

DDT #000057
BQP Qualification Program Cover Letter

Date: March 25th, 2019

Subject: DDT QUALIFICATION SUBMISSION

DDT Type: Biomarker Qualification

ATTN: CDER-Biomarker Qualification Program

C/O CDER Document Room: Upon receipt notify:

CDER-BiomarkerQualificationProgram@fda.hhs.gov

Biomarker DDT Tracking Number: #000057

Check Here	Submission Type
<input checked="" type="checkbox"/>	Letter of Intent
<input type="checkbox"/>	Qualification Plan
<input type="checkbox"/>	Full Qualification Package
<input checked="" type="checkbox"/>	Update of Above (Check two, this box and one above)
<input checked="" type="checkbox"/>	Other (Integrated Response to FDA QRT LOI Feedback):

Biomarker Name(s): Blood Eosinophil Count

Context of Use: Describe the intended drug development use for the biomarker named above (1 to 2 sentences, see the graphic below for how to write the context of use.)

Proposed Context of Use
Blood eosinophil count is qualified as a predictive biomarker to enrich for subject populations more likely to respond to current and novel pharmacological COPD interventions in clinical trials.

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Purpose Statement: To provide responses to FDA questions and comments, received 12/18/2017, including an updated Letter of Intent.

In addition, we would like to request a meeting with the BQT (assuming the updated LOI is accepted to enter the program) to review our data evidentiary plan as we work toward the

DDT #000057
BQP Qualification Program Cover Letter

more detailed Qualification Plan documentation. If the LOI is accepted our current plan is to move forward with a literature-based approach as opposed to full data integration but would like BQRT's thoughts on if that is an acceptable approach.

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Additional Instructions for LOI/QP/FQP¹ submissions: For every electronic submission, a comprehensive table of contents should be submitted containing three or four levels of detail, with the appropriate bookmarks to key referenced sections in the document.

¹ LOI: Letter of Intent; QP: Qualification Plan; FQP: Full Qualification Plan

CBQC Eosinophil Letter of Intent
Response to FDA Letter Dated December 18, 2017

General Comments Regarding Support for LOI Decision

FDA Comments

- 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 methodology will be used to support the COU.

Context of Use (COU) Considerations

FDA Comments

Requestor's COU: "Blood eosinophil count is qualified as a predictive biomarker to improve the selection of subjects for enrolment 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.

CBQC Response

We are interested in using blood eosinophil counts as a predictive biomarker to enrich for subject populations more likely to respond to current and novel pharmacological COPD interventions in clinical trials. We do not wish to develop blood eosinophils as a prognostic biomarker.

Considerations for a prognostic COU

FDA Comments

- As described in the BEST (Biomarkers, Endpoints, and other Tools) Resources (I), 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 cut-offs, 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.

CBQC Response

Clinical trials of ICS/LABA versus LABA and triple therapy versus long acting bronchodilator treatments have shown an increased exacerbation rate in patients with higher blood eosinophil counts who were not randomised to ICS treatment. This provides some evidence that blood eosinophil counts are a prognostic biomarker in high risk patients who were not treated with ICS. Cohort studies have produced conflicting results regarding the potential of blood eosinophil counts as a prognostic biomarker(13-15); this is partly due to the inclusion of low risk patients and the confounding effects of ICS use. Currently, we are not interested in developing blood eosinophils as a prognostic biomarker.

Considerations for a predictive COU

FDA Comments

- 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 more 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.**

CBQC Response

The rationale for the approach to eosinophils as a predictive biomarker is evidence from post-hoc analyses of clinical trials comparing inhaled corticosteroid/long acting beta agonist (ICS/LABA) versus LABA in patients at increased exacerbation risk have shown that blood eosinophils predict the benefit of ICS on exacerbation prevention. For example, a large post-hoc analysis of 3 clinical trials (n=4,528) comparing ICS/LABA with LABA showed a significant ICS effect at > 100 cells/ μ L, with the effect size increasing with higher blood eosinophil counts(1). Similar findings have been reported in earlier post-hoc analyses of clinical trials comparing ICS/LABA versus LABA(2, 3). Post-hoc analyses of ICS-withdrawal studies also showed greater ICS effects on exacerbations and other clinically relevant endpoints when stratifying the data using blood eosinophils(4-6) . Three clinical trials comparing “triple therapy” (ICS/LABA plus long acting muscarinic antagonist; LAMA) against LAMA monotherapy or LABA/LAMA combination (i.e. no ICS treatment) have prospectively shown that blood eosinophil counts predict the effect of the ICS component of triple therapy(7-9) .

Eosinophils have no predictive value in the response to bronchodilators(10), indicating that this is a potential biomarker of anti-inflammatory / immunomodulatory drugs rather than bronchodilators. The anti-IL5 studies showed an effect on exacerbations that was related to blood eosinophil levels in COPD patients at increased exacerbation risk(11). More recently, a post-hoc analysis of roflumilast (a PDE4 inhibitor) studies showed a greater effect on exacerbation reduction in COPD patients with higher blood eosinophil counts(12)Overall, these studies provide evidence of the potential of blood eosinophils as a predictive biomarker for various classes of drugs, including ICS, anti-IL-5 and PDE4 inhibitors, within a population at high risk of exacerbations. Blood eosinophils might have predictive value for pharmaceutical interventions that are in clinical development, including small molecules or monoclonal antibodies that target COPD inflammation associated with increased eosinophils.

The patient population of interest is “high risk” COPD patients with a history of exacerbation(s) in the previous year. This clinical exacerbation history enriches the population for individuals more likely to experience exacerbations in the future. The use of blood eosinophils is intended to subdivide these high-risk patients according to the level of eosinophilic inflammation present.

ICS have broad anti-inflammatory effects on different cell types including eosinophils. ICS are therefore likely to target more than just the eosinophil. The clinical trial evidence that ICS effects in COPD are related to blood eosinophil counts is therefore likely to be due to ICS effects on the eosinophil plus other aspects of inflammation that are associated with increased eosinophil counts; this is the basis for our phrase “eosinophil associated inflammation”. This is the group of drugs for which the COU is intended. An example is anti-IL-5 treatments, which target eosinophilic inflammation; it has been reported that the effects of an anti-IL-5 monoclonal antibody are related to blood eosinophil counts in COPD(11). Comparable results have recently been published for

PDE4(12). We intend to use data from already completed clinical trials of ICS, PDE4 inhibitors and anti-IL5 treatments to evaluate the predictive ability of blood eosinophils in high risk COPD patients.

Analytical Considerations

FDA Comments

1. You identify specific analysers which can be used for blood eosinophil counts, stating that these analysers are FDA cleared. Elsewhere in the LOI, it appears that non-FDA cleared hematology analysers (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 analysed 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.

CBQC Response

We plan to report details of important analytical considerations in the Qualification Plan, including aspects of measurement variability including precision around proposed measurement thresholds.

Clinical Considerations

FDA Comments

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).

CBQC Response

We intend to use the same exacerbation definition that is used in clinical trials.

The COU will be restricted to patients with a history of moderate to severe exacerbations. The patient subgroup that we wish to target are individuals with eosinophilic lung inflammation. Blood eosinophil counts are a practical means of identifying these individuals. The relationship between blood and sputum eosinophil counts in COPD has been reported as statistically significant but with an r value <0.5(16-18), indicating a modest or weak strength of relationship. However, sputum eosinophil sampling is prone to variability, and is by no means a gold standard for measuring eosinophilic lung inflammation. A bronchoscopy study (n=41) evaluating COPD patients with blood eosinophils <150 cells/ μ L versus >250 cells/ μ L showed greater eosinophil numbers in the bronchoalveolar lavage and bronchial mucosa, and increased airway remodelling in the latter group(16). This indicates a distinct inflammatory profile in COPD patients with higher blood eosinophil counts and supports the case to use different pharmacological approaches to treat this subgroup.

COPD is caused by multiple biological mechanisms. Eosinophilic COPD can co-exist with other forms of inflammation / remodelling caused by other mechanisms. There is no accepted classification of COPD according to inflammatory profiles. We intend to use blood eosinophils to identify COPD patients with eosinophilic lung inflammation, which may exist with or without other mechanisms of lung inflammation being present.

FDA Comment

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

CBQC Response

At present, clinical trials of anti-inflammatory drugs commonly use a clinical history of exacerbations to enrich the population for at risk individuals. No other clinical criteria are commonly used. Blood eosinophils are being proposed as a predictive biomarker within this high-risk population. No other biomarkers are presently in widespread use that would influence this proposal.

FDA Comments

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 (JCS) do not affect blood eosinophil count. The literature is unclear on whether there is any statistically significant effect (3-5) of JCS 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 JCS on your measurement of blood eosinophils count.

CBQC Response

Issues concerning SOP: the collection of blood by venepuncture for haematology analysis is routinely performed in clinical practice and research and is a simple procedure. Our proposal will provide guidance (an SOP) on this.

Regarding external variables; the presence of concomitant asthma should not alter the procedure or its interpretation, as it is the level of eosinophilic inflammation in COPD (with or without asthma) that we wish to develop as a predictive biomarker. In cases of parasitic infection or oral corticosteroid use, which can both significantly affect blood eosinophil counts, then this biomarker should not be used. Regarding inhaled corticosteroids, we will evaluate the literature carefully for any effect, but this appears to be small and not sufficient to cause problems with the interpretation of results. For example, post-hoc and prospective analysis using blood eosinophils to predict ICS effects have shown positive predictive results while included patients taking ICS and not taking ICS at the point when blood eosinophils were measured.

FDA Comments

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 favours 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.

CBQC Response

Blood and sputum eosinophils are both surrogate biomarkers of eosinophilic lung inflammation. The problems with using sputum measurements is well documented e.g. many centres lack expertise to perform this method, some patients cannot produce a sample and sputum cell counts can be prone to high variability. Studies have shown a relationship between blood and sputum eosinophils, with r value <0.5(16-18), indicating a modest or weak strength of relationship. However, sputum eosinophil sampling is prone to variability, and is by no means a gold standard for measuring eosinophilic lung inflammation. A bronchoscopy study (n=41) evaluating COPD patients with blood eosinophils <150 cells/µL versus >250 cells/µL showed greater eosinophil numbers in the bronchoalveolar lavage and bronchial mucosa, and increased airway remodelling in the latter group(16).

We have previously mentioned sputum eosinophils as providing supportive evidence that eosinophilic COPD is a distinct entity, and have quoted some evidence to support sputum eosinophils being both a prognostic and predictive biomarker. The published information on sputum eosinophils during exacerbations is mechanistically important, as it shows that some exacerbations have a high level of eosinophilic airway inflammation, which supports the case to target eosinophilic inflammation to prevent exacerbations. However, we wish to be clear that the focus this submission on the development of blood eosinophils as a predictive biomarker.

FDA Comments

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**

CBQC Response

The aim of our submission is to perform a pooled analysis of all available data from clinical trials to determine the predictive ability of blood eosinophils to determine the effects of ICS on exacerbation rates and other important clinical outcomes, e.g. health status and lung function. Additionally, we will study the robustness of the measurement of blood eosinophils, evaluating parameters that may influence reproducibility. To support this analysis plan, then our interpretation of the current literature is set out below.

The relationship between blood eosinophils and exacerbations

Clinical trials of ICS/LABA versus LABA (post-hoc analysis) and triple therapy versus long acting bronchodilator treatments (pre-specified analysis) performed in patients at high risk of exacerbations have shown an increased exacerbation rate in patients with higher blood eosinophil counts who were not randomised to ICS treatment(1-3, 8). This shows that blood eosinophil counts may be a prognostic biomarker in high risk patients who have not been treated with ICS. Cohort studies have produced conflicting results regarding the potential of blood eosinophil counts as a prognostic biomarker; this is

partly due to the inclusion of low risk patients and the confounding effects of ICS use. We are not interested in developing blood eosinophils as a prognostic biomarker.

Post-hoc analysis of ICS/LABA versus LABA

A large post-hoc analysis of 3 clinical trials (n=4528) comparing ICS/LABA with LABA showed a significant ICS effect at > 100 cells/ μ L, with the effect size increasing with higher blood eosinophil counts(1). Similar findings have been reported in other post-hoc analyses of clinical trials comparing ICS/LABA versus LABA(2, 3). Pooling the results of these and other studies with a similar design will increase the statistical power to determine the relevant blood eosinophil threshold levels.

In your interpretation of Siddqui et al, you raise a point about the highest eosinophil quartile having a higher exacerbation rates. In reply, we consider that the rates between 1.4 – 1.51 / year are reasonably similar and do not confound the conclusion. You also raise a point about stratification by percentage showing different results. In reply, one reason for this is the reduced statistical power in such subgroup analysis; this is the purpose of our proposal to pool data for more robust analysis. Also, we will focus on absolute eosinophil counts (not percentage), as percentage are influenced by other blood cell numbers.

In your interpretation of Pascoe et al, you raise a comment in a response article. This post-hoc analysis was the first to generate the hypothesis about the predictive ability of blood eosinophil counts. The pooled analysis that we are planning will have sufficient statistical power to overcome the type of criticism in the response article.

Post-hoc analysis of fluticasone propionate studies

You have mentioned the Pavord et al paper, and Barnes et al, analysing clinical trial data with the ICS fluticasone propionate(19, 20). In the Pavord paper, you express concern that one trial (out of three) included in the paper is not supportive. In response, it should be noted that this trial did not specifically recruit high risk patients (i.e. with a history of exacerbations in the last year), while the two supportive studies in the paper included only high risk patients. It is our intention to focus on the predictive ability of blood eosinophils in high risk patients. The ISOLDE study is also mentioned, which again did not recruit specifically high risk patients. These studies including non-high risk patients are less relevant to our submission.

FLAME trial

It is important to read the subsequent published analysis of blood eosinophils in FLAME, and the subsequent correspondence debate(21). In summary, the effect of ICS/LABA was lowest when blood eosinophils <150 cells/ μ L, which demonstrates a predictive ability of this biomarker. The analysis in the initial paper was pre-specified, but too simplistic (i.e. using a single cut-off to dichotomize the population) to analyse the predictive ability of the biomarker properly.

Biomarker directed exacerbation treatment

The study by Bafadhel et al concerns oral corticosteroid use and provides some mechanistic information that some exacerbations are eosinophilic(22). It is not directly relevant to our submission.

Mepoluzimab studies

We are proposing to evaluate blood eosinophils as a predictive biomarker of drug effects in COPD patients with a history of exacerbations; this is important, as we are intending to use this biomarker only

in this COPD subset. The main “criticisms” of blood eosinophils as an “imperfect biomarker” are listed below, with a *response* against the criticism:

- a) “Blood eosinophils do not consistently relate to exacerbation rate”. *Response:* The inclusion of patients who are at low risk of exacerbations in such cohorts, and the confounding effects of concurrent ICS therapy, causes variation in results between studies(13-15). This contrasts with the consistent findings in clinical trials of patients at high exacerbation risk, where the exacerbation rate is related to blood eosinophil counts in patients not treated with ICS.
- b) “Blood eosinophils do not show a strong correlation with sputum eosinophils”. *Response:* sputum eosinophils are by no means a “gold standard” of eosinophilic inflammation in the lungs. Sputum eosinophils are prone to variability, which contributes significantly to the reported moderate / weak associations between blood and sputum eosinophils. There is a bronchoscopy study that has shown significantly different airway inflammation in COPD patients with blood eosinophils > 250 cells / μ L(16).

Triple therapy studies

Three clinical trials comparing “triple therapy” (ICS/LABA plus long acting muscarinic antagonist; LAMA) against LAMA monotherapy or LABA/LAMA combination (i.e. no ICS treatment) have prospectively shown that blood eosinophil counts predict the effect of the ICS component of triple therapy(7-9). These key studies provide evidence of the potential of blood eosinophils as a predictive biomarker within a population at high risk of exacerbations.

Statistical Considerations

FDA Comments

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 review the revised COU to describe the specific blood eosinophils count threshold that defines the subgroup of COPD subjects of interest (i.e. the severity and frequency of exacerbations or response to therapies.

CBQC Response

Statistical modelling of data from clinical trials involving ICS has already been performed e.g. approximately 10,000 patients in the IMPACT study, and > 4,500 patients in a pooled analysis of ICS/LABA treatment. Other trials have also used statistical modelling, and we will describe these data independently. For PDE4 inhibitors, further analysis will be performed. After this analysis, the threshold(s) proposed will be analysed further regarding device analytical performance.

This document has earlier revised the COU of blood eosinophils as a predictive biomarker in COPD patients at high exacerbation risk.

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2. Pascoe S, Locantore N, Dransfield M, 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 Respiratory Medicine* 2015; 3: 435-442.
3. 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.
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8. Papi A, Vestbo J, Fabbri L, Corradi M, Prunier H, Cohuet G, Guasconi A, Montagna I, Vezzoli S, Petruzzelli S, Scuri M, Roche N, Singh D. Extrafine inhaled triple therapy versus dual bronchodilator therapy in chronic obstructive pulmonary disease (TRIBUTE): a double-blind, parallel group, randomised controlled trial. *Lancet* 2018; 391: 1076-1084.
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10. Iqbal A, Barnes NC, Brooks J. Is Blood Eosinophil Count a Predictor of Response to Bronchodilators in Chronic Obstructive Pulmonary Disease? Results from Post Hoc Subgroup Analyses. *Clin Drug Investig* 2015; 35: 685-688.
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Biomarker Qualification Letter of Intent (LOI) Content Elements

NOTE TO REQUESTORS: FDA is currently developing its policies for submissions under the 21 Century Cures Act (section 507)¹ and expects to issue guidance to aid in the development of submission based on a decade of reviews, input from public meetings, comments to the docket and collaborative public partnerships. In the interim the Agency has assembled this resource to help requestors. Given the changes to the process as defined in section 507, we expect to see further development of this content over time, with more experience and your input. For additional resources on submission content please see prior Biomarker Qualification Program submissions that we have accepted under section 507 [HERE](#). Please also note that certain information contained in submissions will be made publicly available as per section 507, as described in greater detail [HERE](#).

Should you have any questions or want to provide feedback on this or other BQP resources, including the content and format of submissions and the transparency provisions under section 507, please contact us at CDER-BiomarkerQualificationProgram@fda.hhs.gov

COMMENTS: The following information will be made publicly available as per section 507, described in greater detail [HERE](#)

Administrative Information

1. Submission Title:

- Blood eosinophil counts as a predictive biomarker in COPD

2. Requesting Organization:

Name of Organization: COPD Foundation

3300 Ponce de Leon Blvd, Miami, Florida 33134

General Office Phone Number 1-866-731-COPD (2673)

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1. Section 3011 of the 21st Century Cures Act established section 507 of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Supporting or participating individuals or organizations:

The members of the CBQC Working Group for eosinophils include:

Alan Hamilton – Boehringer Ingelheim
Bruce Miller – GSK
Dave Singh – Medicines Evaluation Unit & University of Manchester (UK)*
Chris Compton – GSK*
Christopher Brightling, Institute for Lung Health, Leicester, UK
Christoph Hallmann – Boehringer Ingelheim
Eugene Bleeker – University of Arizona
Malin Fageras – AZ
Fernando Martinez - Cornell
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Jeff Curtis – U. of Michigan
Jeff Snyder – Boehringer Ingelheim
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Norbert Metzdorf - BI
Paul Newbold - Medimmune
Prescott Woodruff – UCSF
Robert Fogel – Novartis
Russell Bowler – National Jewish
Ruth Tal-Singer – GSK
Sally Bruce – GSK
Stefano Petruzzeli – Chiesi
Stephen Rennard – GSK
Ubaldo Martin – AZ*

* *Co-chairs*

3. Submission Dates:

LOI submission date – March 25th, 2019

Drug Development Need Statement

COPD is a 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 (and immune modulator) treatments in COPD patients usually evaluate exacerbation rates to determine pharmacological effects. However, patients with a history of exacerbations have heterogeneous inflammatory profiles (endotypes) [1] and therefore targeted novel drugs are likely to show efficacy in only a sub-population of the exacerbating COPD patient population. Based on recent insights of these sub-populations, a few endotypic biomarkers have emerged however, except for plasma fibrinogen [2], none have been qualified as drug development tools thus far.

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[3-6]; we propose that blood eosinophil counts will be used as an additional biomarker to enable further enrichment and stratification of the population.

Biomarker Information and Interpretation

1. **Biomarker Name:** Blood eosinophil count
2. **Analytical methods:** The absolute eosinophil count is a blood test that measures the number of white blood cells called eosinophils. Eosinophil activation can occur in certain inflammatory conditions and when you have certain allergic diseases, infections, and other medical conditions including inflammation.

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>).

3. **Measurement units and limit(s) of detection:** eosinophils / μ l. Usually measured down to 10 cells/ μ l
4. **Biomarker interpretation and utility:** The measurements obtained from hematology analyzers are expressed as cells/ μ l and so require no conversion. The use of blood eosinophil counts is intended to be used to stratify COPD patients who have a clinical history of exacerbation; this will allow studies to be performed in subgroups according to the potential level of eosinophilic inflammation present.

Context of Use Statement (500 characters)

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.

Analytical Considerations

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.

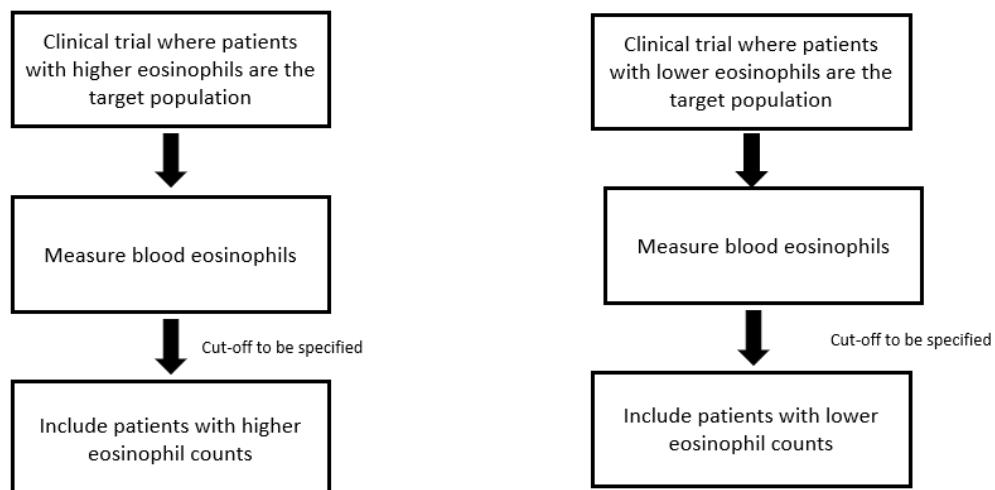
Vendors typically provide device performance data for different hematology analyzers. For example, the Siemens Advia system, commonly used in US clinical trials, has assay performance data on the Siemens web site (<https://usa.healthcare.siemens.com/hematology/systems/advia-2120-hematology-system-with-autoslide/technical-specifications>).

The primary focus will be the predictive value of the baseline eosinophil measurement. We will report details of important analytical considerations in the Qualification Plan, including aspects of measurement variability and precision around proposed measurement thresholds.

Clinical Considerations

The patient population of interest is “high risk” COPD patients with a history of exacerbation(s) in the previous year. This clinical exacerbation history enriches the population for individuals more likely to experience exacerbations in the future (exacerbator phenotype). The use of blood eosinophils is intended to stratify these high-risk patients according to the level of eosinophilic inflammation present (eosinophilic inflammation endotype).

Decision tree for use of blood eosinophil counts to select COPD patients (with increased exacerbation risk) more likely to respond to novel pharmacological interventions



Evidence for the use of blood eosinophils as a predictive biomarker comes from post-hoc analyses of clinical trials comparing inhaled corticosteroid/long acting beta agonist (ICS/LABA) versus LABA in patients at increased exacerbation risk; these analyses have consistently shown that blood eosinophils predict the benefit of ICS on

exacerbation prevention (summarized in appendix 1). Furthermore, pre-specified analysis of 3 clinical trials comparing “triple therapy” (ICS/LABA plus long acting muscarinic antagonist; LAMA) against LAMA monotherapy or LABA/LAMA combination (i.e. no ICS treatment) have shown that blood eosinophil counts predict the effect of the ICS component of triple therapy[3, 4, 6] (summarized in appendix 1). There is also supporting evidence from anti-IL5 studies showing an effect on exacerbations that was related to blood eosinophil levels in COPD patients at increased exacerbation risk[5], and a post-hoc analysis of roflumilast (a PDE4 inhibitor) studies showing a greater effect on exacerbation reduction in COPD patients with higher blood eosinophil counts[7]. Overall, these studies provide evidence of the potential of blood eosinophils as a predictive biomarker for various classes of drugs within a population at high risk of exacerbations. Blood eosinophils might have predictive value for pharmaceutical interventions that are in clinical development, including small molecules or monoclonal antibodies that target COPD inflammation associated with increased eosinophils.

ICS have broad anti-inflammatory effects on different cell types including eosinophils. ICS are therefore likely to target more than just the eosinophil. The clinical trial evidence that ICS effects in COPD are related to blood eosinophil counts is therefore likely to be due to ICS effects on the eosinophil and/or on other aspects of inflammation that are associated with increased eosinophil counts.

We will review and describe the data from completed clinical trials (with active treatment and control arms) that fulfill the following criteria:

- a) Inclusion of patients with a history of 1 or more exacerbations in the last year (i.e. at increased exacerbation risk)
- b) Treatment duration of at least 1 year
- c) Blood eosinophils measured at the start of the study

The aim of our submission is to evaluate the predictive ability of blood eosinophils to determine the effects of different drug classes (ICS, PDE4 inhibitors and anti-IL5 treatment) on exacerbation rates and other important clinical outcomes, e.g. health status and lung function. Additionally, we will study the robustness of the measurement of blood eosinophils, evaluating parameters that may influence reproducibility.

In the submission, we plan to describe all available data from relevant clinical trials to determine the predictive ability of blood eosinophils to determine the effects of ICS, PDE4 inhibitors and anti-IL5 treatment on exacerbation rates and other important clinical outcomes, e.g. health status and lung function. The CBQC believes that with the extensive published data regarding the relationship between blood eosinophils and ICS effects, including the IMPACT study in approximately 10,000 patients[3], and a pooled analysis of ICS/LABA treatment in > 4500 patients[8], there is sufficient data regarding ICS without the need for further analysis, or pooling of data from individual studies. For PDE4 inhibitors, we plan to perform further analyses on retrospective data, as only 1 study is currently published[7].

Supporting Information

The COU will be restricted to patients with a history of moderate to severe exacerbations. We intend to use the same exacerbation definition that is used in clinical trials.

Retrospective analysis of COPD clinical trials has shown that higher blood eosinophil counts (at the start of the

study) 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 / 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). Pre-specified analysis of clinical trials comparing triple therapy (ICS/LABA/LAMA) versus long acting bronchodilator therapy have also shown a greater effect of ICS on exacerbations at higher eosinophil counts; in the largest of these trials (the IMPACT study), the treatment difference for triple therapy versus LABA/LAMA was 32% for patients with blood eosinophils >150 cells/ μL , while below this threshold the effect was 12%.

Blood eosinophil counts are a practical means of identifying individuals with a different profile of airway inflammation that is more responsive to ICS treatment. The relationship between blood and sputum eosinophil counts in COPD has been reported as statistically significant but with an r value <0.5 [9-11], indicating a modest or weak strength of relationship. However, sputum eosinophil sampling is prone to variability, and should not be regarded as the gold standard method for measuring eosinophilic lung inflammation. A bronchoscopy study ($n=41$) evaluating COPD patients with blood eosinophils <150 cells/ μL versus >250 cells/ μL showed greater eosinophil numbers in the bronchoalveolar lavage and bronchial mucosa, and increased airway remodeling in the latter group[9]. This indicates a distinct inflammatory profile in COPD patients with higher blood eosinophil counts and supports the case to use different pharmacological approaches to treat this subgroup.

COPD is caused by multiple biological mechanisms. Eosinophilic COPD can co-exist with other forms of inflammation / remodeling caused by other mechanisms. There is no accepted classification of COPD according to inflammatory profiles. We intend to use blood eosinophils to identify COPD patients with a component of eosinophilic lung inflammation as a “treatable trait” [1], which may exist with or without other mechanisms of lung inflammation being present.

Previous Qualification Interactions and Other Approvals (if applicable)

We originally submitted an LOI on 8/29/2016. FDA responded with a Final Decision letter dated 12/17/17 (DDTBMQ #000057). Our March 2019 submission provides responses to the questions and comments from FDA and includes this associated updated LOI.

Attachments

Attachment 1

High-Level Summary of clinical data relevant to the proposed biomarker

The aim of our submission is to review and describe all available data from clinical trials to determine the predictive ability of blood eosinophils to determine the effects of ICS on exacerbation rates and other important clinical outcomes, e.g. health status and lung function. We will also analyze PDE4 inhibitor data, which may be pooled. The data on anti-IL5 treatment will be described. Additionally, we will study the robustness of the measurement of blood eosinophils, evaluating parameters that may influence reproducibility. To support this analysis plan, our interpretation of the current literature is set out below.

Post-hoc analysis of clinical trials comparing ICS/LABA versus LABA

A large post-hoc analysis of 3 clinical trials (n=4528) comparing ICS/LABA with LABA showed a significant ICS effect at > 100 cells/ μ L, with the effect size increasing with higher blood eosinophil counts[8]. Similar findings have been reported in other post-hoc analyses of clinical trials comparing ICS/LABA versus LABA[12, 13]; 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]. Pascoe et al reported that 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].

FLAME trial

The FLAME trial compared ICS/LABA with LAMA/LABA in patients with a history of exacerbations. A post-hoc analysis [14] showed that the effect of ICS/LABA was lowest for patients with blood eosinophils <150 cells/ μ L.

Prospective analysis of Triple therapy studies

Three clinical trials comparing “triple therapy” (ICS/LABA plus long acting muscarinic antagonist; LAMA) against LAMA monotherapy or LABA/LAMA combination (i.e. no ICS treatment) have prospectively shown that blood eosinophil counts predict the effect of the ICS component of triple therapy[3, 4, 6]. These key studies provide evidence of the potential of blood eosinophils as a predictive biomarker within a population at high risk of exacerbations. In the largest of these trials (the IMPACT study), the treatment difference for triple therapy versus LABA/LAMA was 44% for patients with blood eosinophils >150 cells/ μ L, while below this threshold the effect was 12%

Mepoluzimab studies

Anti-IL-5 treatments target eosinophilic inflammation; it has been reported that the effects of an anti-IL-5 monoclonal antibody on exacerbations are related to blood eosinophil counts in COPD[5]

PDE4 inhibitors

There is one study that has shown a relationship between the effects of roflumilast and blood eosinophil counts[7]. Other studies, including the PDE4 inhibitor cilomilast, will be analyzed.

The relationship between blood eosinophils and exacerbations

Clinical trials of ICS/LABA versus LABA (post-hoc analysis) and triple therapy versus long acting bronchodilator treatments (pre-specified analysis) performed in patients at high risk of exacerbations have shown an increased exacerbation rate in patients with higher blood eosinophil counts who were not randomized to ICS treatment[4, 8, 12, 13]. This shows that blood eosinophil counts may be a prognostic biomarker in high risk patients who have not been treated with ICS. Cohort studies have produced conflicting results regarding the potential of blood eosinophil counts as a prognostic biomarker; this is partly due to the inclusion of low risk patients and the confounding effects of ICS use. We are not interested in developing blood eosinophils as a prognostic biomarker.

Common criticisms of blood eosinophils as a COPD biomarker

The main “criticisms” of blood eosinophils as an “imperfect biomarker” are listed below, with a *response* against the criticism:

- a) “Blood eosinophils do not consistently relate to exacerbation rate”. *Response:* In cohort studies, the inclusion of patients who at low risk of exacerbations in such cohorts, and the confounding effects of concurrent ICS therapy, causes variation in results between studies[15-17]. This contrasts with the consistent findings in clinical trials of patients at high exacerbation risk, where the exacerbation rate is related to blood eosinophil counts in patients not treated with ICS.
- b) “Blood eosinophils do not show a strong correlation with sputum eosinophils”. *Response:* sputum eosinophils are not a “gold standard” of eosinophilic inflammation in the lungs. Sputum eosinophils are prone to variability, which contributes significantly to the reported moderate / weak associations between blood and sputum eosinophils. There is a bronchoscopy study that has shown significantly different airway inflammation in COPD patients with blood eosinophils > 250 cells / μ L[9]. It is further plausible that systemic eosinophilic inflammatory processes predisposing to lung inflammatory processes may be relevant, independent of active eosinophilic airway inflammation.
- c) Blood eosinophil count is a variable measure which will limit its utility as a biomarker. *Response:* 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.

Attachment 2

References

1. Agusti, A., et al., *Precision medicine in airway diseases: moving to clinical practice*. Eur Respir J, 2017. **50**(4).
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3. 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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12. Pascoe, S., et al., *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 Respiratory Medicine, 2015. **3**(6): p. 435-442.
13. Siddiqui, S.H., et al., *Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease*. Am J Respir Crit Care Med, 2015. **192**(4): p. 523-5.
14. Roche, N., et al., *Blood Eosinophils and Response to Maintenance COPD Treatment: Data from the FLAME Trial*. Am J Respir Crit Care Med, 2017.
15. Casanova, C., et al., *Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD*. Eur Respir J, 2017. **50**(5).
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Additional Information & Submission Information:

None.