LETTER OF INTENT
DETERMINATION LETTER

DDTBBQ000099
August 7, 2020

Resoundant, Inc.
Attention: Kay Pepin, Ph.D.
421 1st Ave SW STE 204W
Rochester, MN 55902, United States

Dear Dr. Pepin,

We are issuing this letter to Resoundant, Inc. to notify you of our determination on the project submitted to the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) Biomarker Qualification Program (BQP). We have completed our review of the Letter of Intent (LOI) deemed reviewable on April 20, 2020 and have determined to accept it into the CDER and CBER BQP[1]. We agree there is an unmet need and encourage your ongoing development of this biomarker which has potential to advance drug development within the specified context of use (COU).

Your next submission, a Qualification Plan (QP), contains details of the analytical validation plan for the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its context of use (COU), and includes descriptions of knowledge gaps and how you propose they will be mitigated. If future studies are planned, please include detailed study protocols and the statistical analysis plan for each study as part of your QP submission.

Below, we provide you with specific considerations and recommendations to help improve your preparation for, and submission of the QP. As this biomarker development effort is refined, the submitted data, the specifics of your context of use (including the target patient population), and the design of study(ies) used in the clinical validation of the biomarker will ultimately determine which of these considerations and recommendations are most applicable. For more information about your next submission and a QP Content Element outline, please see the BQP Resources for Biomarker Requestors web page.[2]

[1] In December, 2016, the 21st Century Cures Act added section 507 to the Food, Drug, Cosmetic Act (FD&C Act). FDA is now operating its drug development tools (DDT) programs under section 507 of the FD&C Act.

[2] https://www.fda.gov/drugs/cder-biomarker-qualification-program/resources-biomarker-requestors

CONSIDERATIONS & RECOMMENDATIONS

Drug Development Need Considerations

1. Chronic liver disease (CLD) with its progression to cirrhosis and liver cancer account for approximately 2 million deaths per year worldwide. Cirrhosis and liver cancer are the #11 and #16 most common causes of death overall, moving up from #13 and #20 since 2000. Treating CLD represents an area of unmet medical need, and trial participation often requires liver biopsy to confirm level of fibrosis for inclusion criteria. Level of fibrosis is one of the strongest predictors of adverse clinical outcomes including liver related mortality. Liver biopsy is the current standard for determining level of fibrosis but is an invasive test with measurable morbidity and mortality. Therefore, non-invasive screening tools for fibrosis have the potential to spare trial participants unnecessary biopsy if they are unlikely to meet histologically-based inclusion criteria. For trials treating non-alcoholic fatty liver disease (NAFLD), one the most common CLDs, FDA guidance suggests F2 level of fibrosis or higher as the targeted study population. Moreover, significant improvement in fibrosis is an accepted surrogate endpoint. The FDA encourages biomarker development to supplant liver biopsy and accelerate drug development for NAFLD. Therefore, tissue "stiffness", as measured by magnetic resonance elastography (MRE), as a biomarker for fibrosis could fill an important need.

Biomarker Description Considerations

2. The biomarker described by this submission is the magnitude of the complex shear modulus |G*|, a parameter corresponding to tissue "stiffness", as measured by magnetic resonance elastography (MRE). The submission represents a diagnostic radiographic biomarker.

COU Considerations

Requestor's COU Statement:

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.

FDA COU Recommendation:

A diagnostic biomarker to pre-screen patients with clinical risk factors for chronic liver disease for enrolment in clinical trials to identify those at high risk of having histopathologic findings of significant fibrosis (≥F2), advanced fibrosis (≥F3), or cirrhosis (F4) on liver biopsy.

Drug Development Utility

3. Available literature on complex shear modulus (|G*|) as a measure of liver stiffness by magnetic resonance elastography (MRE) supports its potential utility in drug development. It has the potential to accelerate drug development, decrease misclassification bias compared to liver biopsy, and decrease trial participant morbidity.

4. Development for the proposed context of use will need to address patient- and disease-specific issues that could pose challenges in misclassification. Acute inflammation of the liver, vascular outflow obstruction of the liver (i.e., hepatic congestion), and measurement in the fed state can induce variability in MRE readings, as would application across various CLD diagnoses (e.g., hemochromatosis, heterogenous fibrosis in primary sclerosing cholangitis (PSC)). Thus, prospective validation of current kPa cut-off values across different CLD diagnoses will be necessary using clinical trial and real-world data.

5. In addition, there are little data regarding MRE accuracy in the pediatric population. There is good evidence that NAFLD begins in childhood, and some children and adolescents will develop significant fibrosis. Please attempt to address this need as much as possible.

6. To address quality of supporting data and expedite review of your QP, we recommend the following organization of references and referred data in future documents.

    6a. Provide a description of your referenced studies including the:

        1. elements of your search methodology and inclusion criteria for identified studies: search terms utilized, databases searched, date search was performed, and number of unique publications found.
        2. description of the quality assessment applied to the individual publications and the threshold applied to select your corpus of supporting publications. A CONSORT table modified for this purpose will be helpful to summarize this process.
        3. description of any efforts to obtain the primary data supporting your qualification and effort to engage patient stakeholders, academia, and industry to assemble patient-level data for this qualification.

    6b. Provide key reference data that includes digital object identifiers (doi).

    6c. The data should represent unique subjects. Please be mindful of double counting in patient tallies. The Singh CGH 2015 meta-analysis paper includes 4 other studies in your table creating potential double counting.

6d. Similarly, provide specifics about how many patients included in the analyses had chronic liver disease and both MRE and biopsy. The Eaton, JGH 2016 study had 266 PSC patients, but we believe only 20 had liver biopsies. In Yin, Radiology 2017, only 158 patients had untreated chronic liver disease with a liver biopsy within a year.

6e. Studies with the shortest intervals between MRE and comparator (e.g., biopsy or elastography) in chronic liver disease patients are preferred when such comparative data are presented.

Statistical Considerations

7. When preparing your Qualification Plan, please clarify the following aspects of your LOI:

   We acknowledge that your proposed thresholds for staging fibrosis: 3.3 kPa (significant fibrosis, ≥F2), 3.9 kPa (advanced fibrosis, ≥F3), and 4.8 kPa (cirrhosis, F4) are obtained by using cutoff thresholds from studies listed in your attachment 2 (Evidence base summary). You also state that these thresholds have been determined from an extensive literature review and will need to be prospectively validated. It appears that you used roughly the average of the thresholds across the listed studies. It is unclear what is the role of study by Yin (2007, CGH) as there were no sample sizes for either normal or diseased individuals, though there was a 'threshold' listed with uncertain interpretation of its reported sensitivity, specificity, AUROC.

   7a. The estimated NPV for fibrosis stage ≥ F3 is 88% with 95% confidence interval of 3% to 100% (see Table 1 on p.5 of LOI submission). Explain the wide range reported.

   7b. Provide the range of prevalence with justification applied to obtain the PPV and NPV by fibrosis stage in Table 1.

   7c. Indicate the reference standards used for studies included in Table 2 (Appendix 2: Evidence Base Summary of the LOI).

8. Please provide the information by study and in view of clinical comments above regarding types of study versus study disease population as part of your Qualification Plan. We note that 20% equivalence or non-inferiority margin used to conclude diagnostic performance of MRE as compared to biopsy in Morisaka et al. (2018) is likely to be too wide. The database from the validation study, if agreed upon, may be the basis for assessment of biomarker performance.

9. In your Qualification Plan, please include a Statistical Analysis Plan (SAP) that describes the statistical methods you intend to use in your analysis with sufficient details to support validation of your proposed thresholds for |G*|. Our preliminary statistical comments can be found below. We may have additional comments on your planned approach after review of the submitted Qualification Plan.

10. Your Qualification Plan should prospectively pre-specify what studies will be used to validate your biomarker performance. We recommend that you provide descriptions of design elements including study population, reference standards, sample size, and how the individual subject data will be collected and available by study.

    10a. You proposed |G*| as a diagnostic biomarker for 'chronic liver disease', which includes a wide range of liver pathology and disease etiology. To demonstrate the utility of the biomarker under this broad spectrum of disease, you should investigate performance of your biomarker for as broad of a set of specific disease for drug development consideration. Ensure that you have sufficient numbers of patients representing each specific disease (e.g., NASH), and present diagnostic accuracy (i.e., specificity and sensitivity) for each one separately.

    10b. You proposed three thresholds for staging fibrosis: 3.3 kPa (significant fibrosis, ≥F2), 3.9 kPa (advanced fibrosis, ≥F3), and 4.8 kPa (cirrhosis, F4). Ensure that you have sufficient numbers of patients in all four categories of fibrosis stage (i.e., <F2, F2, F3, and F4) and present diagnostic accuracy (i.e., specificity and sensitivity) for each category separately.

    10c. You should investigate the possibility that a patient may have low |G*| measured by MRE, but have fibrosis based on liver biopsy. Thus, for the validation study, you should not screen patients based on a biomarker to assess diagnostic performance.

Please address each of the specific considerations and recommendations and any data requests cross-referencing the numbered list above in a separate addendum to your QP submission.

When evaluating biomarkers prospectively in clinical trials, requesters are encouraged to submit study data using Clinical Data Interchange Consortium (CDISC) standards to facilitate review and utilization of data. Data sharing and the capability to integrate data across trials can enhance biomarker development and utilization. If sponsors plan to use the biomarker prior to qualification to support regulatory review for a specific Investigational New Drug (IND), New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) development program, they should prospectively discuss the approach with the appropriate CDER or CBER division.

The BQP encourages collaboration and consolidation of resources to aid biomarker qualification efforts. Any individuals or groups (academia, industry, government) that would like to join in this effort, have information or data that may be useful can contact Dr. Pepin (email: kpepin@resoundant.com).

Should you have any questions or if you would like a teleconference to clarify the content of this letter, please contact the CDER Biomarker Qualification Program via email at CDER-BiomarkerQualificationProgram@fda.hhs.gov with reference to DDT BMQ#000099 in the subject line. For additional information and guidance on the BQP please see the program's web pages at the link below.[3]

Sincerely,

Christopher L. Leptak -S

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[3] https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/cder-biomarker-qualification-program

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