Biomarkers Qualification Review for Plasma Fibrinogen

EXECUTIVE SUMMARY

This is a summary of the reviews and recommendations by the members of the Biomarker Qualification Review Team (BQRT) of a submission by the Chronic Obstructive Pulmonary Disease (COPD) Foundation Biomarker Qualification Consortium (CBQC) for the qualification of plasma fibrinogen measured at baseline as a prognostic biomarker along with other subject demographic and clinical characteristics including prior history of COPD exacerbations to enrich clinical trial populations in COPD clinical trials at high risk for exacerbations and/or mortality for inclusion in interventional clinical trials.

a. Background

COPD is the third leading cause of death in the US and the fourth leading cause of death world-wide[1] and is primarily caused by smoking and environmental toxins which cause lung inflammation. These inflammatory changes are not limited to the lung. COPD is a disease characterized by systemic inflammation, and increases in levels for biomarkers such as fibrinogen and C- reactive protein have been suggested to be indicative of the systemic nature of COPD.[2,3]

Fibrinogen is a soluble glycoprotein that is converted to fibrin by thrombin during blood clot formation. Fibrinogen is a major acute-phase reactant and its synthesis is 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 patients with several chronic diseases that have inflammation as an underlying component. Plasma fibrinogen is generally measured using either immunologic assays such as the Kamiya K-assays or functional assays such as the Clauss assays.

The COPD Biomarker Qualification Consortium (CBQC)'s perspective is that up to 50-60% of enrolled subjects in COPD exacerbation trials that typically are 6 to 12 months in duration may not manifest an exacerbation over the course of a trial. Mortality trials are of long duration (≥ 3 years) and to date, many have not been successful. The goal of the CBQC's qualification effort is

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[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] From COPD to chronic systemic inflammatory syndrome? *Lancet* 2007 370: 797-799
[3] Association between chronic obstructive pulmonary disease and systemic inflammation: a systematic review and a meta-analysis. *Thorax (2004)* 59: 574-580

to use plasma fibrinogen to enrich a clinical trial population for subjects likely to have an exacerbation event over the duration of a clinical trial or at greater risk of mortality. The CBQC proposed that using plasma fibrinogen as an enrichment biomarker in exacerbation or mortality trials would have some benefit in drug development with reduction in sample sizes in such trials.

b.   Sources of Data and Major Findings

In support of the use of fibrinogen as prognostic biomarker for COPD exacerbation or mortality, the final submission package from CBQC included study reports and datasets for five studies in the integrated dataset. Referenced literature was also provided. CBQC proposed that the use of an integrated database combining the outcome of five independently conducted studies would demonstrate the robustness of fibrinogen as a biomarker of adverse COPD outcomes across various patient populations and time periods.

The BQRT noted that only one study, the ECLIPSE study, was designed to enroll COPD patients and also was the only study to have collected fibrinogen data prospectively. Among the remaining four studies, one was a general population-based sample survey (NHANES III) and three were cohort studies (ARIC , CHS and Framingham) of the elderly population (45+ years at time of enrollment) in selected communities (e.g., 4 communities for ARIC). Also, the Kamiya K-assay® (k993482), a direct immunologic detection method, was used to measure fibrinogen in the ECLIPSE study whereas the Clauss method, a method for assessment of fibrinogen function, was used in the other studies. It is difficult to compare the fibrinogen data derived by these two types of methods, especially since no bridging studies were conducted to compare the methods. The BQRT decided that these four studies had limited utility in evaluating fibrinogen for the proposed COU and that that ECLIPSE would be the principal study to assess fibrinogen for the proposed COU. In addition, the ECLIPSE study included samples that appear to be similar to the patient population historically used in COPD clinical trials.

The reviewers' analyses showed that higher baseline fibrinogen level is associated with a higher incidence of mortality and exacerbations. These were consistent with CBQC's analyses (details in **section c** below).

c.   Data Considerations

Minor discrepancies were noted in the analysis plan, written results provided and datasets provided. Information requests were made and clarifications received from the submitter. FDA agreed with the submitter that these discrepancies were small and would not significantly

affect the outcome of overall analyses assessing the utility of plasma fibrinogen as a prognostic, enrichment biomarker.

The BQRT deliberated the following considerations associated with the CBQC submission to understand the strengths and limitations of the data:

i. <u>Assay considerations</u>

As noted in **Section b**, two different methods, functional and direct, were used for evaluation of plasma fibrinogen for the proposed COU in the selected clinical studies. Since the technological principles for the two types of assays are different, results generated by these assays could be different. Thus, bridging studies are essential to ensure that the data from two or more studies where different assays have been used are comparable. The absence of bridging studies contributed to the BQRT decision to consider the ECLIPSE study as the principal study to assess fibrinogen for the proposed COU. The BQRT understands that CBQC has collected available data from studies that were not designed for qualification of fibrinogen for the proposed COU.

ii. <u>Threshold considerations</u>

The submitter investigated four different cutoff values at baseline for fibrinogen assessment (250, 300, 350 and 400 mg/dL). The data were analyzed for utility of fibrinogen ("low" category if below threshold value and "high" category, if above threshold value) in subjects with and without a history of COPD exacerbations. The lowest cutoff value, 250 mg/dL, seems to have limited utility with the ECLIPSE dataset, because over 97% of the subjects are in the "high" category regardless of exacerbation history. The utility of the 400 mg/dL cutoff value also seems to be limited with the ECLIPSE dataset, because more than half of subjects would be in the "low" category and would be excluded from inclusion in the clinical trials. Thus, the 300 and 350 mg/dL cutoff values were expected to have more utility than the 250 and 400 ng/dL values, based on the data used to support qualification of fibrinogen as an enrichment biomarker for the proposed COU. The submitter has proposed the use of 350 mg/dL as the cutoff value for fibrinogen levels when used as a prognostic biomarker.

During biomarker development, FDA recommended that the submitter examine whether plasma fibrinogen classification into "low" and "high" fibrinogen in

patients remained sufficiently consistent. The submitter compared the patients' baseline classification with that at 6 months, 1, 2 and 3 years. The classification changed in many patients over time. For example, for a threshold of 350 mg/dL, about 30% to 50% of subjects classified as "high" at baseline were classified as "low" at a subsequent time point and about 15% to 20% of subjects classified as "low" at baseline were classified as "high" at a subsequent time point.

Please note that the Kamiya K-assay® <u>Fibrinogen</u> (k993482) was used in the ECLIPSE study to measure <u>fibrinogen levels and the threshold considerations are limited to this assay</u>. The recommendations of this guidance do not alter the labeling recommendations of the fibrinogen assay for use in the medical care of patients, and cut-off values specified in the device labeling should continue to be used.

iii.   <u>Enrichment considerations</u>

The goal of this submission is to qualify fibrinogen as an enrichment biomarker to identify subjects with COPD at high risk for all-cause mortality or COPD exacerbations for inclusion in interventional clinical trials. The BQRT discussed the data provided to determine if the biomarker could be used as an enrichment biomarker in future COPD clinical trials.

The number and percentage of subjects experiencing an exacerbation within the first 12 months or death within 36 months of the study for the different cutoffs, with or without a history of exacerbations, was examined in the ECLIPSE dataset since, this dataset was the principal dataset used to assess fibrinogen for the proposed COU, as mentioned earlier. Patients who experienced an event generally had higher plasma fibrinogen levels. Cox proportional hazards modeling with the occurrence of at least one COPD exacerbation or mortality as the dependent variable indicated that "high" plasma fibrinogen classification using a threshold of 350 mg/dL or 400 mg/dL is associated with increased risk of a subsequent COPD exacerbation and/or mortality.

- *Enrichment in exacerbations as clinical outcome*

    Kaplan-Meier plots for time to first COPD exacerbation for patients with "high" versus "low" plasma fibrinogen level indicated that the occurrence of the event is sooner and more frequent in patients in the "high" category for all the thresholds examined. It was noted that the increase in the percentage

of patients experiencing an event was very small; for example, a 9.2% increase in time to first hospitalized COPD exacerbation within 12 months was observed in the fibrinogen "high" group with history of exacerbation compared to the fibrinogen "low" group using the submitter-proposed cutoff of 350 mg/dL with the ECLIPSE data. The results were similar in the subjects with and without a history of exacerbation.

- *Enrichment in all-cause mortality as clinical outcome*

  Kaplan-Meier plots for time to death within 36 months for patients with "high" versus "low" plasma fibrinogen levels indicated a higher risk for mortality among patients in the "high" category (as defined above for thresholds of 350 mg/dL and 400 mg/dL) in subgroups of patients categorized by exacerbation history. A 4.4% increase in time to death within 36 months was observed in the fibrinogen "high" group with history of exacerbation compared to the fibrinogen"low' group using the submitter-proposed cutoff of 350 mg/dL with the ECLIPSE data.

iv.   Sample size considerations

Sample size estimates for studies with and without plasma fibrinogen as an enrichment biomarker were compared. These estimates are based on an assumption that the survival rates for the control group would be equal to the survival estimates from the Cox Models fit to the ECLIPSE data. With a requirement for plasma fibrinogen to exceed a threshold of 350 mg/dL, a reduction in the necessary sample size of approximately 12% can be expected for a COPD exacerbation study and 8% for a mortality study. The reader is referred to tables 6 and 7 in the Statistical Review for description of the assumptions used for these sample size calculations.

d.   BQRT Conclusions

Based upon consideration of the strengths and limitations of the data, the BQRT has concluded that the data support qualification of plasma fibrinogen as a reasonable enrichment factor, in addition to standard inclusion/exclusion criteria, to consider in COPD clinical development programs for exacerbation and /or mortality trials with the following considerations:

i.   Since ECLIPSE was considered as the principal study for FDA analyses and this study employed the FDA-cleared Kamiya K-assay® (k993482), the BQRT

considered the thresholds used by the submitter to determine "high" vs "low" fibrinogen levels in the ECLIPSE data. The proposed threshold of 350 mg/dL for enriching clinical trials for COPD subjects at high risk for a COPD exacerbation(s) as well as for subjects more likely to experience all-cause mortality during a COPD clinical trial appears reasonable; however, the BQRT recognizes that there could be clinical situations where a different fibrinogen cutoff may be more appropriate with this assay.

ii.   Multiple <u>fibrinogen</u> assays were used in the studies and optimal enrichment thresholds for the different fibrinogen assays used have not been determined. Therefore, for trials with COPD exacerbations as the primary endpoint, a threshold value for plasma <u>fibrinogen</u> should be discussed with the FDA. Depending on the objective, i.e. enrichment of COPD subjects at high risk for exacerbations or all-cause mortality, the selection of the appropriate threshold to define "high" or "low" level of <u>fibrinogen </u>should be proposed by the drug sponsor and discussed with the agency during the protocol development phase<u>.</u>

e.   **BQRT Recommendations**

Based upon consideration of the strengths and limitations of the data, the BQRT has concluded that the data support qualification of plasma fibrinogen as a reasonable inclusion criterion to consider in COPD clinical development programs for exacerbations and/or mortality trials. Further, as a prognostic biomarker used to enrich the patient population in a clinical trial, the use of fibrinogen in this context does not mean that COPD patients with a "low" fibrinogen level who are otherwise at risk for experiencing the event (i.e. patients with a history of exacerbations) would not benefit from the therapeutic intervention that was studied. Additional recommendations are provided below:

Specimen source and Assay:

For the FDA- cleared Kamiya K-assay® (k993482), blood samples should be collected in EDTA tubes and plasma isolated CLSI[4] H21-A5 recommendations for specimen collection, transport and processing should be followed.

Performance characteristics of the assay for the qualification of plasma fibrinogen :

An analytically validated assay should be used for measurement of plasma fibrinogen. If sponsors decide to include a fibrinogen assay other than the Kamiya K-assay® Fibrinogen in any future study, the BQRT recommends the utilization of a fibrinogen assay with validated analytical performance characteristics. For this performance assessment, analytical parameters such as precision and reproducibility should be determined. Performance characteristics may differ between fibrinogen assays because many of them are immunology-based while others are functional assays. Sponsors should discuss their plans with FDA prior to conducting clinical trials.

Threshold:

Depending on the objective, the selection of the appropriate threshold to define "high" or "low" level of fibrinogen may need to be determined by a drug sponsor. Before deciding on the threshold for plasma fibrinogen, the BQRT recommends that the sponsor consider the impact of enrollment of patients with "high" fibrinogen at baseline and "low" at a subsequent visit(s) as well as that of enrollment of patients with "low" fibrinogen at baseline and "high" at a subsequent visit(s)). Based on the ECLIPSE data, for a threshold of 350 mg/dL as determined for the Kamiya K-assay , the approximately 30% to 50% of patients with "high" fibrinogen at baseline recorded "low" fibrinogen at a subsequent visit and approximately 15% to 20% of patients with "low" fibrinogen at baseline recorded "high" fibrinogen at a subsequent visit.

Patient populations:

Patients enrolled in COPD interventional trials should have a clinical history of COPD according to the ATS/ERS[5] definition prior to enrollment and obstructive lung physiology consistent with an increased risk for exacerbations and/or all-cause mortality (i.e. GOLD[6] stage 2 or higher). Patients enrolled in COPD exacerbation trials should have a history of COPD exacerbations in the year prior to enrollment in the clinical trial.**Sample Size:**

The following three tables are included to assist in the selection of the appropriate fibrinogen threshold for interventional clinical trials in which baseline plasma fibrinogen is used to enrich clinical trial populations of patients with COPD at high risk for exacerbations and/or all-cause mortality. Table 1 provides the estimated probability of no event (i.e., no hospitalized COPD exacerbation, no death) based on Cox proportional hazards modeling of ECLIPSE data for subjects with a history of COPD exacerbation. This table identifies: (1) the proportion of subjects without a hospitalized COPD

exacerbation each month over a one-year period and (2) the proportion of subjects surviving at four month invtervals over a three-year period.

Table 1. Estimated Probability of No Hospitalized COPD Exacerbation or No Death from Cox Models* Fit to ECLIPSE Data for Subjects with a History of COPD Exacerbation.

Fibrinogen Threshold	Proportion of Subjects Without a Hospitalized COPD Exacerbation Within 1 Year (Measured Every Month)	Proportion of Subjects Surviving Within 3 Years (Measured Every 4 Months)
No Threshold	0.97, 0.95, 0.93, 0.91, 0.89, 0.87, 0.86, 0.84, 0.82, 0.81, 0.79, 0.77	0.99, 0.99, 0.97, 0.97, 0.95, 0.94, 0.93, 0.92, 0.91
>250 mg/dL	0.97, 0.95, 0.93, 0.90, 0.89, 0.87, 0.86, 0.84, 0.82, 0.80, 0.79, 0.77	0.99, 0.99, 0.97, 0.97, 0.95, 0.94, 0.93, 0.92, 0.91
>300 mg/dL	0.97, 0.95, 0.92, 0.90, 0.88, 0.86, 0.85, 0.83, 0.81, 0.80, 0.78, 0.76	0.99, 0.99, 0.97, 0.96, 0.95, 0.94, 0.93, 0.92, 0.91
>350 mg/dL	0.97, 0.94, 0.92, 0.89, 0.87, 0.85, 0.84, 0.82, 0.79, 0.78, 0.76, 0.74	0.99, 0.98, 0.97, 0.96, 0.95, 0.93, 0.93, 0.91, 0.90
>400 mg/dL	0.97, 0.94, 0.91, 0.88, 0.86, 0.84, 0.83, 0.80, 0.78, 0.76, 0.74, 0.72	0.99, 0.98, 0.96, 0.96, 0.94, 0.92, 0.91, 0.90, 0.89

* Cox proportional hazards modeling with ties processed using Efron's approximation with a variable selection process. Variables that were found to be significant comprised the final model. As such, the covariates included in the final model varied across thresholds as indicated below.

- For hospitalized COPD exacerbation:

  — No threshold: Baseline FEV1
  — 250-400 mg/dL: Baseline FEV1 and corresponding fibrinogen threshold
- For mortality:
  — No threshold: Baseline FEV1, age, and cardiovascular disease
  — 250 mg/dL: Baseline FEV1, age, cardiovascular disease, and fibrinogen threshold
  — 300-400 mg/DL: Baseline FEV1, age, and corresponding fibrinogen threshold

The following two tables provide the sample sizes needed to achieve approximately 80% power for a hypothetical study evaluating the effect of a new treatment versus placebo on COPD exacerbation (Table 2) and all-cause mortality (Table 3) in patients with COPD , assuming the true hazard ratio for treatment versus control is 0.6 and 0.8. Necessary

sample sizes are projected for five cases: that is, when baseline plasma fibrinogen is not used as an inclusion criterion and when baseline plasma fibrinogen level is required to be greater than or equal to 250, 300, 350, and 400 mg/dL for inclusion in the study. For each threshold value being evaluated, the event rate for the control group is assumed to be the rate observed for the subset of ECLIPSE study subjects with fibrinogen levels exceeding that value at baseline, i.e., as if the study population had been enriched. Similarly, it is assumed that standard inclusion/exclusion criteria (e.g., prior history of exacerbation) will be incorporated into the study because only ECLIPSE study subjects who had a history of exacerbation were utilized in estimating the assumed survival rates for the control group.

Table 2. Sample Size Requirements to Provide 80% Power in a COPD Exacerbation Study of Subjects with a History of Exacerbation by Plasma Fibrinogen Threshold.*

Fibrinogen Threshold	Hazard Ratio** of 0.60		Hazard Ratio** of O.80	
	Necessary Sample Size	Sample Size Difference Between Unenriched and Enriched Studies	Necessary Sample Size	Sample Size Difference Between Unenriched and Enriched Studies
No Fibrinogen Threshold	2022	NA	9146	NA
>250 mg/dL	698	-6 (-1%)	3186	-26 (1%)
>300 mg/dL	666	-38 (-5%)	3044	-168 (-5%)
>350 mg/dL	620	-84 (-12%)	2840	-372 (-12%)
>400 mg/dL	572	-132 (-19%)	2620	-592 (-18%)

* The sample sizes are calculated to provide approximately 80% power assuming inference from the trial is drawn froma two-sided log rank test of size 0.05 comparing the survival curves between treatment groups and assuming equal sample sizes per group and 10% loss to follow-up.

** The hazard ratio equals the treatment versus control.

*** Unenriched sample

Table 3. Sample Size Requirements to Provide 80% Power in a COPD All-Cause Mortality Study of Subjects with a History of Exacerbation by Plasma Fibrinogen Threshold.*

Fibrinogen Threshold	Hazard Ratio** of 0.60		Hazard Ratio** of O.80	
	Necessary Sample Size	Sample Size Difference Between Unenriched and Enriched Studies	Necessary Sample Size	Sample Size Difference Between Unenriched and Enriched Studies
No Fibrinogen Threshold***	2022	NA	9146	NA
>250 mg/dL	2072	+50 (2%)	9380	+234 (3%)
>300 mg/dL	1970	-52 (-3%)	8916	-230 (-3%)
>350 mg/dL	1866	-256 (-8%)	8446	-700 (-8%)
>400 mg/dL	1614	-408 (-20%)	7318	-1828 (-20%)

* The sample sizes are calculated to provide approximately 80% power assuming inference from the trial is drawn froma two-sided log rank test of size 0.05 comparing the survival curves between treatment groups and assuming equal sample sizes per group and 10% loss to follow-up.

** The hazard ratio equals the treatment versus control.

*** Unenriched sample