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Biomarker Qualification Letter of Intent (LOI) from Template

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If there is a prior, current, or planned submission to other regulatory agencies, list the agencies and dates as appropriate:

No other prior, current, or planned submissions.

Context of Use

Proposed Context of Use (COU) (limited to 500 characters)

The magnitude of the complex shear modulus (|G*|) is a diagnostic biomarker that can be used to non-invasively screen individuals with clinical risk factors for chronic liver disease to identify those at high risk of having histopathologic findings of significant (≥F2), advanced fibrosis (≥F3) or cirrhosis (F4). This biomarker can be used to reduce the number of biopsies required for enrollment in all phases of drug development clinical trials.

Drug Development Need

Describe the drug development need that the biomarker is intended to address, including (if applicable) the proposed benefit over currently used biomarkers for similar COUs (limited to 1,500 characters).

Chronic liver disease (CLD) is an area of unmet medical need, with a complex disease pathway that creates challenges for drug development. Often, CLD progression begins with sustained insult to liver cells, subsequent necro-inflammation, and progressive hepatic fibrosis. As fibrogenesis advances, patients are at increased risk for cirrhosis, portal hypertension, hepatocellular carcinoma and other complications of end-stage liver disease. Among the histopathologic markers of CLD, fibrosis stage has the strongest relationship to prognosis and mortality. The use of liver biopsy in clinical trials is limited by cost, inconvenience, discomfort for patients, inherent risks and sampling variability.

The FDA issued guidance that highlights the need for noninvasive staging of liver fibrosis. To this end, the magnitude of the complex shear modulus (|G*|), (one of several similar but *not* identical physical tissue properties that are commonly referred to as "liver stiffness") has been shown to correlate extremely well with all stages of fibrosis, independent of the etiologic cause of CLD. The diagnostic performance of this biomarker for staging liver fibrosis has been described as "on par with liver biopsy" [1], while providing lower variability and higher inter- and intra-reader agreement. In trials of CLD where the intended patient population must have histopathologic evidence of fibrosis for enrollment, |G*| can be employed as a rule-out diagnostic. This would non-invasively narrow the patient cohort to only those with a high probability of meeting eligibility criteria based on histopathology. This can ethically reduce the number of biopsies in trials where they are required, leading to reductions in individual subject risk and cost of enrollment for drug development trials.

Biomarker Information

Provide a general description of what aspect of the biomarker is being measured and by what methodology (e.g. radiologic findings such as lesion number, specific measure of organ size, serum level of an analyte, change in the biomarker relative to a reference such as baseline) (limited to 1,500 characters).

In materials science, shear stress-strain properties of a viscoelastic material are described by the *shear modulus* (G*). (G*) includes a real part called *storage modulus* (G') and an imaginary part called *loss modulus* (G"), which are related to the elastic and viscous tissue properties, respectively. The magnitude of the complex shear modulus |G*| is expressed in units of kiloPascals (kPa), and is computed as follows:

$$|G^*| = (G'^2+G''^2)^{1/2}$$

|G*| is a parameter corresponding to tissue "stiffness". All FDA-cleared implementations of magnetic resonance elastography (MRE, described below) generate tissue "stiffness" images (elastograms) depicting |G*|. In contrast, tissue "stiffness" measured by most FDA-cleared ultrasound elastography techniques report "stiffness" in terms of shear wave group velocity, or in an estimate of shear modulus or Young's modulus based on a square of the shear wave

group velocity. Due to intrinsic differences in the spectra of shear waves used with each of these techniques, and due to fundamental differences in the metric that is calculated, the measurements of “stiffness” produced by these techniques cannot be directly equated.

|G*| has been extensively studied and validated for fibrosis staging, as documented in over 50 publications cited for this COU (Attachment 2). Liver fibrosis is due to fibro-inflammatory processes which lead to an excessive accumulation of extracellular matrix proteins. This leads to a increased tissue stiffness, measured as an increase in |G*|. Published evidence shows a strong correlation between |G*| and fibrosis stage, as determined by pathology, and supports the qualification of the quantitative biomarker |G*| of liver tissue for fibrosis staging to meet clinical trial enrollment criteria. As a diagnostic screening biomarker, |G*| can be used to reduce the number of biopsies required by narrowing the cohort to only those with a high probability of meeting eligibility criteria.

Is the biomarker test/assay currently available for public use. **Yes**

Indicate whether the biomarker test/assay is one or more of the following:

___Laboratory Developed Test (LDT)

___Research Use Only (RUO)

_X_FDA Cleared/Approved. Provide 510(k)/PMA Number: K083421, K121434, K140666, K183193

If the biomarker is qualified, will the test/assay be performed in a Clinical Laboratory Improvement Amendments (CLIA) – certified laboratory? **No**

Is the biomarker test currently under review by the Center for Devices and Radiological Health or the Center for Biologics Evaluation and Research? **No**

Is there a standard operating procedure (SOP) for sample collection and storage? **No – no sample collection or storage**

Is there a laboratory SOP for the test/assay methodology? **No**

Biomarker Measurement Information

Describe the extent of analytical validation that has been performed (e.g., sensitivity, specificity, accuracy, and/or precision of the assay or method) (limited to 1,500 characters)

|G*| is measured by MRE, a noninvasive imaging technology that uses shear waves to quantitatively assess tissue stiffness. This measurement technique requires an MRI scanner that is equipped to generate and image vibrations, producing a quantitative map of |G*|, measured on a continuous scale[2-3]. Regions of interest for |G*| can be manually drawn by a radiologist or experienced analyst, or automatically generated and reviewed using MREplus+, an FDA-cleared analysis tool (Attachment 3)[4].

The diagnostic accuracy of |G*| has been estimated to be near to or equivalent with that of liver biopsy[1]. The reported diagnostic performance is summarized in Table 1 (Attachment 2). Diagnostic performance of |G*| has not been shown to be dependent on the etiology of CLD and

is not affected by steatosis and other patient specific factors including age, sex, and body mass index[5-7]. The Quantitative Imaging Biomarker Alliance developed a consensus profile addressing the precision of MRE for |G*| measurement, stating "a measured change in hepatic stiffness of 19% or larger indicates that a true change in stiffness has occurred with 95% confidence" [8,9].

Table 1: Diagnostic Accuracy of Liver |G*| for Fibrosis Staging

Fibrosis Stage	AUROC	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
≥F2	0.92 (0.76-1)	86 (65-100)	90 (60-100)	89 (65-100)	86 (54-100)
≥F3	0.95 (0.83-1)	87 (71-100)	91 (72-100)	83 (48-100)	88 (3-100)
F4	0.95 (0.85-1)	89 (73-100)	92 (81-100)	72 (27-97)	95 (72-100)

Values reported as mean (min-max). AUROC = area under the receiver operating curve; PPV = positive predictive value; NPV = negative predictive value.

Overall, |G*| has high diagnostic accuracy for staging significant fibrosis, advanced fibrosis, and cirrhosis, independent of BMI and etiology of CLD, which may lead to improved subject screening for clinical trial enrollment[7].

Additional Considerations for Radiographic Biomarkers

How as the method for image acquisition, analysis, and integration of the data been optimized? (Limited to 1,000 characters)

The FDA-cleared products from GE, Siemens, and Philips all use the same mechanical driver hardware, default shear wave frequency of 60 Hz, comparable pulse sequences, and an equivalent data processing algorithm to compute |G*|. The image acquisition and analysis process has been synchronized across field strengths and pulse sequences, which has been validated by multiple studies in both normal volunteers and patients with CLD [10-15]. Following the image acquisition, quantitative stiffness maps are automatically generated using a mathematical inversion algorithm and interpreted by a radiologist or experienced reader. Regions of interest are manually drawn, and the mean value is reported. Inter-observer agreement is very high, with intra-class correlation (ICCs) of 0.92-0.99 and intra-reader correlation [1,16-18].

Does data currently exist to support the proposed cut point(s), if imaging results are not reported as a continuous variable?

|G*| is a continuous variable, however thresholds are used to correlate the measured stiffness with fibrosis stage. Several studies have characterized the diagnostic performance of |G*| for the staging of liver fibrosis in CLD, reporting a range of threshold values used for fibrosis staging. Although liver biopsy is considered the standard reference of the diagnosis of liver fibrosis, there are several important limitations including; the effects of sampling error and inter- and intra-observer variability, invasiveness, expense, and limited application for monitoring treatment response. Determining liver stiffness thresholds for fibrosis staging may be

confounded by these inaccuracies, where misclassification of fibrosis stage can occur in up to 25% of cases[3]. Proposed thresholds for |G*| based on published evidence are (Attachment 2):

- Significant fibrosis (≥F2): 3.3 kPa
- Advanced fibrosis (≥F3): 3.9 kPa
- Cirrhosis (F4): 4.8 kPa

Provide the name and version of the software package to be used for image acquisition and analysis (limited to 500 characters).

Image acquisition + analysis: MR Elastography (Philips, Siemens Healthineers), MR Touch (GE Healthcare)

Optional image analysis tool: MREplus+ (Resoundant, Inc.)

Supporting Information

Please summarize existing preclinical or clinical data to support the biomarker in its COU (e.g., summaries of literature findings, previously conducted studies) (limited to 2,000 characters).

Data from 56 publications for staging liver fibrosis using |G*| on 9605 patients with CLD is included in Attachment 2. The majority of these studies were on patients with biopsy-proven NAFLD, though many also included patients with other CLD or non-acute infectious liver disease. In terms of applicability and technical performance, measurement of |G*| has been shown to be unaffected by common confounding factors for other "liver stiffness" measurements such as wave speed, and reliable measurements of |G*| can be obtained in obese patients and in those with hepatic steatosis [7,19-21].

|G*| has been used in over 50 clinical trials registered on clinicaltrials.gov and in the clinical management of CLD since the availability of the measurement technique (MRE) as an FDA-cleared product in 2009. Demonstrating the biomarker adoption and therefore ease of use in clinical trials, this biomarker is recommended in several current clinical practice guidelines, including recommendations by the American Gastroenterological Association (2017) [22], American Association for the Study of Liver Disease (2017) , and American College of Radiology (2017) [23]. In its application to the AMA seeking approval of a new CPT code for MRE in 2016, the American College of Radiology presented practice survey data that estimated the annual number of clinical MRE scans to be 60,000, demonstrating widespread adoption of |G*| as a biomarker of liver fibrosis stage. Taken together, the technology to measure |G*| is already a widely available and powerful clinical tool, making it ideal for seamless adoption into all clinical trial phases for fibrosis staging as a drug development tool.

Please summarize any planned studies to support the biomarker and COU. How will these studies address any current knowledge gaps? (limited to 2,000 characters)

|G*| for the staging of liver fibrosis has been well established in the existing published literature (Attachment 2). However, |G*| thresholds corresponding to fibrosis stage have traditionally been

[3]

determined for each study individually. The thresholds included in this letter have been determined from an extensive literature review and will need to be prospectively validated. There are several ongoing clinical trials that utilize |G*| for the staging of liver fibrosis including the Non-Invasive Biomarkers of Metabolic Liver Disease (NIMBLE) trial sponsored by the Foundation for the National Institutes of Health (FNIH)and multiple liver trials currently registered on clinicaltrials.gov. The proposed thresholds will be prospectively validated in multiple trials for this COU.

Previous Regulatory Interactions

None.

Attachments

Please provide a list of publications relevant to this biomarker development proposal

- Attachment 1: References
- Attachment 2: Evidence base summary
- Attachment 3: 510(k) summaries
- Attachment 4: Flow Chart for Subject Enrollment using |G*| for Screening