EVALUATION OF AUTOMATIC CLASS III DESIGNATION FOR
ADVIA Centaur Enhanced Liver Fibrosis (ELF™)

DECISION MEMORANDUM

A. DEN Number:

DEN190056

B. Purpose for Submission:

De Novo request for evaluation of automatic class III designation for the ADVIA Centaur Enhanced Liver Fibrosis (ELF™)

C. Measurand:

The test reports an ELF score derived from the measurement of hyaluronic acid (HA), amino-terminal propeptide of type III procollagen (PIIINP), and tissue inhibitor of metalloproteinase 1 (TIMP-1)

D. Type of Test:

Quantitative immunoassay

E. Applicant:

Siemens Healthcare Diagnostics Inc.

F. Proprietary and Established Names:

ADVIA Centaur Enhanced Liver Fibrosis (ELF™)

G. Regulatory Information:

Regulation	Classification	Name	Product Code	Panel
21 CFR 862.1622	II	Prognostic test for assessment of liver related disease progression	QQB	Chemistry (75)

H. Indications for Use:

1. Indications for Use:

   ADVIA Centaur® Enhanced Liver Fibrosis (ELF™) is for in vitro diagnostic use in the determination of an ELF score based on the combined quantitative measurements of hyaluronic acid, amino-terminal propeptide of type III procollagen, and tissue inhibitor of matrix metalloproteinase 1 in human serum using the ADVIA Centaur XP system.

   ADVIA Centaur ELF is indicated as a prognostic marker in conjunction with other laboratory findings and clinical assessments in patients with advanced fibrosis (F3 or F4) due to non-alcoholic steatohepatitis (NASH), to assess the likelihood of progression to cirrhosis and liver-related clinical events.

2. Special conditions for use statement(s)

   - For *in vitro* diagnostic use.
   - For Prescription Use Only.
   - **CAUTION**
     Federal (USA) law restricts this device to sale by or on the order of a licensed healthcare professional.
   - The ADVIA Centaur ELF test is not for use in the diagnosis of NASH, or for staging of fibrosis.
   - ADVIA Centaur ELF is not for use in the serial monitoring of disease progression or for the monitoring of effects of therapeutic products.
   - Test results are intended to be used in conjunction with other clinical and diagnostic findings, consistent with professional standards of practice, including information obtained by alternative methods, and clinical evaluation as appropriate.
   - Measurements for HA, PIIINP, and TIMP-1 must be obtained within 8 hours of one another for the ELF score to be valid.
   - ADVIA Centaur ELF is limited to the detection of HA, PIIINP and TIMP-1 in human serum.
   - Only use results obtained on ADVIA Centaur XP systems to calculate ELF scores.
   - Do not use hemolyzed samples.
   - Do not use in patients taking biotin supplements.
   - Do not use samples that contain fluorescein. Samples with fluorescein may cause falsely depressed results. Evidence suggests that patients undergoing retinal fluorescein angiography can retain amounts of fluorescein in the body for up to 72 hours post-treatment. In cases of patients with renal insufficiency, including many diabetics, retention could be longer.
   - Patient samples may contain heterophilic antibodies that could react in immunoassays and cause falsely elevated or depressed results. This assay is designed to minimize interference from heterophilic antibodies. Additional information may be required for diagnosis.

- An ELF score <9.8 is associated with a lower prognostic risk, but disease progression is still possible for patients with ELF measurements below this threshold.
- An ELF score ≥ 11.3 is associated with a higher prognostic risk, but disease progression may not occur in patients with ELF measurements above this threshold.

3. Special instrument requirements:

For use on the ADVIA Centaur XP. Versions 7 and higher of the Centaur XP software include updates that allow the system to run and calculate multi-component scores. The ELF Test can be run on earlier versions of the Centaur XP but requires manual calculation of the ELF Score.

I. Device Description:

The ADVIA Centaur ELF test contains the following:

Reagents: Lite Reagent and Solid Phase reagents for HA, PIIINP and TIMP-1, and Ancillary Well reagents for HA and PIIINP are contained within ReadyPack® reagent packs. Each ReadyPack reagent cartridge has a barcode label used to automatically transfer information to the instrument when loaded into the instrument.

Calibrators: ADVIA Centaur ELF Calibrator kit contains 2 levels of calibrators (Low and High). Calibration is performed using Low and High Calibrators of known value (as per the Calibrator Assigned Value card provided in the ELF Calibrator kit).

Controls: The ADVIA Centaur ELF QC kit contains 3 controls (Level 1, Level 2, Level 3).

J. Standard/Guidance Documents Referenced:

Clinical and Laboratory Standards Institute (CLSI) EP05-A3: Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Third Edition

CLSI EP06-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline

CLSI EP07-A2: Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition

CLSI EP17-A2: Evaluation of Detection Capability for Clinical Laboratory Measurement Procedures; Approved Guideline—Second Edition

K. Test Principle:

The ADVIA Centaur ELF test provides a single ELF score by combining in an algorithm the quantitative measurements of HA, PIIINP and TIMP-1 in human serum.

The ELF score calculation for samples tested on ADVIA Centaur XP is the following:

$$\text{ELF score} = 2.278 + 0.851*\ln(C_{HA}) + 0.751*\ln(C_{PIIINP}) + 0.394*\ln(C_{TIMP\text{-}1})$$

The ADVIA Centaur HA reagents comprise a fully automated, two-site sandwich assay using direct chemiluminometric technology. The assay uses hyaluronic acid binding protein (HABP) for both capture and detection of HA. The Lite Reagent contains HABP conjugated with acridinium ester and the Ancillary Well Reagent contains HABP conjugated with FITC. The Solid Phase contains an anti-FITC monoclonal antibody covalently bound to paramagnetic particles. A direct relationship exists between the amount of HA activity in the patient sample and the amount of relative light units (RLUs) detected by the system.

The ADVIA Centaur PIIINP reagents comprise a fully automated, two-site sandwich immunoassay using direct chemiluminometric technology. The assay uses two monoclonal mouse antibodies (MAb): The first antibody in the Lite Reagent is an acridinium ester-labeled anti- PIIINP antibody. The second antibody in the Ancillary Well Reagent is a biotin-labeled anti-PIIINP antibody. The Solid Phase contains streptavidin-coated paramagnetic particles. A direct relationship exists between the amount of PIIINP activity in the patient sample and the amount of relative light units (RLUs) detected by the system.

The ADVIA Centaur TIMP-1 reagents comprise a fully automated, two-site sandwich immunoassay using direct chemiluminometric technology. The assay uses two monoclonal mouse antibodies (MAb) that bind to TIMP-1 in the Lite Reagent: an anti-TIMP-1 F(ab)2 antibody labeled with acridinium ester and an FITC-labeled anti-TIMP-1 antibody. The Solid Phase contains an anti-FITC monoclonal antibody covalently bound to paramagnetic particles. A direct relationship exists between the amount of TIMP-1 activity in the patient sample and the amount of relative light units (RLUs) detected by the system.

L. Performance Characteristics:

1. <u>Analytical performance:</u>

   a. *Reproducibility/Precision:*

   A 20-day precision study was performed according to CLSI EP5-A3. Samples included 8 serum samples with varying concentrations of HA, PIIINP and TIMP-1 to result in a varied range of ELF scores. For each assay, samples were assayed in 3 replicates, 2 times a day, for 20 days for a total of 120 measurements using 1 lot of reagents. The precision of the HA, PIINP and TIMP-1 measurements were also evaluated.

Sample	Mean (ELF Score)	Repeatability		Within-lab	
		SD	%CV	SD	%CV
1	7.49	0.03	0.4	0.05	0.7
2	11.61	0.03	0.2	0.04	0.4

Sample	Mean (ELF Score)	Repeatability		Within-lab	
3	12.70	0.03	0.2	0.05	0.4
4	9.91	0.03	0.3	0.04	0.4
5	12.53	0.02	0.2	0.04	0.3
6	13.78	0.04	0.3	0.05	0.3
7	9.27	0.03	0.3	0.04	0.4
8	7.99	0.02	0.3	0.04	0.6

Reproducibility

The ADVIA Centaur ELF multi-site precision study was performed on an ADVIA Centaur XP instrument at each of three (b) (4) sites using (b) (4) lot for each of the ADVIA Centaur HA, PIIINP and TIMP-1 reagents. Samples included (b) (4) erum samples with varying concentration of HA, PIIINP and TIMP-1 to result in a varied range of ELF scores. Each sample was assayed in three replicates per run, with (b) (4) runs per day separated by at least (b) (4) hours, for (b) (4) days yielding a total of (b) (4) runs, and (b) (4) replicates on each of the (b) (4) instruments/sites for a total of (b) (4) measurements.

Results for all sites overall for the multi-site reproducibility study are provided in the following table. The precision of the HA, PIINP and TIMP-1 measurements were also evaluated.

Sample	Mean (ELF)	Repeatability		Within-Lab		Reproducibility	
		SD	%CV	SD	%CV	SD	%CV
1	10.13	0.04	0.4	0.05	0.5	0.06	0.6
2	13.59	0.05	0.4	0.06	0.4	0.06	0.4
3	12.85	0.06	0.4	0.06	0.5	0.06	0.5
4	12.06	0.05	0.4	0.06	0.5	0.06	0.5
5	11.35	0.05	0.5	0.05	0.5	0.06	0.5
6	10.90	0.05	0.4	0.05	0.5	0.05	0.5
7	7.87	0.06	0.7	0.06	0.7	0.06	0.8
8	5.98	0.05	0.9	0.08	1.4	0.09	1.4

The sponsor also provided information demonstrating that (b) (4) lots of reagents yielded similar performance.

b. *Linearity/assay reportable range:*

Linearity of ADVIA Centaur HA, PIIINP and TIMP-1 measurements was performed according to CLSI EP06-A. High serum patient pools were prepared by spiking serum with high levels of HA, PIIINP or TIMP-1. Low pools were obtained from diluting serum with low levels of HA, PIIINP and TIMP-1 with negative basepool. Each dilution series comprised (b) (4) levels that were prepared

by mixing the high and low pools. Testing was performed on an ADVIA Centaur XP instrument with measurements made using (b) (4) replicates per level. The data supported the linearity of the score as well as the HA, PIINP and TIMP-1 measurements across the measuring interval of each component.

The sponsor provided data to support that the claimed measuring range of the ELF test is 3.85 to (b) (4)

Dilution Recovery:

Auto-dilution recovery were assessed using multiple samples above the claimed measuring range for each of the components and the ELF score. The sponsor provided information to support that samples can be diluted (b) (4) according to the instructions for use with the directed diluent and then measured. Samples yielded acceptable results when compared to the concentration of the undiluted samples.

The sponsor claims that ELF concentrations up to (b) (4) can be measured using the recommended dilution scheme.

Hook Effect:

The sponsor provided information to support that no hook effect can be expected for individual components of the test.

c. *Traceability, Stability, Expected values:*

Traceability:

The ADVIA Centaur ELF test is traceable to internal standards.

Calibrations Stability:

Information was provided from (b) (4) patient samples assessed at multiple time points after calibration to demonstrate that calibration is stable over the claimed interval of 14 days.

Detection limit:

Limit of Blank (LoB):
Limit of Blank was determined for the ADVIA Centaur ELF Test using (b) (4) ots of reagents on (b) (4) ADVIA Centaur XP instrument. (b) (4) determinations per lot were obtained by testing (b) (4) blank serum samples in (b) (4) replicates during tw (b) (4) runs each day for five (b) (4) days.

The LoB was calculated non-parametrically (i.e. non-Gaussian data set) as the dose at

the ranked position (152.5 in this study) using the following equation:

(b) (4)

The LoB of the ELF score, calculated from the LoB derived for each component separately is 2.19.

Limit of Detection (LoD):
Limit of Detection was determined for the ADVIA Centaur ELF assays using (b) (4) ots of reagents on (b) (4) ADVIA Centaur XP instrument. (b) (4) determinations per lot were obtained by te ng (b) (4) low analyte serum samples and (b) (4) blank samples in (b) (4) replicates during (b) (4) runs each day for (b) (4) days.

The Limit of Detection was determined using the precision profile approach as described in EP17-A2.

The LoD of the ELF score, calculated from the LoD derived for each measurand separately, is 3.20.

Limit of Quantitation (LoQ):
The LoQ was derived using a precision profile approach using data from the low-end region of the measuring interval for each component of the ADVIA Centaur ELF Test. Results from testing of the (b) (4) blank samples and (b) (4) low samples included in the LoB/LoD study were used for calculation of the LoQ. The LoQ for each combination of reagent lot was determined as the analyte concentration corresponding to the intersection of the acceptance criterion precision goal with the precision profile. The LoQ was defined as the concentration at 20% CV. The largest LoQ determined across all lots tested was taken as the LoQ claim. In all cases, the LoQ was below the LoD. Therefore, the claimed LoQ was set to be slightly higher than the claimed LoD. The LoQ for the ELF score, calculated from the LoQ derived for each measurand separately is 3.85.

d. *Analytical specificity:*

Cross Reactivity:

Potential cross-reactivity of drugs and metabolites on the ADVIA Centaur ELF test were assayed in triplicate samples using the reagents identified as potentially subject to the cross-reactivity. Samples were selected to cover the expected range of ELF scores.

The cross-reactivity specification of ≤1% was exceeded for MMP-2 (activated) in the high TIMP-1 sample pool. In addition, elevated cross-reactivities were observed for MMP-1 (activated) and MMP-9 (latent) in the high TIMP-1 sample pool. Percent

interference was calculated for all potential cross-reacting substances in the high TIMP-1 sample pool. The interference specification of ≤10% was met in all cases. The level of MMP-2 resulting in the identified cross-reactivity and the highest level measured without significant cross reactivity for all other molecules are above the concentration expected in the intended use patient population.

Cross Reactant	Concentration tested (ng/mL)
Chondroitin Sulfate A	1000
Chondroitin Sulfate A	1000
Chondroitin Sulfate A	1000
Fibronectin	500
Heparin Sulfate	200
Laminin	500
Type I Collagen	2000
Type IV Collagen	200
Type VI Collagen	50
TIMP-2	4000
MMP-1 (activated)	2500
MMP-2 (activated)	5000
MMP-2 (latent)	5000
MMP-3 (latent)	5000
MMP-9 (activated)	5000
MMP-9 (latent)	3500

Drug Interference:

Serum patient pools were prepared to contain either low, mid or high levels of HA, PIIINP and TIMP-1 to cover the expected range of ELF scores. Pools were divided and designated as "control sample" (no therapeutic drug present but spiked with the applicable diluent for the respective therapeutic drug) or "test sample" (therapeutic drug present). Testing was performed in replicates of (b) (4) per sample on an ADVIA Centaur XP instrument. Concentrations were either as recommended by CLSI EP37-1 Supplemental Tables for Interference Testing in Clinical Chemistry or at levels (b) (4) times the estimated C_{MAX}.

No significant interference (defined as ≥ 10% change in a component assay or ≥ 0.3 change in ELF score) was observed for the following drugs at the listed concentration:

Therapeutic Substance	Highest Concentration Tested
Acetaminophen	200 µg/mL
Acetylsalicylic acid	652 µg/mL
Azathioprine	2.58 µg/mL

Therapeutic Substance	Highest Concentration Tested
Cetirizine	4.35 µg/mL
Diphenhydramine	774 ng/mL
Disulfiram	1.14 µg/mL
Glyburide	850 ng/mL
Hydroxzyine	267 ng/mL
Ibuprofen	219 µg/mL
Interferon α2a	10 ng/mL
Interferon α2b	10 ng/mL
Ledipasvir	969 ng/mL
Liraglutide	168 ng/mL
Loratadine	87 ng/mL
Mesalamine	20.4 µg/mL
Metformin	12 µg/mL
Methotrexate	1.36 mg/mL
Obeticholic Acid	540 ng/mL
Pioglitazone	4.76 µg/mL
Ribavirin	25 µg/mL
Rifampicin	48 µg/mL
Sofosbuvir	1.85 µg/mL
Tenofovir	978 ng/mL
Tolazamide	45 µg/mL
Ursodiol (UDCA)	169 µg/mL

Significant interference was identified for both biotin and fluorescein. Serial dilution testing was performed to identify the concentration of each drug at which interference was observed.

While concentrations of biotin above approximately 65 ng/mL cause more than 10% interference with ADVIA Centaur PIIINP measurements, clinically significant interference (change of ≥ 0.3) in the ELF score was not observed up to biotin concentrations of 150 ng/mL.

The sponsor includes the following information in their labeling:

Specimens that contain biotin at a concentration of 150 ng/mL demonstrate a less than or equal to a 0.3 unit change in results for the ADVIA Centaur ELF Test. Biotin concentrations greater than these may lead to falsely depressed results for patient samples. Do not use in patients taking biotin supplements.

The recommended adult daily dietary intake for biotin is 30 µg/day. Over the counter dietary supplements promoted for use in hair, skin and nail health may contain 5 – 100 mg of biotin, with recommendations to take multiple pills per day. Pharmacokinetic studies in healthy adults have shown that, in subjects ingesting 5 mg, 10 mg, and 20 mg of biotin, serum concentrations of biotin can reach up to 73 ng/mL, 141 ng/mL, and 355 ng/mL, respectively. Subjects who take up to 300 mg of

biotin per day may have serum biotin levels as high as 1,160 ng/mL. These studies were performed in a small number of apparently healthy subjects. Clearance of biotin could be different in other patient populations, such as in patients with impaired renal function, which could lead to higher concentrations of biotin in serum or plasma.

Clinically significant interference for the ELF score (change of ≥ 0.3) was observed at 850 ng/dL Fluorescein.

The sponsor includes the following limitation in their labeling:

Do not use samples that contain fluorescein. Samples with fluorescein may cause falsely depressed results in this assay. Evidence suggests that patients undergoing retinal fluorescein angiography can retain amounts of fluorescein in the body for up to 72 hours post-treatment. In cases of patients with renal insufficiency, including many diabetics, retention could be longer.

Endogenous Interference:

Serum patient pools were prepared that contained either low, mid or high levels of HA, PIIINP and TIMP-1 to cover the expected range of ELF scores. Pools were divided and designated as "control sample" (no endogenous substance present but spiked with the applicable diluent for the respective substance) or "test sample" (endogenous substance present). Testing was performed in replicates of 3 per sample on an ADVIA Centaur XP instrument.

No significant interference (greater than 10% or a change in ELF score of greater than 0.3) were met for bilirubin (conjugated), bilirubin (unconjugated), cholesterol, fructose, glucose, hemoglobin, protein (albumin), protein (total), and Intralipid (representative of triglycerides). The sponsor claims that no interference was observed at the following concentration:

Substance	Test Concentration
Bilirubin (Conjugated)	60 mg/dL
Bilirubin (Unconjugated)	60 mg/dL
Cholesterol	400 mg/dL
Glucose	1000 mg/dL
Fructose	18 mg/dL
Hemoglobin	1000 mg/dL
Intralipid	3500 mg/dL
Protein (Albumin)	6 g/dL
Protein (Total)	15 mg/dL

Heterophile Interference:

Human anti-mouse antibody (HAMA) and rheumatoid factor (RF) positive serum samples were used to identify possible interference from HAMA or RF. For each assay, a minimum of (b) (4) HAMA and (b) (4) RF samples were tested.

No significant interference was seen in the HAMA and RF interference studies.

The sponsor indicated that although the study is generally representative of the types of HAMA and RF expected in a clinical setting, these interferents are biologically variable. Therefore, the labeling includes the following limitation:

Patient samples may contain heterophilic antibodies that could react in immunoassays and cause falsely elevated or depressed results. This assay is designed to minimize interference from heterophilic antibodies. Additional information may be required for diagnosis.

e. *Assay Cut-off:*

The sponsor previously conducted a separate clinical study to determine the clinically relevant cut off ELF scores of (b) (4) and (b) (4)

f. *Specimen Stability*

Information was provided to support the specimen stability claims described in the labeling:

- Samples may be stored at room temperature for up to 24 hours prior to centrifugation.
- Samples are stable for 8 hours onboard the system, for 48 hours at room temperature, and for 7 days at 2–8°C.
- Tightly capped specimens may be stored on the clot for up to 48 hours at 2–8°C.
- Freeze samples ≤ -20°C if the test is not completed within 7 days.
- Samples are stable at ≤ -20°C for up to 12 months. Avoid more than 4 freeze-thaw cycles. Do not store in a frost-free freezer. Thoroughly mix thawed samples and centrifuge them before using.

2. Comparison studies:

a. *Method comparison*

Not applicable.

b. *Matrix Comparison*

Equivalency of glass serum and serum separator tubes (SST) was assessed with (b) (4)

normal matched pairs and (b) (4) samples spiked with various amounts of analyte across the assay ranges. All samples were tested in duplicate on HA, TIMP-1, and PIIINP.

For the ELF Score, the following agreement was observed between glass tubes and serum separator tubes (b) (4)

The data demonstrated that the test can be used with both glass tubes and serum separator tubes.

3. Clinical studies:

   a. *Clinical Sensitivity*

      Not applicable.

   b. *Clinical Specificity*

      Not applicable.

   c. *Other clinical supportive data (when a. and b. are not applicable)*

      Information was provided from (b) (4) trials comprised of patients with bridging fibrosis and cirrhosis due to NASH. The information was gathered from trials intended to assess various investigational therapeutic substances but only data from the placebo arms of each trial was considered. Data was analyzed separately for patients by severity of fibrosis at the onset of the data collection period.

      Cirrhotic population:
      Three studies (trials 1 through 3) were provided in patients with cirrhosis at study entry. Each study assessed the ELF score ability to predict development of liver-related clinical outcomes over the extent of each patient's follow up time.

      Outcomes evaluated in cirrhotic trials:
      - All-cause mortality*
      - Liver transplantation
      - Qualification for liver transplantation (Model for End-Stage Liver Disease (MELD) ≥ 15)
      - Esophageal variceal bleeding requiring treatment
      - Clinically apparent ascites requiring treatment
      - Hepatic encephalopathy of Grade 2 or above (according to Westhaven criteria) and requiring treatment
      - Newly diagnosed varices in a subject without prior varices (Trial 1 and 3 only)
      - Progression from small to medium or large varices (Trial 3 only)

*Trial (b) (4) included a different definition of mortality, but no deaths were observed during this trial.

NASH F4 (Trial 1)
The median follow-up time for patients included in the analysis was (b) (4) months (interquartile range (b) (4) months).

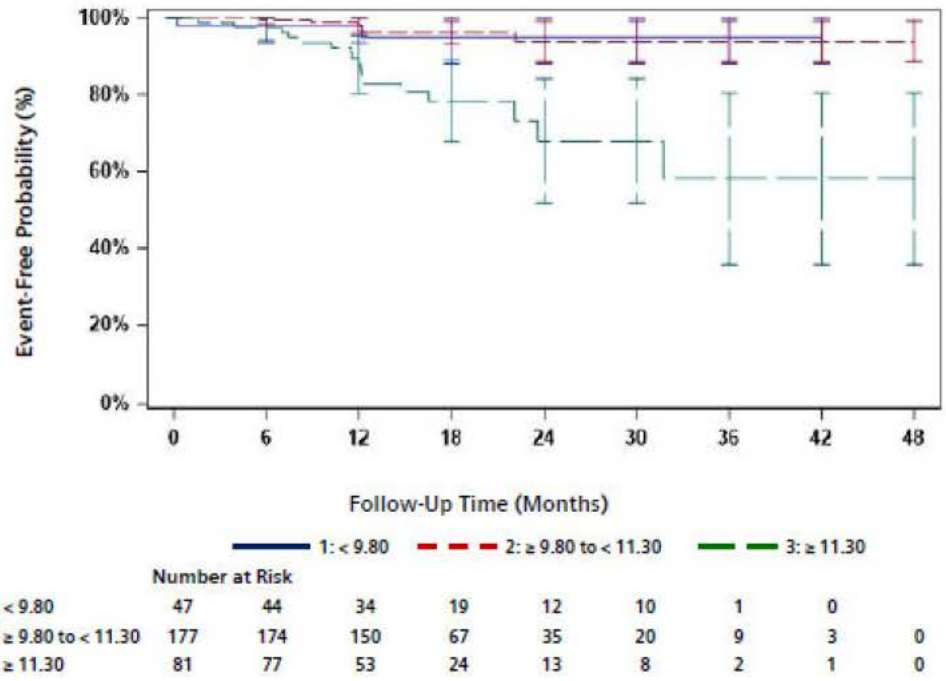
NASH F4 (Trial 2)
The median follow-up time for patients included in the analysis was (b) (4) months (interquartile range (b) (4) months).

NASH F4 (Trial 3):
The median follow-up time for patients included in the analysis was (b) (4) months (interquartile range (b) (4) months).

The device is labeled with the following pooled performance across the 3 placebo arms:

Group based on ELF Score	Total subjects (n)	Liver Related Event		Risk of Event (95% Confidence Intervals
		Yes	No	
<9.8	47	2	45	4.3% (0.0-10.0%)
9.8-<11.3	177	7	170	4.0% (1.1-6.8%)
>11.3	81	17	64	21.0% (12.1-29.9%)
All	305	26	279	8.5% (5.6 -12.2%)

The confidence intervals included in the table above were calculated using the pooled data without ability to adjust for differences in study population or length. Confidence intervals may overstate the statistical confidence of these measurements.



Bridging fibrosis population:
Two studies (trials [(b)(4)] and [(b)(4)] were provided in patients with bridging fibrosis at study entry. Each study assessed the ELF score ability to predict development of cirrhosis over the extent of each patient's follow up time.

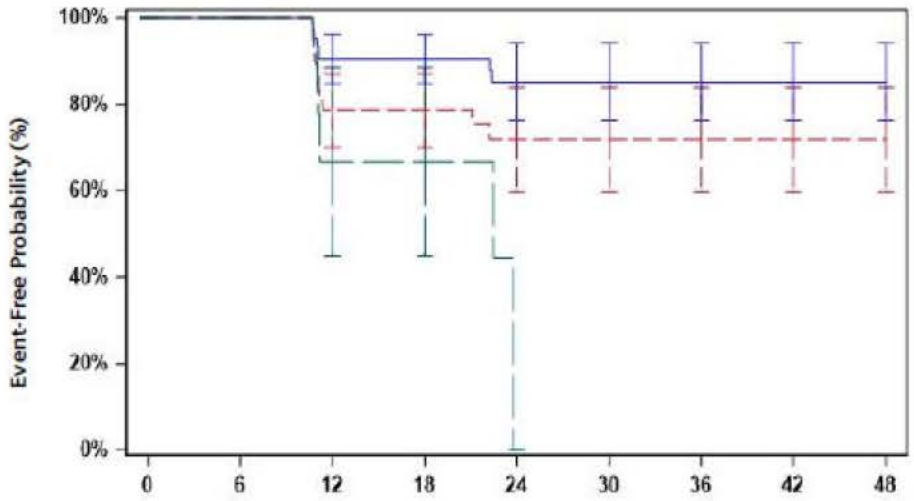
NASH F3 (Trial 4)
The median follow up time for patients included in the analysis was [(b) (4)] months (interquartile range [(b) (4)] months).

NASH F3 (Trial 5)
The median follow up time for patients included in the analysis was [(b) (4)] months (interquartile range [(b) (4)] months).

The device is labeled with the following pooled performance:

Group based on ELF Score	Total subjects (n)	Liver Related Event		Risk of Event (95% Confidence Intervals
		Yes	No	
<9.8	105	12	93	11.4% (5.3-17.5%)
9.8-<11.3	89	21	68	23.6% (14.8-32.4%)
>11.3	18	8	10	44.4% (21.5-67.4%)
All	212	41	171	19.3% (14.2 -25.3%)

The confidence intervals included in the table above were calculated using the pooled data without ability to adjust for differences in study population or length. Confidence intervals may overstate the statistical confidence of these measurements.



Number at Risk									
1: < 9.80	105	105	94	50	29	16	11	1	0
2: ≥ 9.80 to < 11.30	89	89	70	41	16	5	1	1	0
3: ≥ 11.30	18	18	12	5	0				

The sponsor provided information to support the long-term stability of the samples in these clinical studies.

The sponsor includes the following summary in their labeling:
Interpret the ELF score using the following guidelines:

ELF Score	Risk of Disease Progression (Development of Cirrhosis or Liver-Related Events)
<9.80	Lower
≥9.80-11.30	Mid*
≥11.30	Higher

*In the Mid group, the risk of disease progression is similar to the pre-test risk. Pre-test risk refers to the likelihood of disease progression in the overall intended use population without considering the ELF score.

Results should always be interpreted in conjunction with the patient's medical history, clinical presentation, and other findings.

Expected Values in a reference population

Expected values of ADVIA Centaur ELF were established on the ADVIA Centaur XP system with (b) (4) samples from US blood donors of known sex, ethnicity, and age. The study subjects were selected to be representative of the US population including the presence of individuals undiagnosed for type 2 diabetes mellitus or early stage undiagnosed NAFLD.

Reference intervals were determined by calculating the 2.5th, 5th, 95th, and 97.5th percentiles and the distribution of values.

Ethnicity	Gender	N	ELF Scores			
			Mean	Median	95% Lower limit (2.5th percentile)	95% upper limit (97.5th percentile)
African American	Female	68	7.62	7.66	6.13	9.17
	Male	236	7.64	7.69	5.77	9.05
	Combined	304	7.64	7.68	5.81	9.03
Caucasian	Female	86	7.74	7.77	6.41	9.03
	Male	198	7.85	7.81	6.61	9.33
	Combined	284	7.82	7.79	6.61	9.22
All*	Female	154	7.69	7.75	6.2	9.02
	Male	440	7.74	7.74	6.01	9.09
	Combined	594	7.72	7.74	6.16	9.08

*All category includes an additional 6 Hispanic male subjects

A reference was provided to a peer-reviewed study using the ADVIA Centaur XP system conducted in (b) (4) apparently healthy East Asian subjects (Yoo et al, Normal enhanced liver fibrosis (ELF) values in apparently healthy subjects living liver donors in South Korea, Liver International 2013.)

Ethnicity	Gender	N	ELF Scores		
			Mean	90% Lower limit (5th percentile)	95% upper limit (95th percentile)
Asian	Female	(b) (4)			
	Male				
	Combined				

In all ethnic groups, the reference ranges are entirely below the lowest clinical cut-off for the device (ELF score of (b) (4).

M. Other Supportive Instrument Performance Characteristics Data Not Covered In the "Performance Characteristics" Section above:

Not applicable.

N. Proposed Labeling:

The labeling supports the decision to grant the De Novo request for this device.

O. Patient Perspectives:

This submission did not include specific information on patient perspectives for this device.

P. Identified Risks to Health and Identified Mitigations:

Identified Risks to Health	Identified Mitigations
False negative results leading to delayed assessment or treatment	Certain design verification and validation activities, including certain clinical studies Certain labeling information, including certain warnings and performance information
False positive results leading to unnecessary medical procedures	Certain design verification and validation activities, including certain clinical studies Certain labeling information, including certain warnings and performance information

Q. Benefit/Risk Analysis

Summary of the Assessment of Benefit

The probable benefit from the use of the ELF test is to improve patient management for patients with advanced F3 and F4 fibrosis due to NASH by providing additional information that could aid in the assessment of risk of progression to cirrhosis and liver related clinical events. Identifying patients that may be at increased risk for progression to cirrhosis and liver related clinical events may provide for opportunities for better clinical management of these advanced liver disease patients and therefore serves an unmet medical need. This test is expected to help in the clinical management of this group of advanced liver disease patients.

Summary of the Assessment of Risk

Associated device risks include false positive results (i.e., patient categorized by ELF as moderate/higher risk but patient is actually at lower risk) and false negative results (i.e., patient categorized by ELF as lower risk for disease progression but should be considered moderate/higher risk). A false positive ELF score that leads the clinician to incorrectly assess the patient to have a higher risk of progressing to cirrhosis or to adverse liver related events could increase the risk of unnecessary follow-up monitoring and evaluations (e.g., imaging, liver biopsy). A false negative result that leads a clinician to incorrectly conclude that the patient's risk of progressing to cirrhosis or to adverse liver related events is less than it truly is could lead to the risk of delaying potential treatment and delaying additional monitoring (e.g., for evidence of portal hypertension), or delaying evaluation for liver transplantation listing.

Summary of the Assessment of Benefit-Risk

General controls are insufficient to mitigate the risks associated with the device. However, the probable clinical benefits outweigh the probable risks for the assay, considering the mitigation of the risks provided for in the special controls. Design verification and validation, including a clinical validation study, the results of which will be included in the labeling, along with limitations, performance information, and information on the interpretation of the test, will help ensure that the device functions as intended and mitigate the risk of false positive and false negative test results. In addition, the device is intended to be used in conjunction with other laboratory findings and clinical assessments. Overall, the probable benefits outweigh the probable risks of incorrect test results for the proposed indications for use, in light of the special controls and general controls.

R. Conclusion:

The De Novo request is granted and the device is classified under the following and subject to the special controls identified in the letter granting the De Novo request:

Product Code: QQB
Device Type: Prognostic test for assessment of liver related disease progression
Class: II
Regulation: 21 CFR 862.1622