assay performance data on the Siemens web site

(<https://usa.healthcare.siemens.com/hematology/systems/advia-2120-hematology-system-with-autoslide/technical-specifications>).

Biomarker Measurement (Clinical)

- **Characterization of biomarker for COU: supporting clinical study data include;**

There is evidence from some COPD cohort longitudinal follow up studies that increased blood eosinophil counts are associated with increased exacerbation rates. This suggests that exacerbations may be associated with increased eosinophilic activity. References provided.

Retrospective analysis of COPD clinical trials have shown that higher blood eosinophil counts predict a greater reduction in exacerbation rates with inhaled corticosteroid/long acting beta agonist (ICS/LABA) combinations compared to LABA. For example, Siddique et al, showed that the exacerbation rate reduction for ICS/LABA versus LABA was 46% (p<0.001) for patients in the upper quartile of eosinophil counts (>279.8 cells / μ L), while it was 22% (p=0.113) in patients within the lowest quartile (<110.4 cells / μ L)(7). A similar pattern of results were reported by Pascoe et al.; the exacerbation rate reduction for ICS/LABA versus LABA was 42% (p=0.002) for patients with eosinophil counts >6%, while it was 10% (p=0.28) for patients with eosinophil counts <2%(8). 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.

- **Non-clinical Study data supporting the biomarker:** None.

- **Type of data available to support the proposed COU of the biomarker:** Retrospective data.

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- **Planned future studies:** None.
- **Statistician participating in biomarker qualification:** Yes.
- **Previous Qualification/Scientific advice received:** None.

Appendix 1: High-Level Summary relevant to the proposed biomarker

A subgroup of COPD patients have eosinophilic airway inflammation (5, 10, 11), and prospective clinical trials have shown that higher sputum eosinophil counts in stable COPD patients predict a greater clinical response to ICS (10, 11). This suggests that eosinophil measurements can be used to predict anti-inflammatory drug effects in COPD patients.

Measuring sputum eosinophils is technically challenging and time consuming; some patients are not able to provide adequate samples for analysis (5). Blood eosinophil measurements are widely available and less time-consuming. There is a correlation between sputum and blood eosinophil counts within the same individual(5), suggesting that blood eosinophil counts can be used to identify COPD patients with corticosteroid responsive eosinophilic airway inflammation.

There is evidence that airway eosinophil numbers are increased in a subset of COPD patients experiencing exacerbations (12). Some of these events occur in the absence of pathogen detection, implicating the increase in eosinophilic airway inflammation as a driver of these exacerbations. This provides a rationale for selective targeting of eosinophils to prevent exacerbations associated with excessive eosinophilic inflammation. Furthermore, oral corticosteroid treatment during exacerbations has a greater effect in COPD patients with higher blood eosinophil counts (13).

There is evidence from some COPD cohort longitudinal follow up studies that increased blood eosinophil counts are associated with increased exacerbation rates (14). This suggests that exacerbations may be associated with increased eosinophilic activity.

Retrospective analysis of COPD clinical trials have shown that higher blood eosinophil counts predict a greater reduction in exacerbation rates with inhaled corticosteroid/long acting beta agonist (ICS/LABA) combinations compared to LABA alone. For example, Siddique et al, showed that the exacerbation rate reduction for ICS/LABA versus LABA was 46% ($p < 0.001$) for patients in the upper quartile of eosinophil counts (> 279.8 cells / μL), while it was 22% ($p = 0.113$) in patients within the lowest quartile (< 110.4 cells / μL)(7). A similar pattern of results were reported by Pascoe et al.; the exacerbation rate reduction for ICS/LABA versus LABA was 42% ($p = 0.002$) for patients with eosinophil counts $> 6\%$, while it was 10% ($p = 0.28$) for patients with eosinophil counts $< 2\%$ (8). 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. These studies have not established cut-off / threshold values, and we aim to pool all these data for the purpose of establishing appropriate thresholds.

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