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Draft qualification opinion on plasma fibrinogen as a prognostic biomarker (drug development tool) for all-cause mortality and COPD exacerbations in COPD subjects

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Introduction

The COPD Foundation, COPD Biomarker Qualification Consortium (CBQC) has presented the background information, proposed contexts of use, and data analyses to support their proposal for the qualification of plasma fibrinogen as a drug development tool (prognostic biomarker) to identify COPD subjects at high risk for all-cause mortality or COPD exacerbations for inclusion in interventional clinical trials. The intent is to enable trials which utilize these important endpoints to be conducted more efficiently (reduced subject numbers, reduced study costs) by study sponsors with improved confidence in the study outcomes.

Background of development and intended context of use

Rationale for Biomarkers in COPD

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive lung disease that is thought to result from persistent inflammation resulting in damage to and destruction of the conducting airways and lung parenchyma. In Europe, as well as throughout the world, COPD is a major public health concern and is a leading cause of mortality and morbidity, significantly impacting healthcare resources. COPD is now the third leading cause of death in the United States.[3]

Patients with COPD generally present with highly heterogeneous measures of disease severity and disease activity.[4,5] The progressive decline in lung function in patients with COPD is associated with significant morbidity and mortality. Approved medical treatments for COPD are targeted primarily to the relief of respiratory symptoms and the prevention and reduction of COPD exacerbations. Reductions in the number or severity of exacerbations or an impact on mortality are both of high interest for organizations developing novel candidate COPD therapies. However, the efficient use of these important clinical endpoints can present a number of challenges. For studies that specify exacerbations and/or mortality as key outcomes, it is important that the study population be composed of subjects who are likely to have the event(s) of interest during the duration of the trial. Currently, selection of subjects for inclusion in such studies relies primarily on clinical characteristics (e.g., subjects with respiratory symptoms and/or a prior history of COPD exacerbations), yet in most clinical trials of COPD patients, there is evidence that 50%–60% of enrolled subjects will not experience a COPD exacerbation over the course of a typical 6–12 month exacerbation trial. As a result, outcome studies have required very large sample sizes or prolonged durations to ensure that a sufficient number of events occur over the course of a study to provide appropriate statistical power which will allow a proper assessment of the efficacy of the intervention. Additional patient characteristics which will help to optimize the enrollment of subjects will increase clinical trial efficiency and reduce the costs of COPD clinical trials, by reducing the number of subjects needed and the study duration whilst minimizing exposure of a relevant patient population to investigational medicines prior to at least some determination of their safety and effectiveness. Most importantly, an enrichment strategy may improve the ability to detect potential clinical benefits earlier in development (i.e., in Phase II studies which typically include fewer study subjects and are of shorter duration than studies that support registration).

Systemic inflammation (as reflected by blood biomarkers such as IL-6, C-reactive protein (CRP), fibrinogen, and leukocytes) has long been considered a hallmark of COPD and is likely associated with many of the pulmonary and extra-pulmonary manifestations of COPD. Moreover, elevated concentrations of biomarkers of systemic inflammation have been found to be associated with poorer clinical outcomes in COPD patients, including COPD exacerbations and mortality.[6-8]

While COPD subjects, on average, consistently have elevated concentrations of circulating biomarkers of inflammation, it is becoming apparent from studies with large subject numbers that not all COPD subjects present with evidence of systemic inflammation.[9] Though additional data are needed, subjects with persistent measures of systemic inflammation may constitute a distinct COPD subgroup or phenotype. The use of a biomarker or biomarker(s) that reflects systemic inflammation may improve the identification of subjects more likely to experience COPD exacerbations or those who have a higher mortality risk.

Of the various biomarkers that are available to assess systemic inflammation, plasma fibrinogen appears to be one of the most suitable. The reasons for this include: (1) well defined protocols for sample collection and processing, (2) well established, standardized, controlled, reproducible, and widely available testing methods for determining plasma fibrinogen concentration in most clinical laboratories, (3) relative stability and reproducibility of plasma fibrinogen concentration in stable disease, and (4) evidence from numerous prospective and retrospective studies demonstrating associations between elevated plasma fibrinogen and adverse clinical outcomes in COPD (i.e., COPD exacerbations, COPD-related hospitalizations, and mortality).

Proposed Biomarker

Fibrinogen is a soluble glycoprotein (MW ~ 340,000). The complete fibrinogen molecule is a hexamer composed of three distinct polypeptide chains that are inter-linked by disulphide bonds. Fibrinogen is primarily synthesized in the liver by hepatocytes. Circulating fibrinogen is a major protein component of blood (the major circulating coagulation protein by mass) and the primary determinant of blood viscosity, and is a key component of the coagulation cascade (thrombin-mediated conversion of fibrinogen to fibrin). The half-life of plasma fibrinogen is approximately 3–5 days. Fibrinogen is also a major acute-phase reactant, its synthesis being significantly up-regulated in response to inflammatory mediators, with IL-6 being an important cytokine influencing fibrinogen production by the liver. As a result of up-regulation by inflammatory mediators, elevated concentrations of plasma fibrinogen are observed in subjects with several chronic diseases that have inflammation as an underlying component. These include cardiovascular disease, rheumatoid arthritis, diabetes, and COPD. In addition to disease status, several demographic characteristics can influence plasma fibrinogen concentration including age, gender, smoking status, body mass index (BMI), and physical activity.[10] Several marketed and investigational pharmaceutical agents have been reported to influence plasma fibrinogen concentration. For most of these molecules, the mechanism by which they increase or decrease plasma fibrinogen is unclear, as is the impact of alteration of fibrinogen on efficacy or safety.

If qualified as a drug development tool, the use of plasma fibrinogen should not be difficult. Standardized methods for measurement, along with appropriate quality control processes to ensure both short-term and long-term reproducibility, are well established in most clinical testing laboratories. Plasma fibrinogen is often measured, or can be easily incorporated in the panel of clinical laboratory procedures typically used to evaluate and screen subjects for eligibility to participate in a clinical trial. Thus, assessment of plasma fibrinogen should not impose any significant additional burden on subjects or clinical staff during the conduct of a clinical trial.

Context of Use

The Applicant proposes that plasma fibrinogen, determined at baseline/screening as part of the overall evaluation of a subject's eligibility for a clinical trial, is a useful biomarker in a number of settings. A minimum plasma fibrinogen threshold of 350 mg/dL (3.5 mg/L) is recommended for both the all-cause mortality and COPD exacerbation contexts of use. This threshold is recommended because it provides a balance between the screening effort required to identify subjects with a high plasma fibrinogen

concentration versus enrichment with subjects more likely to experience the clinical event of interest and the statistical power needed to demonstrate a significant treatment effect over the duration of an interventional clinical trial.

The CHMP considers that three contexts of use should be considered separately, based on the data submitted and the outcomes used in clinical trials in COPD. These are all-cause mortality, hospitalization due to COPD exacerbation and moderate and severe COPD exacerbations.

Methodology

The CBQC has created an integrated database at the subject level comprised of five individual studies, based on pre-defined criteria. All variables included in the integrated database have been coded into a common format according to Study Data Tabulation Model (SDTM) guidelines to allow the database to support integrated analyses pooled at the subject level.

Studies Included in Integrated Data Set

2) *To support the qualification of plasma fibrinogen as a drug development tool for two contexts of use, the CBQC Plasma Fibrinogen Working Group has included five studies in the integrated dataset. These studies are:*

- The National Health and Nutrition Examination Survey III (NHANES III) was conducted from 1988 to 1994 by the National Center for Health Statistics of the United States Centers for Disease Control and Prevention (NCHS 1996). NHANES III is a general population-based study and is a representative sample of the United States (US) civilian population. Plasma fibrinogen concentration and spirometry (pre-bronchodilator) data are available from 8,342 adults aged 40 years and above.
- Framingham Heart Study Offspring Cohort (FHSOC) was initiated in 1971. Over the ensuing decades, several follow-up examinations were conducted. The cohort initially consisted of 5,124 subjects (all subjects were offspring or spouses of offspring of participants in the original FHS). Plasma fibrinogen and pre-bronchodilator spirometry were collected beginning with evaluation visit 5 of the Offspring Cohort study with follow-up hospitalization and vital status information available for a 25-year period.
- Cardiovascular Health Study (CHS) a general population-based study of US participants aged 65 years and older. The study was initiated in 1988. The original CHS cohort comprised 5,201 subjects recruited from four communities: Forsyth County, NC; Pittsburgh, PA, Sacramento County, CA; and Washington County, MD. Plasma fibrinogen and spirometry (non-bronchodilator) were assessed at the baseline visit.
- Atherosclerosis Risk in Communities Study (ARIC) a US general population-based study begun in 1987. The study recruited 15,792 participants in four communities: Forsyth County, NC; Minneapolis, MN; Washington County, MD; and Jackson, MS. Plasma fibrinogen and spirometry (non-bronchodilator) were collected at baseline.
- Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) is a 3-year prospective, observational study conducted in 46 sites in 12 countries. Patients were recruited during the period December 2005 through December 2006 and were followed for 3 years, with assessments at 6-month intervals. The ECLIPSE cohort included 2,164 COPD subjects with moderate to very severe airflow limitation (GOLD stages II, III, and IV) along with smoking and non-smoking control groups. Only the COPD subjects will be included in the

analysis for this submission. Plasma fibrinogen was measured at baseline and longitudinally during the 3 years of ECLIPSE.

Key Measures in the Data Set

1. Definition of COPD

COPD typically has been defined based upon spirometric determination of lung function. Post-bronchodilator spirometry provides the most rigorous definition, which lead the 2011 global initiative on Chronic Obstructive Lung Disease (GOLD) guidelines to recommend, "Spirometry is required to make the diagnosis [of COPD] in this clinical context; the presence of a post-bronchodilator $FEV_1/FVC < 0.70$ confirms the presence of persistent airflow limitation and thus of COPD" (GOLD, 2013). For the NHANES III, CHS, ARIC, Framingham Offspring Cohort studies, spirometry measurements were obtained without the use of a bronchodilator. In the ECLIPSE study both pre- and post-bronchodilator spirometry was obtained. The Applicant argues that pre-bronchodilator lung function will be an adequate measure of lung function impairment for looking at the relationship between plasma fibrinogen concentration and clinical outcomes, based on a comparison of pre- and post-bronchodilator spirometry data from the ECLIPSE and COPDGene studies. The results indicate that for COPD subjects included in ECLIPSE and COPDGene, pre-bronchodilator spirometry, when compared with post-bronchodilator spirometry, can accurately identify COPD subjects.

2. Definition of Clinical Outcomes

An important consideration for the proposed contexts of use is the definition of clinical events used for the analyses. For the mortality endpoint, all-cause mortality was used; for the studies included in the integrated database, cause of death was either not adjudicated or is not available in the integrated dataset. Data on COPD hospitalized exacerbations is available from 3 of the 5 studies (ARIC, CHS, ECLIPSE). COPD exacerbations for all studies, with the exception of ECLIPSE, were defined by hospital discharge diagnoses, including ICD codes extracted from hospital records and all other information available from hospital records. For the ECLIPSE study, COPD exacerbation information (non-hospitalized and hospitalized exacerbations) was captured for each reported event during the study. In ECLIPSE, exacerbations were categorized as moderate or severe based on healthcare resource utilization (i.e., a moderate exacerbation was one in which oral corticosteroids and/or antibiotics were prescribed and a severe exacerbation was one in which the subject was hospitalized).

3. Plasma Fibrinogen Determination

An important issue that applies to the use of plasma fibrinogen as a biomarker is potential variability due to factors such as fibrinogen stability within individuals over time, assay type, threshold for defining high fibrinogen, definition of COPD, and definition of COPD outcomes. Analyses described in this submission were conducted to assess the degree of variation present between study samples. When collapsibility could be supported, either directly or through calibration, we have pooled data across studies and populations and presented results adjusted for the effects of covariates when appropriate. Our aim was to provide a statistically robust strategy for analyzing plasma fibrinogen concentration as a biomarker for enriching clinical trial populations.

Several laboratory methods are available for the determination of plasma fibrinogen and these can be classified into two categories: (1) indirect or functional methods that measure "clottable" fibrinogen, and (2) direct methods that quantify the fibrinogen protein. In the five studies used for the integrated database, Clauss-based methods were used in four studies (ARIC, CHS, Framingham Offspring Cohort,

NHANES III), while an immunologic method was used in the ECLIPSE study. The performance criteria available, primarily intra- and inter-assay imprecision indicate that, despite differences in methods, the intra- and inter-assay variability is similar across the methods.

Longitudinal data are required to assess intra-subject variability of plasma fibrinogen concentration over time and to help determine the "stability" of the plasma fibrinogen concentration. Of the studies proposed for inclusion, only the ECLIPSE study has appropriate longitudinal plasma fibrinogen concentration assessments available. In ECLIPSE, plasma fibrinogen concentration was obtained on multiple occasions over the 3 years of the study for a large subset of subjects.

Analysis of Plasma Fibrinogen and Clinical Outcomes

Statistical Analyses to Assess the Relationship between Fibrinogen and COPD Exacerbations

The relationship between plasma fibrinogen concentration, potential covariates, and COPD outcomes was tested in several ways. First, the crude relationship of plasma fibrinogen concentration to the risk of COPD outcomes was tested with a logistic regression model, with the presence of mortality or at least one hospitalized COPD exacerbation as the dependent variable. After the crude relationship between fibrinogen and COPD exacerbations was described, univariate analyses were performed to assess the relationship between covariates and the outcomes of interest. Clinically relevant characteristics that were available in each study were eligible for inclusion in the models. Cox proportional hazards models were used to present the association between fibrinogen and COPD outcomes, after adjustment for the effects of relevant covariates. Kaplan-Meier curves were also used to present the time to COPD outcomes in the integrated dataset and individual studies.

Determination of a Fibrinogen Threshold

As discussed previously, the selection of a threshold requires a trade-off between the added benefit of increased risk of COPD outcomes at higher thresholds and the time and cost required to enroll subjects with high levels of fibrinogen. The analyses described here assess the distribution of fibrinogen among a robust sample of subjects with COPD, as well as the relationship between fibrinogen and COPD outcomes. While the CBQC will recommend a fibrinogen threshold which appears to maximize the benefit of identifying patients at increased risk for outcomes and minimize the cost of enrollment of subjects with higher levels of fibrinogen, institutions may wish to choose a separate fibrinogen threshold based on the data presented here.

Results

Characteristics of Subjects in the COPD Integrated Database

Among the five studies, analyzed baseline COPD populations varied with respect to the reported median age (range: 46.0 years in Framingham Heart Study Offspring Cohort (FHSOC) to 71.5 years in CHS), race (range: 77.6% white in NHANES to 97.7% white in ECLIPSE), and smoking status. In the integrated dataset, 61.6% of COPD subjects were men. Some of the diversity in subject characteristics is attributable to the different study designs, as both NHANES and FHSOC evaluated COPD subjects recruited from the general population, whereas CHS and ARIC focused on subjects with increased cardiovascular risk, and ECLIPSE recruited subjects from specialist centers who conduct clinical intervention studies in COPD. All COPD subjects in the ECLIPSE cohort were either current or former smokers, whereas the percentage of never smokers ranged from 12.8% in ARIC to 23.2% in NHANES.

COPD subjects were similar at baseline with respect to their reported weight (pooled mean: 75.6±16.8kg), height (pooled mean: 169.1±9.2 cm), BMI (pooled mean: 26.5±5.1 kg/m²), and heart

rate (pooled mean 73.1±13.0 BPM) across the five studies. A history of any cardiovascular (CV) comorbidity was common and reported in 70.5% of subjects across the five studies. The frequency of COPD subjects with prior CV comorbidities was highest in the ARIC (79.3%), CHS (94.0%), and FHSOC (77.9%) study populations. However, ARIC and CHS also reported the most CV comorbidities when compared with the other three studies included in this analysis. Hypertension was the most commonly reported CV outcome, with 55% of subjects experiencing this comorbidity, collectively, among the five studies. This was followed in frequency by circulatory problems (15.9%) as reported in the CHS and ECLIPSE studies, as well as self-reported history of a heart attack or myocardial infarction (13.2%), which was reported in every study but FHSOC. COPD was the most commonly reported non-CV condition at baseline with a pooled proportion of 54.1% across the five studies. Nearly the entire population of the ECLIPSE COPD Cohort was diagnosed with COPD at enrollment (99.4%) with the exception of protocol violators. Within ECLIPSE, 47.4% of subjects had experienced a COPD exacerbation. The NHANES program and ARIC study enrolled the lowest proportion of subjects with COPD at baseline, with 27.3% and 28.2% of subjects reporting this comorbidity, respectively. Arthritis was reported in 22.6% of subjects among four of the five trials, with the exception of the ARIC study, which did not capture subject data for this outcome. The pooled percentage of subjects reporting arthritis across studies is largely influenced by CHS, where 63.3% of COPD subjects reported this comorbidity at baseline, compared to NHANES, FHSOC, and ECLIPSE where less than 31.5% of subjects had a history of arthritis. The proportion of subjects with diabetes across the five studies was 16.3% (range: 11% in ECLIPSE and NHANES to 25.2% in ARIC). Over half (59.3%) of the subjects in the integrated dataset reported a history of any pulmonary or chest respiratory illness other than COPD at baseline. Of these, asthma and bronchitis were most commonly reported with 27.1% and 28.0% of subjects in the integrated dataset reporting these comorbidities at baseline, respectively.

The pooled mean baseline fibrinogen level was 351.7 ±89.3 mg/dL (n=6,376) among COPD subjects included in the integrated dataset. Among the individual studies, subjects in ECLIPSE reported the highest mean fibrinogen level of 397.3±91.9 mg/dL (after adjustment of -13.6% to account for the use of EDTA plasma instead of citrate plasma), while the study population from ARIC had the lowest mean fibrinogen at a level of 322.2±74.3 mg/dL. Less than 10% of subjects in the integrated dataset had a baseline fibrinogen level <250 mg/dL, while approximately 25% had a baseline fibrinogen level of ≥400 mg/dL.

The ratio of FEV_1/FVC ranged from 44.2±11.1, as reported in ECLIPSE to high of 60.9±9.1 recorded in FHSOC subjects. The pooled mean of FEV_1/FVC was 53.7±12.2 across the five studies. The mean FEV_1 % predicted at baseline was lowest in ECLIPSE (43.8%) and highest among COPD subjects in ARIC (63.8%).

Hospitalized exacerbations occurring within 12 months were reported for ARIC, CHS, and ECLIPSE with 10.5% subjects reporting this outcome within 12 months among the three studies. The proportion of subjects with hospitalized exacerbations within 12 months was highest in CHS (18.3%) and lowest in ARIC (5.4%). The pooled mortality rate within 36 months was 9.2% across the five studies. NHANES reported the highest percentage of subjects who died (14.1%) while the lowest mortality was observed in ARIC (4.8%).

Time to First COPD Exacerbation (Kaplan-Meier Curves)

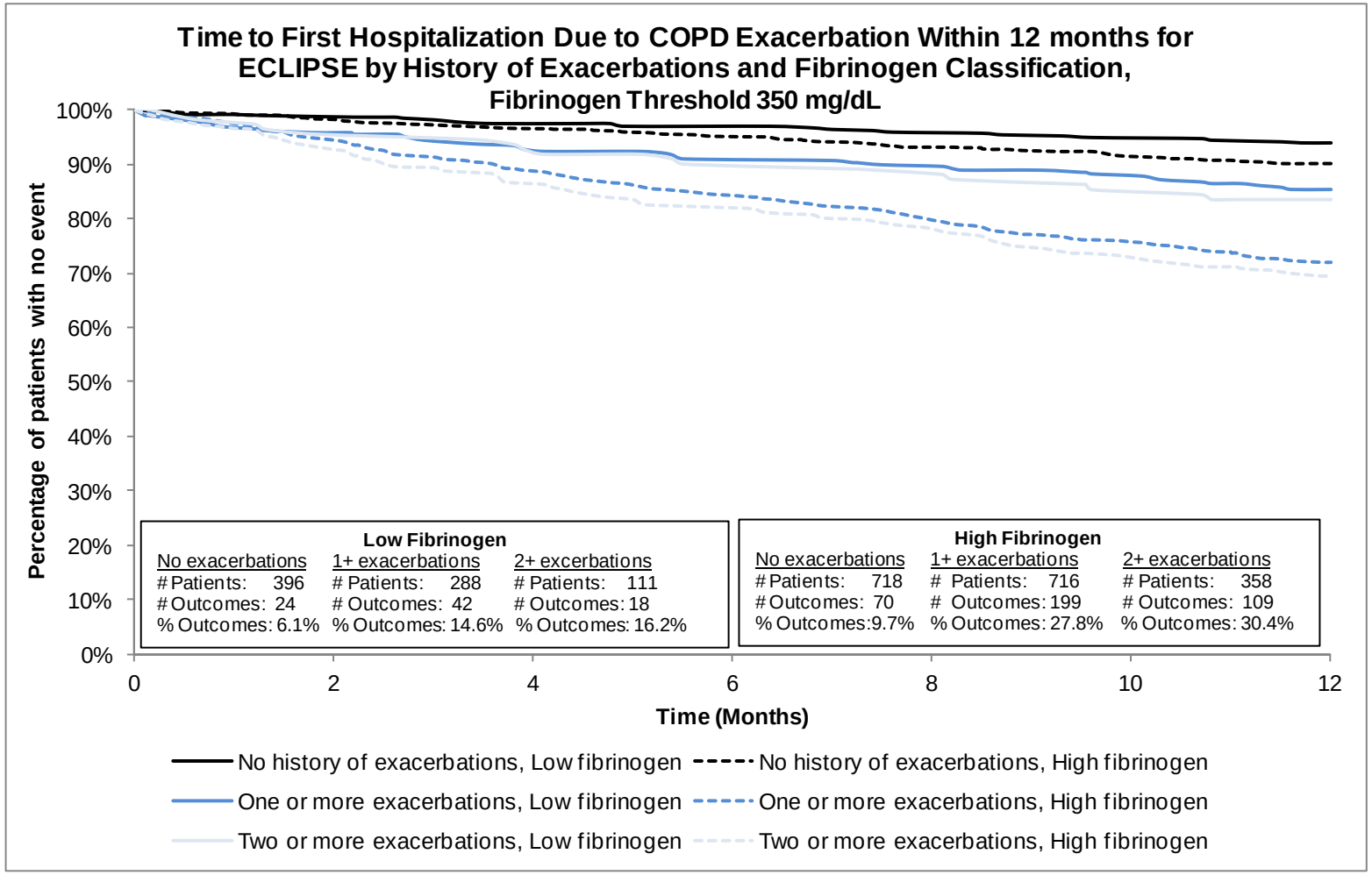
Kaplan-Meier curves are used to present the time to first hospitalized exacerbation within 12 months in ARIC, CHS, ECLIPSE, and in the integrated dataset of all three studies for each fibrinogen threshold

assessed, as well as time to first COPD exacerbation (including both moderate and hospitalized exacerbations) in ECLIPSE.

At a threshold of 350 mg/dL, 9.5% (266/2,807) of subjects with low fibrinogen in ARIC, CHS, and ECLIPSE had a hospitalized exacerbation within 12 months, compared to 16.8% (401/2,392) subjects with high fibrinogen. The percentage of subjects with high fibrinogen who experienced a hospitalized exacerbation exceeded that of those with low fibrinogen in each study assessed.

Figure 1 shows the percentage of subjects with one or more prior exacerbations and high fibrinogen who experienced a hospitalized exacerbation within 12 months (27.8%) was nearly double that of those with one or more prior exacerbations and low fibrinogen (14.6%). Among ECLIPSE subjects with high fibrinogen and a history of two or more exacerbations, 30.4% had a hospitalized exacerbation within 12 months.

Figure 1


Time to First Hospitalization Due to COPD Exacerbation Within 12 months for ECLIPSE by History of Exacerbations and Fibrinogen Classification, Fibrinogen Threshold 350 mg/dL
Percentage of patients with no event
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
2
4
6
8
10
12
Time (Months)
Low Fibrinogen
No exacerbations
Patients: 396
Outcomes: 24
% Outcomes: 6.1%
1+ exacerbations
Patients: 288
Outcomes: 42
% Outcomes: 14.6%
2+ excerbations
Patients: 111
Outcomes: 18
% Outcomes: 16.2%
High Fibrinogen
No exacerbations
Patients: 718
Outcomes: 70
% Outcomes: 9.7%
1+ exacerbations
Patients: 716
Outcomes: 199
% Outcomes: 27.8%
2+ exacerbations
Patients: 358
Outcomes: 109
% Outcomes: 30.4%
No history of exacerbations, Low fibrinogen
No history of exacerbations, High fibrinogen
One or more exacerbations, Low fibrinogen
One or more exacerbations, High fibrinogen
Two or more exacerbations, Low fibrinogen
Two or more exacerbations, High fibrinogen

Cox Models for subjects with Hospitalized COPD Exacerbation within 12 Months

A Cox proportional hazards model, at the 350 mg/dL and 400 mg/dL thresholds, assessed the risk of hospitalized COPD exacerbations within 12 months among subjects with high vs. low fibrinogen. In general, the risk of having a hospitalized exacerbation increased among subjects with high fibrinogen as the threshold increased from 250–400 mg/dL. Using a threshold of 250 mg/dL, COPD subjects in ARIC, CHS, and ECLIPSE with high fibrinogen appeared to be at higher risk of experiencing an outcome (adjusted hazard ratio [HR]: 1.41), but this difference was not statistically significant (95% confidence interval [CI]: 0.97–2.05). No covariates were found to be statistically significant in the model of subjects in the integrated dataset.

With a threshold of 300 mg/dL, COPD subjects with high fibrinogen in ARIC, CHS, and ECLIPSE were at an increased risk of experiencing a hospitalized COPD exacerbation within 12 months (HR: 1.49; 95% CI: 1.21–1.82). No statistically significant covariates were identified in the multivariate model of the integrated dataset. ECLIPSE subjects with a history of COPD exacerbations and high fibrinogen were also at increased risk of future hospitalized exacerbations within 12 months, although this association was not observed among ECLIPSE subjects with no prior history of exacerbations and high fibrinogen.

Using a threshold of 350 mg/dL, high fibrinogen was again found to be associated with an increased risk of hospitalized COPD exacerbations within 12 months (HR: 1.64; 95% CI: 1.39–1.93) among the total population of COPD subjects in ARIC, CHS, and ECLIPSE. No covariates were found to be statistically significant in the model of the total dataset.

The strongest association between high fibrinogen and hospitalized exacerbations within 12 months was observed among subjects in ARIC, CHS, and ECLIPSE when using a threshold of 400 mg/dL (HR: 1.81; 95% CI: 1.54–2.14). As seen in prior models, no statistically significant covariates remained in the model using the total dataset.

Association of Fibrinogen and Any Exacerbation

In ECLIPSE subjects without a history of exacerbations, using a threshold of 350 mg/dL, 41.4% of subjects with low fibrinogen (164/396) had any exacerbation (moderate or hospitalized exacerbations) within 12 months, compared to 48.3% (347/718) with high fibrinogen. ECLIPSE subjects with a history of one or more COPD exacerbations and high fibrinogen were at similar risk for another exacerbation of any type within 12 months when compared to subjects with a history of exacerbations and low fibrinogen (75.6% vs. 70.5%). Kaplan-Meier curves reporting time to exacerbation are presented in Figure 2.

Association of Fibrinogen and All-cause Mortality

Using a threshold of 350 mg/dL, high fibrinogen was again found to be associated with an increased risk of death within 36 months (HR: 1.94; 95% CI: 1.62–2.31) among the total sample of subjects from ARIC, CHS, ECLIPSE, FHSOC, and NHANES. As seen at lower fibrinogen threshold, increased age was associated with an increased risk of death (HR: 1.07; 95% CI: 1.06–1.08), while increases in FEV_1 at baseline (HR: 0.66; 95% CI: 0.56–0.78) were found to be associated with a lower risk of death. Interestingly, results stratified by COPD exacerbation history indicate a similar mortality risk in ECLIPSE subjects with no history of COPD exacerbations (HR: 1.67; 95% CI: 1.04–2. 68) compared to the total ECLIPSE study population (HR: 1.49; 95% CI: 1.07–2.08). However, at a threshold of 400 mg/dL, analysis results stratified by COPD exacerbation history indicate a higher mortality risk in ECLIPSE subjects with one or more prior exacerbations (HR: 1.60; 95% CI: 1.08–2.37).

To assess the effect of fibrinogen thresholds on the sample size of COPD subjects who would need to be enrolled in a clinical trial assessing exacerbations or mortality, power analyses were conducted for each fibrinogen threshold examined.

In general, the sample size needed to achieve a power of 0.8 decreased as the fibrinogen threshold was increased from 250 mg/dL to 400 mg/dL based on the number of hospitalized exacerbations observed in the integrated dataset in 12 months. For example, at a hazard ratio of 0.6, a sample size of 962 subjects would be required in each study arm using a threshold of 250 mg/dL, compared to 632 subjects when using a threshold of 400 mg/dL, a 34.3% decrease (Table 1). Larger sample sizes would be required for hazard ratios of 0.7 or higher. When restricted to subjects with a history of exacerbations (based on estimates from ECLIPSE), the sample size of a study arm decreased only modestly from 152 subjects using a threshold of 250 mg/dL, to 144 subjects using a threshold of 400 mg/dL (Table 2).

Similar trends were observed for power analyses of a hypothetical clinical trial designed to assess mortality among COPD subjects within 3 years. Again, the sample size needed to achieve a power of 0.8 decreased as the fibrinogen threshold was increased from 250 mg/dL to 400 mg/dL, based on the number of deaths observed in the integrated dataset in a 3-year period. At a hazard ratio of 0.6, a sample size of 2,162 subjects would be required in each study arm using a threshold of 250 mg/dL, compared to 1,318 subjects using a threshold of 400 mg/dL (a 39.0% decrease).

CHMP Assessment of Data

Background and Methods

The submission does not discuss any *in vivo* models or *in vitro* data in support of the scientific rationale and does not propose a mechanistic basis for a relationship between fibrinogen and COPD. A cursory literature search identified a number of biomarker discovery publications in COPD-relevant animal models where fibrinogen was identified, and a number of studies investigated potential mechanistic links between COPD pathophysiology and fibrinogen production. There is significant discussion in the literature around differential modulation of serum fibrinogen after steroid treatment in COPD patients with acute exacerbations compared to stable COPD. Nonetheless, we can agree that there is sufficient epidemiological data to pursue fibrinogen as a potential biomarker in COPD.

We support the inclusion of the five studies in the database. We can also agree that while the definition of COPD is not in keeping with current standards in 4 out of 5 studies, it is unlikely to lead to erroneous conclusions in the current context. However, several concerns regarding the sourcing and accuracy of laboratory and clinical data, have been identified. The determination of a hospitalized exacerbation in the ARIC and CHS studies used ICD-9 codes (490, 491, 492 and 496) and other sources. SAWP noted that for the ARIC and CHS studies, only 25% of the diagnoses were made based on ICD9 codes. However, many of these codes are not specific for COPD exacerbation but rather capture a diagnosis of bronchitis, chronic bronchitis or emphysema. In addition, ICD coding of hospital admissions for COPD are often inaccurate. In one study, discharge summaries were reviewed for errors in coding for COPD admissions and the recoding led to a change in the primary diagnosis in 16% of the patient stays and an additional secondary diagnosis in 18% of hospital stays. (International Classification of Disease Coding for Obstructive Lung Disease: Does It Reflect Appropriate Clinical Documentation? Philip Marcus,Sidney S. Braman, Chest. 2010;138(1):188-192. Further detail on the accuracy of the diagnosis of COPD exacerbation events was requested. Per the SAWP request, the CBQC reviewed the data that was used to construct the integrated database. For ARIC and CHS, the categorization of hospitalizations was obtained from a combination of ICD hospital discharge codes and follow-up interviews with study subjects. While they acknowledged the existence of some uncertainty

regarding the accuracy of the event categorization (which is always the case to some extent when using ICD codes or subject interviews), when analyzed separately each of the individual studies yields similar results, i.e. plasma fibrinogen provides additional value as a prognostic factor for COPD exacerbations and all-cause mortality even after adjustment for identified covariates. The CBQC does acknowledge, as discussed at the February 10 CBQC/SAWP meeting, that the ECLIPSE study is the only one in the integrated database that specifically enrolled COPD subjects with inclusion criteria similar to those that would be used for an intervention clinical trial (along with the use of a definition of exacerbations that is typically used in clinical trials).

Regarding the measurement of the biomarker, in the five studies used for the integrated database, Clauss-based methods were used to measure fibrinogen in four studies (ARIC, CHS, Framingham Offspring Cohort, NHANES III), while an immunologic method was used in the ECLIPSE study. Further detail on the methods and validity of assays, the comparability of results obtained with the Clauss/modified-Clauss and the immunologic assays and the relevance of cut-off values to clinical practice was requested. In response to the request, further method details were provided; while some data has been provided to demonstrate that the assays used are controlled within the context of each study, insufficient information has been provided to support that the assays used in the studies have been appropriately validated (linearity, accuracy etc.). It is confirmed that within each study, a single testing laboratory carried out the assays however, there is no comment on the cross validation of the methods used between the different studies (when it is intended to pool data). Furthermore, it has not been confirmed that the reference standards used across the studies were qualified against an international reference standard. In the absence of a clear demonstration of comparability of results obtained using the different methods/reference standards, the pooling of data from the different studies could be questioned. The information provided in relation to a comparison of Clauss and immunologic methods is unclear; there is no confirmation that this information relates to the exact methods used in the actual studies relevant to this procedure, rather the information appears to relate generally to various Clauss methods. Furthermore, while there seems to be a correlation between results obtained with the immunosassay and Clauss methods, the applicant does not comment on the differences observed in terms of the absolute value of fibrinogen measured or how this could impact on the pooling of datasets across methods. The correction factor applied during the immunological assay relates to the use of EDTA vs Citrate plasma and is not a correction factor applied in relation to the use of different assays; immunoassay vs Clauss.

Results

There was considerable heterogeneity in baseline characteristics in the five studies which could confound results as the higher baseline age in CHS is associated with higher mortality in that study. Similarly, the higher baseline FEV1 in ARIC may explain the lower mortality rate seen in this study. The proportion of never-smokers in some of the studies was 20% or higher which would be unusual for a COPD trial population and begs the question if some of these subjects have asthma rather than COPD.

On the raw data, there appears to be an association between higher fibrinogen levels and the outcomes of interest, COPD exacerbations and mortality. For the exacerbation endpoints, it is possible to explore the additional risk that fibrinogen confers when factoring for a history of prior exacerbations. There seems to be a definite association between high fibrinogen and hospitalized exacerbations, regardless of fibrinogen threshold. Within the ECLIPSE data, it appears to be present even after factoring for prior history of exacerbations, a known risk factor for further exacerbations (Figure 1 of briefing package). There does not seem to be a strong association between all exacerbations

(moderate and severe) and high fibrinogen, regardless of prior history of exacerbation or not (Figure 2 of briefing package). The key factor influencing risk of an exacerbation in this dataset appears to be a prior history of an exacerbation.

The degree to which these associations are due to the severity of COPD was of interest to CHMP. The CBQC conducted analyses of the individual studies and the integrated dataset to generate Kaplan-Meier curves to show the relationship of each GOLD stage with all exacerbations within the first 12 months of follow up, hospitalized exacerbations within the first 12 months of follow up, and all-cause mortality within 36 months of follow up. The Kaplan-Meier plots, univariate, and multivariate models show an association between GOLD stage and the outcomes of interest, as expected.

When analyses are done to estimate how these findings would translate into sample sizes for clinical trials, reductions in sample size seem substantial when based on three studies which provided data on (Table 1) hospitalized exacerbations but only a modest decrease in sample size is required from 296 to 284 at 0.7 HR when using all exacerbations from the ECLIPSE data (Table 2). The patient selection in this study is probably more in line with that currently is use in clinical trial design in COPD where a prior history of at least one exacerbation in the previous year would usually be an inclusion criterion. Furthermore, the assumptions used to calculate the sample sizes may not be correct and other scenarios could influence the outcome.

With regard to the association between baseline fibrinogen and all-cause mortality, using a threshold of 350 mg/dL, high fibrinogen was found to be associated with an increased risk of death within 36 months (HR: 1.94; 95% CI: 1.62–2.31) among the total sample of subjects from ARIC, CHS, ECLIPSE, FHSOC, and NHANES, with HRs ranging from 1.07 to 3.82 across the individual studies (figure 3). How much of this is due to increased CV mortality associated with high CV morbidity is not clear. In particular, 2 of the large studies recruited subjects with high CV risk and therefore higher mortality in the high fibrinogen groups would be expected, based on CV association alone. The SAWP was interested in assessing how much of the mortality noted in the Qualification Package is due to the cardiovascular risk vs. COPD and requested analyses exploring the added risk of fibrinogen when severity of COPD disease is taken into account. CBQC noted that the impact of co-morbidities was an important consideration in the analysis, but the ability to tease out the contribution is difficult. It is important to note that when the analysis plan was developed, potential co-morbidities and co-variates were statistically assessed. Those that had an impact of at least 10% or which were statistically significant were carried through the analysis and used for adjustment of the final hazard ratio models. After the adjustments were made, plasma fibrinogen remained as a significant predictor of exacerbation risk and all-cause mortality.

The SAWP was also interested in assessing the added benefit of including plasma fibrinogen as an enrichment factor in trials with mortality as an endpoint, over and above current enrichment factors based on COPD stage and history of exacerbations. Looking at the ECLIPSE data alone, the percent of ECLIPSE subjects with one or more prior exacerbations and high fibrinogen who died within 36 months (12.4%) was fifty percent larger than that of those with one or more prior exacerbations and low fibrinogen (8.0%), which would seem to indicate that fibrinogen increases the risk independently of exacerbation history.

When analyses are done to estimate how this would translate into sample sizes for clinical trials, reductions in sample size seem substantial when based on the full dataset, with sample size reductions of 30% (table 3). The SAWP requested similar analyses based on the ECLIPSE data alone. This shows that more modest decrease in sample size are expected based on this dataset, 8-14%, depending on whether a prior history of exacerbation was included as a factor or not (table 4).

Qualification Opinion

The evidence from these observational data supports the role of plasma fibrinogen as a prognostic biomarker in COPD. However, the strength of the association is quite modest and confounded by other factors. Furthermore, the pooling of data from several studies which used different fibrinogen assays, the retrospective sourcing of key data and the associated validation issues outlined above pose limitations in terms of interpreting the data and in terms of recommending a specific threshold for use in clinical practice.

The CHMP agrees that, based on the data, an increase in plasma fibrinogen is associated with an increased risk of all-cause mortality and hospitalized exacerbations and this is present, albeit with a weaker association, even after adjusting for confounding variables. From the available dataset, the identified threshold that is considered most useful is 350mg/dl. However, given the difference in assay methods in the different studies in the dataset and the lack of a centralized laboratory to determine plasma fibrinogen levels, the applicant (CQBC) is suitably cautious in their recommendation on the threshold and advise that institutions may wish to choose a separate fibrinogen threshold based on the data presented here. This cautious approach is endorsed. Plasma fibrinogen can be a useful enrichment factor/biomarker in the context of a trial where all-cause mortality or hospitalized exacerbation is an outcome of interest, since it is estimated that sample size reductions of 8-30%, depending on whether the ECLIPSE or full dataset is used, could be anticipated.

While it is agreed that plasma fibrinogen is a reasonable additional selection criterion to enrich the study population for demonstrating an effect on all-cause mortality or hospitalized exacerbations, the extrapolation of results demonstrated in this enriched population to the wider COPD population would have to be addressed. From a regulatory perspective, a clinical development solely in an enriched population might only support a claim for an indication in that restricted population. The magnitude of the benefit in that select population may be different to that in an unselected population resulting in a different risk/benefit profile. In addition, if elevated plasma fibrinogen is a predictor of response to a particular agent, the effects seen in the selected population may not be predictive of response in a broader COPD setting. While the evidence on the association of increase in plasma fibrinogen and increased incidence of severe exacerbations is reasonably clear, the quantitative estimation of the 'increased incidence' for a given threshold cannot be considered to be equally robust due to the potential difference in standards of treatment across the supporting data set. Therefore it is recommended that the sample size estimation using these data should use a conservative approach.

The CHMP also agrees that, based on the ECLIPSE data, an increase in plasma fibrinogen is associated with an increased risk of moderate and severe exacerbations. However, there is insufficient evidence to qualify it as a prognostic biomarker in the context of a trial where moderate and severe exacerbations is an outcome of interest since the association appears to be linked to severity of disease and history of exacerbations. This may indicate that a particular phenotype of COPD patients with increased inflammatory markers and more frequent exacerbations is selected by the fibrinogen cut-off. The proposed biomarker does not add substantially to the clinical criteria already in use to enrich trial populations as evidenced by the small reduction in sample size estimates using various fibrinogen cut-offs. The implications for more efficient use of resources in terms of ability to conduct smaller studies in a more timely manner through its incorporation into clinical trial design is not very convincing.

When plasma fibrinogen is used as patient selection criteria to enrich the study population, it is recommended that the measurement of plasma fibrinogen at baseline for determining eligibility should be in samples obtained from patients with stable COPD (e.g. no exacerbation or use of systemic

steroids within last 4 weeks). The effects of treatment for COPD on plasma fibrinogen levels and impact on desired outcomes are not known.

Suggestions for further work

The CHMP advises that investigators incorporate thresholds for fibrinogen into clinical trial design to substantiate if and to what extent this prognostic factor determines outcomes of interest, the likelihood for extrapolation from an enriched population to a broader COPD population, what impact it has on recruitment time and screening failures and to what extent it reduces study size in phase II and III development.

Figure 2.

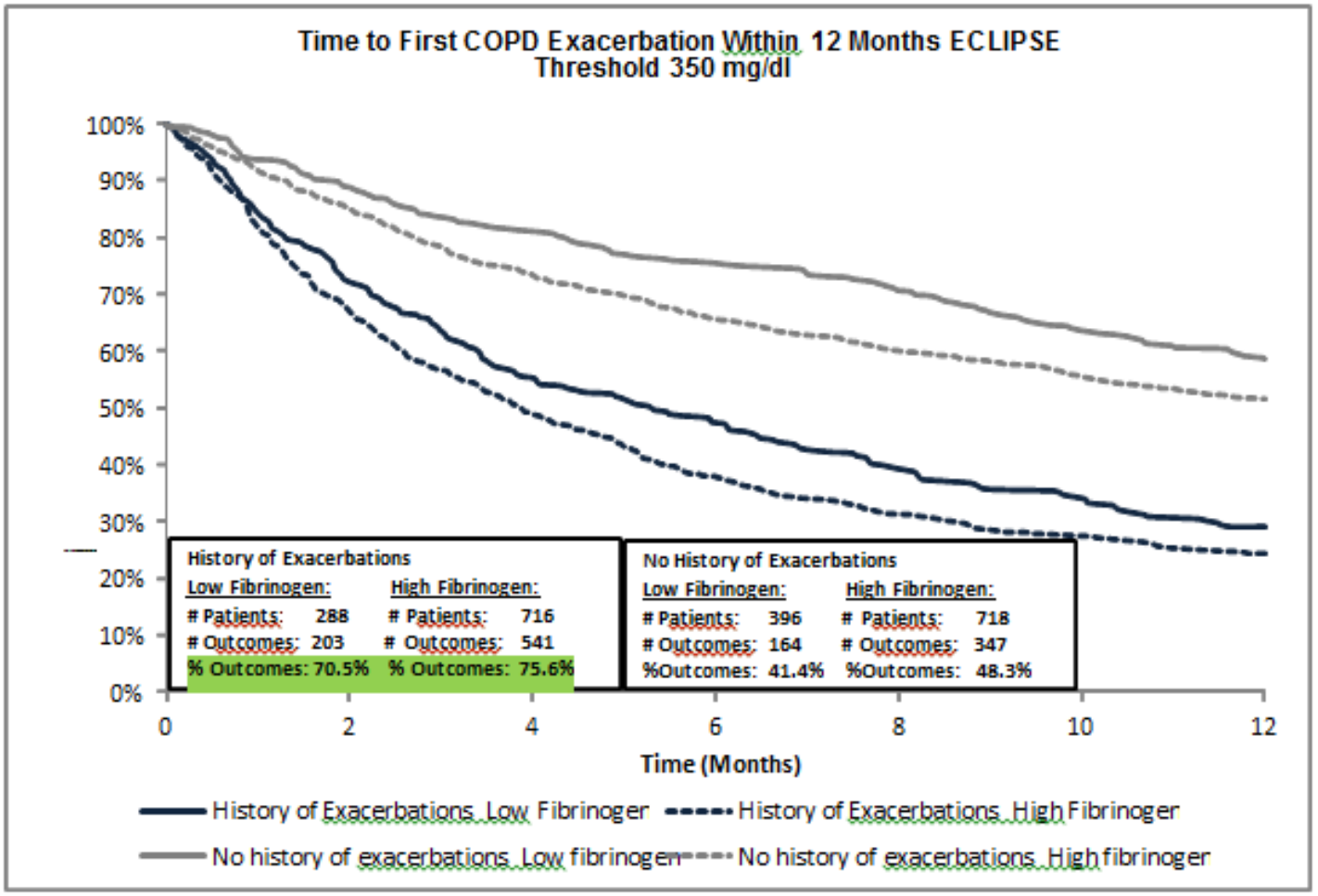

Time to First COPD Exacerbation Within 12 Months ECLIPSE
Threshold 350 mg/dl
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
2
4
6
8
10
12
Time (Months)
History of Exacerbations
Low Fibrinogen:
Patients: 288
Outcomes: 203
% Outcomes: 70.5%
High Fibrinogen:
Patients: 716
Outcomes: 541
% Outcomes: 75.6%
No History of Exacerbations
Low Fibrinogen:
Patients: 396
Outcomes: 164
%Outcomes: 41.4%
High Fibrinogen:
Patients: 718
Outcomes: 347
%Outcomes: 48.3%
History of Exacerbations Low Fibrinoger
History of Exacerbations High Fibrinoger
No history of exacerbations Low fibrinogen
No history of exacerbations High fibrinoger

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Table 1: Sample sizes by fibrinogen level and hazard ratio to achieve a power of 0.8 in a study comparing survival curves for “control” and “treatment” groups based on the number of hospitalized COPD exacerbations over a 12 month time-period

	Total sample size by hazard ratio			
Fibrinogen level	0.60	0.70	0.80	Survival estimates from Cox model (monthly)
> 250	962	1,826	4,366	0.99, 0.98, 0.96, 0.95, 0.94, 0.93, 0.92, 0.91, 0.90, 0.89, 0.88, 0.87
> 300	874	1,658	3,966	0.99, 0.97, 0.96, 0.95, 0.94, 0.92, 0.91, 0.90, 0.89, 0.88, 0.86, 0.85
> 350	750	1,426	3,414	0.99, 0.97, 0.95, 0.94, 0.93, 0.91, 0.90, 0.88, 0.87, 0.86, 0.84, 0.83
> 400	632	1,202	2,880	0.98, 0.96, 0.94, 0.92, 0.91, 0.89, 0.88, 0.86, 0.84, 0.83, 0.81, 0.80

Table 2: Sample sizes by fibrinogen level and hazard ratio to achieve a power of 0.8 in a study comparing survival curves for "control" and "treatment" groups based on the number of exacerbations over a 12 month time-period, among subjects with a history of exacerbations in ECLIPSE

	Total sample size by hazard ratio			
Fibrinogen level	**0.60**	**0.70**	**0.80**	**Survival estimates (monthly)**
> 250	152	296	726	0.83, 0.69, 0.51, 0.51, 0.46, 0.41, 0.37, 0.34, 0.30, 0.29, 0.27, 0.25
> 300	150	294	724	0.83, 0.68, 0.59, 0.51, 0.45, 0.40, 0.36, 0.33, 0.30, 0.29, 0.26, 0.25
> 350	150	292	716	0.83, 0.68, 0.58, 0.50, 0.45, 0.40, 0.36, 0.33, 0.29, 0.28, 0.26, 0.24
> 400	144	284	696	0.82, 0.66, 0.57, 0.48, 0.43, 0.38, 0.34, 0.31, 0.27, 0.26, 0.24, 0.22

Power analysis specifications:

1) Power = 0.8

2) One-tailed log rank test comparing two survival curves with $\square = 0.05$

3) 10% loss to follow-up

4) Equal sample size between groups

Assumptions:

1) Loss to follow-up has an exponential distribution

2) Survival rates for control group equal to estimates obtained from Cox regression models for high fibrinogen classes

3) Estimation of treatment group survival curve based on proportional hazards

Figure 3.

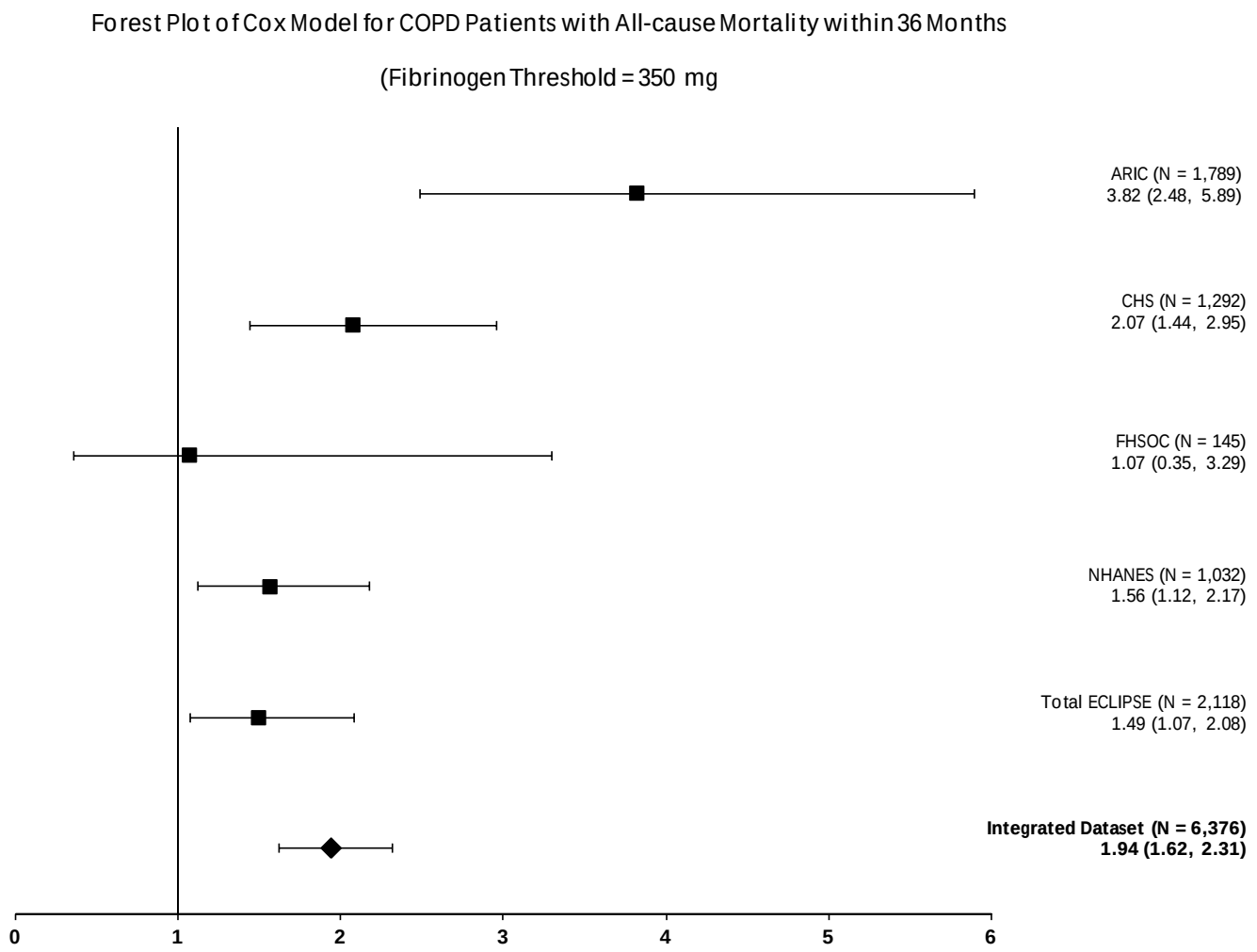
Forest Plot of Cox Model for COPD Patients with All-cause Mortality within 36 Months
(Fibrinogen Threshold = 350 mg
ARIC (N = 1,789)
3.82 (2.48, 5.89)
CHS (N = 1,292)
2.07 (1.44, 2.95)
FHSOC (N = 145)
1.07 (0.35, 3.29)
NHANES (N = 1,032)
1.56 (1.12, 2.17)
Total ECLIPSE (N = 2,118)
1.49 (1.07, 2.08)
Integrated Dataset (N = 6,376)
1.94 (1.62, 2.31)
0
1
2
3
4
5
6

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Table 3: Sample sizes by fibrinogen level and hazard ratio to achieve a power of 0.8 in a study comparing survival curves for “control” and “treatment” groups based on the number of deaths over a 3 year time-period

	Total Sample Size by Hazard Ratio			
Fibrinogen Level	0.60	0.70	0.80	Survival Estimates (every 4 months)
> 250	2,162	4,092	9,768	0.996, 0.989, 0.980, 0.974, 0.966, 0.959, 0.950, 0.941, 0.933
> 300	1,804	3,416	8,156	0.995, 0.986, 0.975, 0.969, 0.958, 0.950, 0.940, 0.929, 0.920
> 350	1,486	2,814	6,724	0.994, 0.983, 0.970, 0.962, 0.949, 0.939, 0.928, 0.915, 0.903
> 400	1,318	2,500	5,974	0.993, 0.981, 0.966, 0.957, 0.943, 0.931, 0.918, 0.904, 0.891

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Table 4: Sample size (95% CI) estimates by plasma fibrinogen concentration thresholds and hazard ratios based on the number of deaths over a 3-year time-period for ECLIPSE subjects by history of exacerbation

Fibrinogen Level	N	N (%) of subjects with mortality within 36 months*	Total Sample Size by Hazard Ratio*			
			HR=0.70	Difference over no threshold, n (%)	HR=0.80	Difference over no threshold, n (%)
Without a history of exacerbation						
No Threshold	1,114	32 (3%)	4,744 (3,836-6,116)		11,398 (9,164-14,956)	
> 250	1,082	30 (3%)	4,862 (3,806-6,364)	+118 (2%)	11,606 (9,094-15,188)	+208 (2%)
> 300	973	28 (3%)	4,888 (3,986-6,512)	+144 (3%)	11,670 (9,520-15,540)	+272 (2%)
> 350	718	27 (4%)	4,090 (3,254-5,384)	-654 (-14%)	9,766 (7,778-12,852)	-1,632 (-14%)
> 400	441	20 (5%)	3,790 (2,906-5,172)	-954 (-20%)	9,052 (6,948-12,344)	-2,346 (-21%)
With history of exacerbation						
No Threshold	1,004	37 (4%)	3,830 (3,024-4,640)		9,146 (7,228-11,078)	
> 250	985	35 (4%)	3,926 (3,206-4,868)	+96 (3%)	9,380 (7,662-11,622)	+234 (3%)
> 300	901	34 (4%)	3,732 (2,948-4,568)	-98 (-3%)	8,916 (7,050-10,908)	-230 (-3%)
> 350	716	28 (4%)	3,536 (2,782-4,414)	-294 (-8%)	8,446 (6,652-10,540)	-700 (-8%)
> 400	488	24 (5%)	3,062 (2,374-3,916)	-768 (-20%)	7,318 (5,684-9,356)	-1,828 (-20%)