Qualification of Biomarker—Plasma Fibrinogen in Studies Examining Exacerbations and/or All-Cause Mortality in Patients With Chronic Obstructive Pulmonary Disease

Draft Guidance for Industry

Drug Development Tool (DDT) Type: Biomarker
Referenced Biomarker(s): Plasma fibrinogen

Fibrinogen is an acute phase protein that is elevated in inflammation. It is a soluble plasma glycoprotein that is converted by thrombin to fibrin during blood clot formation.

I. SUMMARY OF GUIDANCE

A. Purpose of Guidance

This draft guidance provides a qualified context of use (COU) for the biomarker plasma fibrinogen, in interventional clinical trials of patients with chronic obstructive pulmonary disease (COPD) at high risk for exacerbations and/or all-cause mortality. This draft guidance also describes the experimental conditions and constraints for which this biomarker is qualified through the CDER Biomarker Qualification Program. This biomarker can be used by drug developers for the qualified COU in submissions of investigational new drug applications (INDs), new drug applications (NDAs), and biologics license applications (BLAs) without the relevant CDER review group reconsidering and reconfirming the suitability of the biomarker.

DDT Tracking Number: [DDTBMQ-000021]

B. Application of Guidance

This guidance applies to the use of plasma fibrinogen in investigational studies for exacerbations and/or all-cause mortality in COPD patients. It does not change any regulatory status, decisions, or labeling of any in vitro diagnostic test used in the medical care of patients.

Fibrinogen use in drug development outside of the qualified COU will be considered by FDA on a case-by-case basis in regulatory submissions. In such cases, additional information relevant to the expanded use may be requested by the CDER product review team.

II. CONTEXT OF USE

A. Use Statement

This draft guidance provides qualification recommendations for the use of plasma fibrinogen, measured at baseline, as a prognostic biomarker to select patients with COPD at high risk for exacerbations and/or all-cause mortality for inclusion in interventional clinical trials. This biomarker should be considered with other demographic and clinical characteristics, including a prior history of COPD exacerbations, as an enrichment factor in these trials.

B. Conditions for Qualified Use

1. *Assay*

   An analytically validated assay should be used for measurement of plasma fibrinogen. (Please see supporting documentation for details at Biomarker Qualification Program: Qualified Biomarkers and Supporting Information.)

2. *Plasma Fibrinogen-Based Patient Selection in Clinical Trials*

   a. PLASMA FIBRINOGEN LEVEL

      The plasma fibrinogen level of patients selected for clinical trials should be determined at baseline.

   b. PATIENT POPULATION

      Patients should have a clinical history of COPD as defined by the American Thoracic Society/European Respiratory Society (ATS/ERS)

standards[1] prior to enrollment, which involves a history of cigarette smoking 10 pack-years or greater and obstructive lung physiology consistent with an increased risk for exacerbations and/or all-cause mortality (i.e., Global Initiative for Chronic Obstructive Lung Disease (GOLD Stage II or higher). Patients enrolled in COPD exacerbation trials should also have a prior history of COPD exacerbations in the year prior to enrollment in the clinical trial.

c. PATIENT SELECTION

Plasma fibrinogen can be used as an enrichment factor, in addition to standard inclusion/exclusion criteria, in COPD clinical trials with endpoints of COPD exacerbation and/or all-cause mortality.

Because fibrinogen was qualified using multiple assays, an optimal enrichment threshold has not been determined. Therefore, a drug sponsor should propose an appropriate threshold for a baseline plasma fibrinogen level and discuss it with FDA during the protocol development phase. (Please see supporting information for details at Biomarker Qualification Program: Qualified Biomarkers and Supporting Information.)

d. MEASUREMENT APPLICABILITY

Fibrinogen was qualified primarily based on the Evaluation of COPD Longitudinally to Identify Predictive Surrogate End-points (ECLIPSE) study data that used an immunological assay that measured a range of fibrinogen concentrations between 100-900 milligrams/deciliter. Any analytically validated method can be used to measure fibrinogen. (Please see supporting information for details at Biomarker Qualification Program: Qualified Biomarkers and Supporting Information.)

e. SAMPLE ACQUISITION AND DOCUMENTATION

Please follow the Clinical and Laboratory Standards Institute (CLSI) H21-A5 recommendations[2] for specimen collection, transport, and processing.

[1] ATS/ERS, 2004, Standards for the Diagnosis and Management of Patients with COPD, available on the Internet at https://www.thoracic.org/copd-guidelines/resources/copddoc.pdf.

[2] CLSI, 2008, Collection, Transport, and Processing of Blood Specimens for Testing Plasma-Based Coagulation Assays and Molecular Hemostasis Assays; Approved Guideline—Fifth Edition, H21-A5, 28(5).