MEMORANDUM

Department of Health and Human Services
Public Health Service
Food and Drug Administration

Date: September 26, 2014

To: COPD Biomarker Qualification Team

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Subject: Fibrinogen Qualification as Biomarker for COPD exacerbation or mortality

Date of Submission: June 27, 2013

Summary

The Chronic Obstructive Pulmonary Disease (COPD) Foundation Biomarker Qualification Consortium (CBQC) submitted a proposal in support of plasma fibrinogen as an enrichment biomarker to facilitate the inclusion of COPD subjects in clinical trials that are more likely to experience all-cause mortality or COPD exacerbations.

Current COPD clinical trial designs are large, with a large number of patients not manifesting symptoms over the course of the study period. The idea is that additional patient characteristics could allow the identification of patients likely to experience an event. Biomarker enrichment would therefore allow for clinical trials to be conducted more efficiently, leading to reduced subject numbers and study costs. In support of the use of fibrinogen as biomarker for COPD mortality or exacerbation, the sponsor proposed the use of an integrated database combining the outcome of five independently conducted studies to demonstrate the robustness of fibrinogen as a biomarker of adverse COPD outcomes across various patient populations and time periods. CBQC evaluated exacerbation and mortality data collected in the five clinical trials utilizing four fibrinogen cut-offs in addition to evaluation in the absence of fibrinogen testing. A number of different *in vitro* diagnostic devices for determination of fibrinogen concentrations with different technologies were employed in the aforementioned studies. CDRH was consulted to review the device related information in the proposal.

Background

Chronic obstructive pulmonary disease:

COPD is an obstructive lung disease characterized by chronically poor airflow resulting in shortness of breath along with cough and sputum production. Systemic inflammation is known as hallmark of COPD leading to expression of IL6, CRP, fibrinogen and leukocytes. Major risk factors in the development of COPD include smoking and environmental pollution. Acute disease exacerbation is often caused by bacterial or viral infections and can lead to a sudden worsening of symptoms that typically lasts for several days. Breathlessness in COPD is usually the first symptom that drives patients to seek a medical consultation. Patients frequently describe their dyspnea as a sense of increased effort to breathe, heaviness, air hunger, or gasping. It is characteristically persistent and progressive. Patients may first notice impairments in daily activities before their disease progresses to a more severe state and they may become confined to their homes. With severe disease, weight loss and anorexia are common. During respiratory infections, hemoptysis can occur, and requires further investigation. The development of cor pulmonale caused by secondary pulmonary hypertension is often seen in advanced COPD and can present with typical signs and symptoms of depression, anxiety, or both. In the USA, the death rate from COPD was 67 per 100,000 in 2000, compared with 44 per 100,000 in the rest of the world. The annual COPD death rate has been increasing in the USA in the past 20 years, in contrast with a decreasing mortality for other major chronic disease. Data from the USA have estimated the total annual economic burden of COPD at $23.9 billion.(8)

Fibrinogen:

Fibrinogen is a 340kDa glycoprotein that consists of three pairs of polypeptide chains linked by a total of 29 disulfide bonds. This protein is converted by thrombin into fibrin during blood clot formation. This protein is part of normal blood coagulation system, in which the coagulation cascade actives the zymogen prothrombin by converting it into the active serine protease thrombin. Thrombin in turn converts the soluble fibrinogen into insoluble fibrin strands. The strands are further cross-linked by Factor XIII to form a blood clot (2). Reduced fibrinogen levels are found in disseminated intravascular coagulation (DIC), a condition characterized by widespread activation of the clotting cascade and subsequent consumption of clotting factors, liver disease, and after large volume transfusion. Increased fibrinogen levels are typically found in older patients, in pregnancy, in the presence of malignancies, and as an acute phase reactant.

Fibrinogen has been identified as potential biomarker for COPD due to its role in the inflammatory process as acute phase reactant and the disease is characterized by the presence of inflammation. Acute phase reactants are expressed within hours or days of most form of acute tissue damage or inflammation, and persist with chronic inflammation and malignancies and therefore, have great importance in the clinical assessment of disease activity (3). During acute phase stimulation, serum fibrinogen levels can increase three-fold in response to increased IL-6 production (4).

Fibrinogen *In Vitro* Assays:

In vitro diagnostic assays for determination of fibrinogen plasma levels are regulated as a class II medical device under 21 CFR 864.7340. A large number of *in-vitro* assays for quantitation of fibrinogen serum concentrations have been cleared by the FDA to date. (Please see http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm for a complete listing). The cleared assays can be categorized into two general methods: Functional methods (e.g. Clauss) and direct methods (e.g. immunological).

Clauss method assays determine the time for fibrin clot formation. In this assay type, diluted patient plasma is exposed to an excess of thrombin (to ensure that clotting times are independent of thrombin concentration) and phospholipid. The reaction is initiated through the addition of calcium to negate the effect of the anticoagulant citrate present in the plasma sample. The fibrinogen plasma concentration is subsequently derived through use of a calibration curve (5).

Immunological assays are mainly enzyme linked immunoabsorbent assays (ELISA). These assays measure a protein concentration rather than the activity of the protein.

Based on the disparate technological principles, results generated by functional and immunological fibrinogen assays may differ in patients with qualitative fibrinogen defects (dysfibrinogenaemia). However, based on description in other patient populations the prevalence of these genotypes is low (6) and we do not anticipate that the prevalence of these mutations would not be altered in the COPD patient population. Additional assays used for assessment of fibrinogen plasma levels such as PT-derived fibrinogen assays and gravimetric assays were not part of the proposal and will therefore not be discussed in this review.

Review of the Device Related Information Provided:

CBQC submitted an analysis of previous literature. The results of five clinical studies (ARIC, CHS, ECLISPE, Framingham Offspring Cohort and NHANES III) were integrated in one dataset. The methods used for fibrinogen assessment are summarized (7):

Table 1: Fibrinogen measurements and assay methods used in the 5 studies of interest

Study	Study Design	Fibrinogen measurements (N)	Follow-up (years)	Fibrinogen Assay Method	Intra-Assay Coefficient of Variation (CV)	Inter-Assay Coefficient of Variation (CV)	Fibrinogen cut-point*
ARIC	Prospective cohort	1	12	Clauss	NR	NR	Data-specific[1]
CHS	Prospective cohort	2	3	Clauss	3.1%[2]	NR	Data-specific[2]
ECLIPSE	Prospective cohort	8	3	Immunologic	1.2%[3]	1.9%[3]	Data specific[4,5]
Framingham Offspring Cohort	Prospective cohort	1	4	Immunologic	6.2%[6]	NR	Data specific[6]
				Clauss	2.6%[6,7]	4.7%[7]	
NHANES III	Cross-sectional survey	1	N/A	Clauss	NR	NR	Detectable level: 3.0 mg/L. Highly elevated: 10.0 mg/L[8]

Recommendation:

Results of the initial analysis showed four of the five studies were of limited value for evaluation of the benefit of fibrinogen as a biomarker for COPD. The ECLIPSE study was the only study determined to have the most scientific value for the following reasons: Study was specifically designed to evaluate COPD patients rather than study a more general population and samples for fibrinogen determination were prospectively collected. However, it is unclear whether the fibrinogen results were generated with a number of different Clauss-based and immunological tests and if this is the case, whether results from these two types of tests could be combined for analysis.

Further analysis of the utility of the fibrinogen biomarker for enrichment of COPD clinical trials for patient events was therefore limited to the ECLIPSE study, which represents the most clinically complete and relevant dataset. The device used in the study is the immunological test, Kamiya K-Assay which was cleared under k993482. Any clinical recommendations made as part of the biomarker qualification review are based only on measurements obtained using the Kamiya K-Assay with samples collected in EDTA. Additional testing methods or sample matrices were not evaluated. The recommendation for use of fibrinogen as a COPD exacerbation biomarker is therefore limited to this specific context of use.

In clinical practice, Clauss-based assays are most commonly used to measure fibrinogen levels. If sponsors decide to include a fibrinogen assay other than the Kamiya K-assay in any future study, we recommend the utilization of an FDA cleared fibrinogen assay with validated analytical performance characteristics. If sponsors intend to use non-FDA cleared fibrinogen assays, the performance characteristics of these assays need to be established prior to inclusion in any clinical studies that use fibrinogen as an enrichment biomarker. In both cases, a bridging study is needed between either FDA cleared or non-FDA cleared fibrinogen assays to the Kamiya K-Assay in order to establish the plasma fibrinogen cut-off appropriate for enrolling COPD subjects in clinical trials. For feedback on the appropriateness of the assay selected for fibrinogen testing, CDRH recommends sponsors in the early stages of development provide details of their study design and assay related information as a Pre-Submission to CDRH for review. For additional information on the Pre-Submission program, please refer to http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf.

If you have any questions or comments regarding this review, please call me at (301) 796-4807 or email me at Claudia.Dollins@fda.hhs.gov.

References:

(1) Centers for Disease Control and Prevention. National Center for Health Statistics. National Vital Statistics Report. Deaths: Final Data for 2010. May 2013; 61(04).

(2) Doolittle, R.F., Fibrinogen and Fibrin. Ann. Rev Biochem. 53:195-229 (1984).

(3) Pepys, M.B., et al., Serum amyloid P-component is an acute-phase reactant in the mouse. Nature 278, 259-261 (15 March 1979).

(4) Duvoix, A, et al., Blood fibrinogen as a biomarker of chronic obstructive pulmonary disease. Thorax (2012).

(5) http://www.practical-haemostasis.com/Screening%20Tests/fibrinogen.html

(6) Jacquemin B, et al. Common genetic polymorphisms and haplotypes of fibrinogen alpha, beta, and gamma chains affect fibrinogen levels and the response to proinflammatory stimulation in myocardial infarction survivors. J Am Coll Cardiol 52:941-952 (2008).

(7) Appendix 2, COPD Biomarker Qualification Consortium provided information.

(8) Burden and clinical features of chronic obstructive pulmonary disease (COPD) Romain A Pauwels, Klaus F Rabe Lancet 2004; 364: 613–2

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