



LOI DECISION LETTER

DDTBMQ #000053

July 31, 2017

Critical Path Institute  
1730 E. River Rd.  
Tucson, AZ 85718

Dear Dr. Sauer:

We have completed our review of your updated Letter of Intent (LOI) submission of May 26, 2017 and have concluded to accept it into the CDER Biomarker Qualification Program. Please note that the 21<sup>st</sup> Century Cures Act was signed into law and adds new section 507 to the Food, Drug, Cosmetic Act (FD&C Act) concerning the qualification of drug development tools (DDTs). For this project, we will be following the 507 process for DDT qualification.

For your project, you have proposed qualification of anatomic features of Crohn's Disease (CD) as assessed by MRE (Magnetic Resonance Enterography) as a pharmacodynamic/response biomarker that can be used as a co-primary clinical trial endpoint as a measure of disease activity.

Based on our review of the LOI, we agree there is an unmet need in CD clinical trials for alternative measures to ileocolonoscopy that provide disease activity information regarding small bowel involvement and extramural manifestations of the disease. We also agree that alternatives that are less invasive, especially for pediatric studies, would be beneficial. Initial studies appear to support the potential use of MRE for this context, but additional information is needed to confirm the acceptability of its use for the proposed context of use.

The comments and questions contained in this document represent CDER's biomarker development recommendations for your proposed context of use. For the 507 DDT qualification process, please prepare a Qualification Plan (QP) submission that addresses the recommendations outlined below and contains details of the analytical validation of the biomarker measurement method, detailed summaries of existing data that will support the biomarker and its COU, and descriptions of knowledge gaps and how they will be mitigated. If future studies are planned, please include the study protocols as part of your QP submission.

**Biomarker Considerations**

***Requestor's Description:*** Anatomic features of Crohn's disease including gut wall thickness, ulceration, edema, and perfusion (quantified by a composite index score, MaRIA). Disease complications, not captured by MaRIA, further include stricturing, abscess, and fistula.

**FDA's recommended biomarker description for continued biomarker development:**

A composite radiographic biomarker index comprised of a weighted sum of the following intestinal anatomic features of Crohn's Disease: gut wall thickness, ulceration, edema, and enhancement.

- Please clarify how each of the above listed anatomic features will contribute to the overall assessment of CD activity. Describe the biologic rationale for any differential weighting of these anatomic features in calculating their contribution to the composite index score.
- Please provide radiographic descriptions of each of the anatomic features to be included in the composite biomarker index. In particular, please distinguish between gut wall thickness and edema if these features are, in fact, distinct. Also, for bowel wall enhancement, please describe the relevance to CD (e.g., as an indicator of perfusion, vascularity, inflammation, or some other manifestation) and the information to support that the radiographic finding has biologic or clinical value.
- For the extramural anatomic features of CD (e.g., abscess, fistulas), we recommend that they not be included in the composite index since they would not be quantified by bowel segment. That said, we acknowledge that an assessment of these features has value in understanding drug effects in a clinical trial setting. One option would be to study these features in an exploratory fashion, separate from this qualification effort, to gain better understanding of how they might be quantified and used as part of efficacy assessment and labeling claims.
- Additionally, while inflammatory stricture only affects a subset of Crohn's disease patients, response or resolution of inflammatory stricture that can be measured by MRE would be of interest. Because this phenotype does not affect the majority of patients with CD, it may be better evaluated separately, rather than included in the composite index.

**Context of Use (COU) Considerations**

***Requestor's COU:*** MRE assessment of changes in anatomic features of Crohn's disease is qualified as a pharmacodynamic/response biomarker that can be used as a co-primary clinical trial endpoint.

**FDA's suggest COU for continued biomarker development:**

Response biomarker that measures Crohn's Disease (CD) activity that can be used as a co-primary endpoint in CD clinical trials in conjunction with an accepted assessment of patient symptoms as the other co-primary endpoint.

- For use of this biomarker in CD clinical trials, what is the anticipated target patient population for enrollment (mild, moderate, and/or severe disease based on current clinical trial enrollment criteria)? Does the composite index have the ability to distinguish changes in disease activity for each of these tiered patient populations based on severity

of disease at time of clinical trial enrollment? In particular, will the index be able to determine the presence or absence of mild disease that may have limited mucosal involvement and therefore minor anatomic changes on MRE?

- We recommend that the composite index be assessed at enrollment (baseline measurement) and again at a specified time point for efficacy assessment, on a patient by patient basis. For comparison to baseline, we also recommend that the composite score index and the individual index components be compared to better understand both the composite index and the role of its components.

### **Analytical Considerations**

- Before submission of your Qualification Plan, we would expect that the analytical validation of the MRE assessment has been largely demonstrated and that any algorithm is finalized before conducting the clinical validation of the biomarker composite index. We acknowledge that it would be desirable to use some of the data for the clinical validation as part of the data for the analytical validation. Please provide the current evidence to support analytical validation and detailed plans for collecting additional evidence to support analytical validation.
- The MaRIA score is a newly introduced metric for which we need to develop a greater understanding. Please describe how the components of the MaRIA score are determined from the MRE data for the bowel wall thickness, relative contrast enhancement (RCE), edema, and ulcer determinations. Please provide the detailed instructions for assessing each component of the score. Please differentiate any portion of the assessment that is automated from any manual measurement.
- Please describe any limitations on MRE image acquisition protocols or image quality acceptance criteria for determining the MaRIA<sub>seg</sub> and MaRIA<sub>global</sub> scores. Please describe how you will standardize MRE preparation/image acquisition/assessment in your proposed clinical study and how you will assess the robustness of the MaRIA score to MRE operating variations. Please also provide a summary of the image acquisition protocols for any MRE data provided within the Qualification Plan.
- A single example acquisition protocol was provided for a Siemens 1.5T scanner. Please clarify whether all study participants will be scanned on exactly the same scanner. If not, please describe how inter-scanner variation (for example, magnetic field strength, MR system manufacturer) will be addressed in your validation study.
- Please provide any quality assurance instructions provided to users to ensure patient measurements are robust. Please differentiate between image quality checks conducted by software and those that require user observation.
- Please provide acceptance criteria or performance specifications for each of the four components of the MaRIA<sub>seg</sub> for each of the five colonic segments individually and MaRIA<sub>global</sub> scores. Please provide data including confidence bounds to support a

conclusion that the performance specifications for each element are satisfied. For any measure of performance for which data do not currently exist, please describe your plans for acquiring these data or explain why this analysis parameter does not contribute to uncertainty associated with the measurement. Please consider the reference standard and appropriate statistical analysis for each element. Some performance characteristics of interest may include:

- Repeatability (i.e., same patient, same scanner, data acquired back-to-back)
- Reproducibility (i.e., same patient/phantom, different scanners, different days, etc.)
- Linearity
- Bias
- Measurement range
- Sensitivity
- Specificity

We recognize that certain aspects may be more appropriate for certain components of the MaRIA score (for example, sensitivity and specificity for the assessment of ulcers and measurement range for the wall thickness).

Please consider the effect of reader variability on MaRIA<sub>seg</sub>, MaRIA<sub>global</sub> and each of the score components. Please describe your plans for characterizing and validating reader agreement/reproducibility for individual score components and MaRIA<sub>seg</sub> values.

### **Clinical Considerations**

- Should your biomarker be qualified for the described context of use, clinical trials would still require ileocolonoscopy (ICS) information, including histologic assessment, to confirm the diagnosis of CD as part of the inclusion criteria.
- In order to validate that an MRE composite score is an accurate way to indirectly measure disease activity to support a claim of efficacy in treatment of CD, a prospective clinical trial to validate its use will be necessary. One approach would be to compare MaRIA scores and ileocolonoscopy findings obtained at the same time points (baseline and multiple post-baseline assessments) in the context of a clinical trial, so that you can demonstrate good correlation between a given MaRIA score and the Simple Endoscopic Score for Crohn's Disease (SES-CD) score of 0-2 which is used to define endoscopic remission. Alternatively, it may be possible to show prospectively that a given MaRIA score or change in MaRIA score correlates with a clinically meaningful endpoint (for example that an early change in MaRIA score of "X" correlates well with achieving remission by Week 52, etc.).
- Please describe the value of the MaRIA score as an alternative to ICS, since the magnitude of change in Crohn's Disease Endoscopic Index of Severity (CDEIS) scores and the magnitude of change in the MaRIA<sub>global</sub> scores showed moderate correlation ( $r=0.51$ ) based on your submitted information.



- Please compare the risks associated with repeated gadolinium based MRE procedures to the risks associated with repeated ICS procedures, including potential mitigation strategies for each.
- You have stated that an added benefit of using the MaRIA score over ICS is the additional evaluation of mucosal inflammation in three proximal small bowel segments (proximal ileum, jejunum, and duodenum). Please describe how these proximal small bowel MaRIA<sub>seg</sub> score information will be used since you have chosen not to include these small bowel segment scores in the MaRIA<sub>global</sub> score. Please discuss how small bowel and large bowel segment scores may be similar or dissimilar based on the known CD biology and disease presentation given that ICS comparative information for small bowel disease activity is not available.
- Please discuss the limitations of using the MaRIA<sub>global</sub> score to evaluate mucosal inflammation since the MaRIA score does not include a histological assessment of the mucosa.
- It is unclear to us how the MaRIA score thresholds were determined. Please clarify and provide a sensitivity analysis for the proposed thresholds.
- Please discuss how differing affected segments at baseline will impact the MaRIA<sub>global</sub> score, a summation of the six MaRIA<sub>seg</sub> scores. If a segment is not affected at baseline and does not change on subsequent assessment at a future time point, how would the MaRIA<sub>global</sub> score be interpreted?
- Please discuss your selection of the threshold for the MaRIA<sub>global</sub> post-treatment score to be <50 to indicate remission regardless of the baseline measurement.
- Please describe your rationale for validating the MaRIA score in a clinical study with only one CD treatment (anti-TNF biologic), when your proposed context of use is for the assessment of the response to all CD treatments.

### **Statistical Considerations**

- Please confirm that the formula of MaRIA<sub>seg</sub> score was derived by Rimola et al. in 2009 and that the formula used model coefficients from the Tobit regression model.
  - The statistical method section stated that there were five independent variables (edema, ulcerations, pseudopolyps, wall thickness and RCE in MR), in the Tobit model. However, the formula for MaRIA<sub>seg</sub> only contained 4 factors (edema, ulcerations, wall thickness, and RCE in MR). Please discuss the rationale for exclusion of pseudopolyps from the formula for MaRIA<sub>seg</sub> or provide the analysis results using a model with only the four factors included in the MaRIA formula.

- In addition, the regression models used in this study were based on data for each of the five segments of colon and the terminal ileum. Each segment was treated independently from other segments of the same set of patients in logistic and Tobit models. In order to make inference based on individual patient's performance, the intra-subject correlations among segments of the same subject could impact the analysis results. To illustrate the impact of segment-based data from the same patient, we recommend you define a segment specific cutoff point and report the sensitivity, specificity and ROC curves for the same segment among all patients.
- Please provide details for your simplified definition of  $\text{MaRIA}_{\text{seg}}$ .
- When considering the change from baseline for  $\text{MaRIA}_{\text{seg}}$  score, the periods of the visits (e.g., 3 days or 7 days) should be the same.
- We observe that a  $\text{MaRIA}_{\text{global}} < 50$  cannot guarantee  $\text{MaRIA}_{\text{seg}} < 7$  for each segment. Therefore, when validating the use of MaRIA score as a response biomarker, it may be problematic to only consider  $\text{MaRIA}_{\text{global}}$ . Similar concerns are raised when considering change in  $\text{MaRIA}_{\text{global}}$  from the baseline measurement.
- Please discuss the extent of evidence to support the determination of the MaRIA cutoff points.
- Please clarify why linear regression could not adequately assess the MRE data and why Tobit regression is the preferred method. It is not clear whether separate logistic/Tobit regressions were used to model each segment. If this is the case, please discuss the statistical output for each of the models, including parameter estimates and model fitting statistics, etc. in the derivation and the validation study.
  - Please describe the properties of the available data (including display/tables) that led to the decision to perform a Tobit regression analysis. The discussion should be made from a technical perspective, describing the specific properties of the Tobit regression which made it preferable. In addition, sensitivity analyses should be performed, comparing the results of the Tobit regression to a linear regression, with attention to why this should/could not be performed. Further sensitivity analyses should be performed for both methods including or excluding the 'problematic' data. The intent of these analyses is to confirm robustness of the results, i.e., to confirm that favourable results do not depend on the analysis method.
  - To assess the robustness of your results, please perform a sensitivity analysis that compares the Tobit analysis model to linear regression for both individual and pooled data and also compares results from analyses with all data to analyses with excluded data.

- Both the derivation study and validation study were conducted in Spain in patients aged 18-35 years. Please clarify whether the biomarker's target CD population will be in a similar age range. If not, please provide approaches to address the generalizability of the proposed biomarker among CD patients in different age groups.
- Study protocol design considerations:
  - Please discuss how you powered your proposed prospective clinical study to detect a correlation coefficient of  $>0.25$  to support your proposed context of use.
  - The proposed study protocol did not provide the specific type of correlation coefficient to be used. Please specify primary endpoints included in Table 1, statistics for concordance, and type of correlation coefficient.
  - Discuss the moderate correlation ( $r=0.51$ ) for the changes in MaRIA and CDEIS in light of the stronger results of the initial derivation/validation studies. A discussion of measures to increase the precision of the information from the planned clinical trial to support the assessment of the final study outcome should be included.
  - Given the sample size of 150 patients, the regression models used in the derivation and validation study can also be applied here to verify the original finding, as supportive analyses.
  - Reports on primary endpoints per study center/region, when practical, are also recommended.

If you have questions, please contact Chris Leptak ([christopher.leptak@fda.hhs.gov](mailto:christopher.leptak@fda.hhs.gov)) through email. We look forward to working with you on this beneficial project.

Sincerely,



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