BIOMARKER QUALIFICATION LETTER OF INTENT (LOI)

COMMENTS: The following information will be made publicly available as per the 21st Century Cures Act

Biomarker Project Information

Biomarker: Anatomic features of Crohn's disease including gut wall thickness, ulceration, edema, and perfusion (quantified by a composite index score, Magnetic Resonance Index of Activity (MaRIA).

Therapeutic area: Gastroenterology, specifically Crohn's disease (CD).

Patient Population: Adult patients with CD.

Administrative Information

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Other regulatory agency submissions: The joint regulatory Letter of Intent was originally submitted to FDA and EMA on March 2nd, 2016. FDA determined they would not be able to review this until December of 2016. The consortium decided to initiate discussions with EMA, and submitted a Briefing Package on November 21st, 2016, and held a face-to-face meeting on March 8th, 2017. All materials and written correspondence with EMA have also been shared with FDA.

The consortium would like to bring FDA and EMA into a joint procedure as soon as possible, and envisions that if a Qualification Plan is invited from and submitted by us, a tri-partite meeting to discuss that plan would be requested.

Drug Development Need

Objective measurement (i.e. imaging) of the inflammatory activity of Crohn's disease. MRE can 1) assess transmural disease and 2) visualize all affected segments of the GI tract, including the proximal ileum where ICS cannot evaluate.

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal (GI) tract which may affect any part of the GI tract from mouth to anus (NIDDK, 2014). Although there are many risk factors associated with its development, CD fundamentally represents dysregulation of the mucosal immune system in a genetically susceptible individual in response to commensal microbiota and other environmental triggers. CD is characterized by patchy, transmural inflammation of the GI tract with areas of normal mucosa interspersed between diseased areas. Patients with CD can present with a variety of symptoms including nausea, vomiting,

abdominal pain, and diarrhea. In addition, patients can present with complications, such as intestinal stenosis (also referred to as stricturing), fistulas or abscesses. CD can affect any age group, but its onset is most common in the second and third decade (teenagers and young adults). Globally, the overall incidence of CD ranges from 0 to 20.2 per 100,000 individuals (Molodecky et al. 2012).

Treatment options help with symptoms, maintain remission, and prevent relapse. However, there are no medications or surgical procedures that can cure CD. Development of novel therapies is hindered by a lack of tools that provide both comprehensive and objective assessment of disease activity, stricturing and penetrating complications, e.g., intraabdominal fistulas and abscesses.

- **Additional improvement by the proposed biomarker upon currently used standards**: Clinical drug development trials of CD therapies have historically involved endpoints including patient reported symptoms and signs of disease, such as the Crohn's Disease Activity Index (CDAI), but more recently ileocolonoscopy measurements have been added as an objective assessment of disease activity and severity. Ileocolonoscopy, however, has several drawbacks when utilized to assess CD activity or response to treatment that are improved upon with MRE.

Table 1. Advantages of MRE as compared to Ileocolonoscopy in CD

	Ileocolonoscopy	MRE
Patient Preparation and Invasiveness	Extensive preparation for imaging assay, including bowel preparation, sedation and anesthesia. Insertion of colonoscope into colon and lower small intestine.	Less preparation and non-invasive, but does include administration of intravenous contrast agent, enema and ingestion of contrast agent.
Risk of Procedure	Small risk of complications, including perforation during procedures and those related to sedation, or anesthesia.[(a)]	No risk of perforation or that related to sedation/aesthesia, but risks associated with magnetic resonance imging procedures[(b)] including those related to use of gadolinium (Gd)-based contrast agents.[(c)]
Utility to image affected regions in CD	Terminal ileum only reached in 72-90% of patients with CD. Cannot reach upper GI nor proximal small intestine.	Cn image all relevant sections of small and large intestine, and assess transmural disease activity.
Utility to assess CD complications	Low sensitivity to detect penetrating complications such as fistulas and abscesses.	High sensitivity to detect strictures, and penetrating complications such as fistulas and abscesses.

(a) http://www.asee.org/assets/0/71542/71544/56321364-c4d8-4742-8158-55b6bef2a568.pdf

(b) http://www.fda.gov/medicaldevices/scienceandresearch/researchprograms/ucm477387.htm

(c)http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm42882.htm

- **Description of limitations for use of the proposed biomarker:** None.

- **Is there potential use of the biomarker across multiple drug development programs?** Yes.

- **The biomarker is a composite biomarker (made up of several individual biomarkers combined in a stated algorithm to reach a single interpretive readout):** Yes.

- **Description of biomarker components and algorithm used:** MaRIA is a composite score that takes into account bowel wall thickness, MR image signal enhancement by gadolinium-based contrast agent (measuring perfusion), and observation of ulceration and edema. As the MaRIA was derived to be concordant with the CDEIS in ICS, and ICS can only visualize the five segments of the large bowel plus the terminal ileum, the initial scoring system was proposed for those six segments. Specifically, a sub-score (MaRIAseg) is calculated for each of the five colonic segments plus the terminal ileum, and a global score (MaRIAglobal) is computed as the sum of the sub-scores.

  MaRIAseg = 1.5 × WT + 0.02 × RCE + 5 × edema + 10 × ulcer

  Here, WT represents bowel wall thickness in mm measured at the thickest point in the segment, edema and ulcer are each assigned a value of 1 when there is evidence of either in the segment (or 0 otherwise), and RCE represents the relative contrast enhancement. Coimbra et al (2016) studied patients at different levels of disease activity, from remission to severe CD, and observed MaRIAseg scores in the range of 3 to 35 units.

  Of note is that the segmental MaRIA score can be calculated for any small or large bowel segment, and the proposed PD/response cutoffs can be applied. Because MaRIA was initially derived to correlate with an endoscopy score, and endoscopy only assesses the five large bowel segments plus the terminal ileum, the global MaRIA score is the sum of only those six segments. Nonetheless, as noted, the segmental score can be used as a cutoff for assessing pharmacodynamic/response as well.

  Beyond the MaRIA score for assessing gut wall thickness, perfusion, ulceration and edema, assessment of strictures, abscess, and fistula can be quantified as present/absent (i.e., not as a composite biomarker).

Biomarker Information

- **Biomarker name (for molecular biomarkers, please provide a unique ID) and type (Molecular/Image/Anatomic, etc.):** MaRIA index score.

- **Biomarker description:** MaRIA index score, a composite score that takes into account bowel wall thickness, MR image signal enhancement by gadolinium-based contrast agent (measuring perfusion), and observation of ulceration and edema.

- **Biomarker Category:** Pharmacodynamic/Response

- **Biological rationale (underlying biological process):** The MaRIA score, reflecting changes in intestinal wall

thickness, edema, perfusion, and ulceration, was designed to be highly concordant to the Crohn's Disease Endoscopic Index of Severity (CDEIS), a widely used, objective endoscopic score.

MRE has emerged as the cross-sectional imaging method of choice for assessing inflammation and penetrating complications in CD both at the patient as well as at the segment level. Early reports of MRE in CD evaluated many MRE signs associated with inflammation and damage, but sensitivities and specificities varied widely. Recognizing that variability may be attributed to protocol differences and definitions of abnormalities, Church et al. (2015) performed a systematic meta-analysis of the literature to identify the MRE signs that most accurately identify inflammation and damage in CD. Studies were only considered eligible if published after the year 2000 because that is when MRE sequences and protocols became relatively standardized. Study design, study population, MRE protocol (MRI scanner field strength and vendor, bowel cleanse, IV gadolinium-based contrast agent, enteral contrast agent and volume, anti-spasmodic agent, GI tract segment examined, time between reference standard and MRE), MRE signs examined, and reference standards of inflammation and/or damage were extracted and evaluated from each study. Reference standards included many measures of active inflammation, including the Crohn's Disease Activity index (CDAI) or Harvey-Bradshaw Index (HBI), and endoscopic scores such as CDEIS or SES-CD. Evidence of structural change (damage) to the GI tract included clinical, endoscopic or surgical detection of fistulae, abscesses and strictures, and also fibrosis observed on surgical histopathology specimens. Of 244 articles reviewed in full, 62 studies met eligibility criteria for inclusion. Key findings from this meta-analysis are the following: for inflammation, high sensitivity was reported for wall enhancement (also referred to as relative contrast enhancement, reflecting perfusion and vascularity), wall thickness, wall T2 hyper intensity (reflecting edema), and motility; high specificity was noted for wall T2 hyper intensity and mucosal lesions (ulcers and pseudo polyps). For damage, abscess, stricture, and fistula had consistently high sensitivity and specificity.

The MaRIA score was specifically noted as a multi-item measure that incorporates 4 of these signs (wall thickness, wall enhancement, T2 hyperintensity, and ulcers) with reported excellent ability to detect endoscopic changes in mucosal appearance related to inflammation. These MRE signs were consistently significant despite considerable variation in MRE protocol, including time between MRE and reference standard assessment, magnet field strength, scanner vendor, pre-scan fast duration, IV gadolinium-based contrast agent, enteral contrast route or agent (as well as rate of administration of both contrast agents), and the spasmolytic and dose.

The heterogeneity assessed in this meta-analysis lends confidence to the generalized applicability, and real-world performance of MRE in CD. That said, the protocol for our prospective study reflects optimal methodologies, as currently understood, to maximize quality image acquisition and analysis.

Context of Use

- **Proposed Context of Use (COU) Statement:**
  Magnetic Resonance Enterography (MRE) assessment of changes in anatomic features of CD is qualified as a pharmacodynamic/response biomarker that can be used as a co-primary clinical trial endpoint.

- **Conditions for Qualified Use Include:**
  Anatomic features of disease inflammation and activity to be assessed are wall thickness, edema, ulcer, and perfusion; these can be quantified for each intestinal segment, or as a global score by a composite

index score, the Magnetic Resonance Index of Activity (MaRIA). Proposed cut-offs for MaRIA are as follows:

i. MaRIAseg score for ALL segments < 7 = disease remission
ii. MaRIAseg score for ALL segments < 11 = ulcer healing
iii. MaRIAglobal score < 50 = disease remission

MRE can also assess Crohn's disease complications of stricture, abscess, and fistula. Visualization of these complications can be utilized in benefit/risk decisions for patients in trials according to anticipated MOA of drug.

MRE evaluation of these features can be performed for small and large bowel as an objective imaging assessment of disease, just as ileocolonoscopy (ICS) is currently used. It is anticipated that sponsors will discuss trial design and the use of either MRE, ICS, or both as clinical trial endpoints with the review division.

As with ICS, MRE should be used with other accepted clinical trial endpoints, e.g. PRO instruments, for assessment of symptoms.

A standardized protocol for patient preparation, image acquisition, and image analysis is included with this qualification and recommended.

- **Drug Development Space for Biomarker Use:**
  - Early-phase clinical trials (e.g., Phase I or II)
  - Late-phase clinical trials (Phase III)

Biomarker Measurement (Analytical)

- **General description of what aspect of the biomarker is being measured and by what methodology**: The composite score is described above in the previous section with regards to the particular anatomic gut features of Crohn's disease being measured.

  MaRIA score cutoffs for segments with disease that is active or in remission, as well as cutoffs for segments with ulceration, have been derived and validated (Rimola et al., 2009; Rimola et al., 2011; Ordas et al., 2014; Takenaka et al., 2015; Coimbra et al., 2016). The cutoffs proposed for confirmation in our prospective study are as follows:

  i. MaRIAseg score for ALL segments < 7 = disease remission
  ii. MaRIA seg score for ALL segments < 11 = ulcer healing
  iii. MaRIAglobal score < 50 = disease remission

  In this scoring, all evaluated segments (at a minimum the five colonic plus the terminal ileum) would have to score below 7 in order to classify the patient as having disease in remission.

  For disease complications not addressed in the MaRIA score, i.e. strictures, fistula, and abscess, these will be evaluated as present/absent.

- **Information about the specific technical platform/software:**
  MRE and MaRIA have been demonstrated to support our COU in many studies that utilized different

technical equipment. The table below summarizes the variable features such as manufacturer, model, or magnet strength between several key studies: no differences in the utility or interpretation of MaRIA were observed.

However, optimization of the MRE protocol, as well as characterization of inter- and intra-reader variability in a multi-center CD trial has been conducted
(Coimbra et al., 2016). We intend to submit a standardized protocol with our qualification as a recommended part of eventual guidance in order to further control and reduce variability.

Publication	Site	Scanner Manufacturer	Scanner Model	Field Strength	GBCA	Number of Patients	Number of MRE Exams
Coimbra et al 2016	A	Siemens	Aera	1.5T	Dotarem	3	6
	B	GE	Optima MR40w	1.5T	Omniscan	3	6
	C	Siemens	Symphony	1.5T	Multihance	6	10
	D	Siemens	Aera	1.5T	Omniscan	2	4
	E	Philips	Achieve	1.5T	Multihance	5	9
	F	GE	Signa HDxt	1.5T	Dotarem	1	2
Rimola et al 2009	Barcelona	Siemens	Tim-Trio	3.0T	Omniscan	50	50
Rimola et al 2011	Barcelona	Siemens	Tim-Trio	3.0T	Omniscan	50	50
Ordas et al 2014	Barcelona	Siemens	Tim-Trio	3.0T	Omniscan	37	69
	Valencia	Philips	Gyroscan	1.5T	Omniscan	8	16
	Galdakao	Philips	Achieve	3.0T	Omniscan	2	4
	Barcelona 2	Philips	Achieve	3.0T	Omniscan	1	2
Stoppino et al 2016	Foggia	Philips	Achieve	1.5T	magnevist	27	54
Taenaka et al 2015	Tokyo	Toshiba	EXCELART Vantage	1.5T	unknown	125	125
					Total=	**320**	**407**

- **The biomarker test/assay is available for public use?** Yes.
- **The biomarker assay/test will be performed in a Clinical Laboratory Improvement Amendments (CLIA) certified laboratory?** No, not applicable as radiological facilities are exempt from CLIA. .
- **The biomarker assay/test is currently under review within the FDA Center for Devices and Radiological Health?** Don't know.
- **A standard operating procedure (SOP) exists for sample collection, storage:** Yes.
- **A laboratory SOP exists for the assay/methodology:** Yes.
- **Performance characteristics for the biomarker assay/tests are defined (sensitivity, specificity, accuracy and precision):** Yes.

Additional Considerations for Radiographic Biomarkers

- **Methods for image acquisition, analysis and interpretation of the data are optimized:** Yes
- **There are supportive data for the proposed cut point(s):** Yes
- **Software package used for image acquisition:** An example of an image analysis software that may be used is Osirix (http://www.osirix-viewer.com). Each MR scanner make/model used in previous studies and for future studies may have a different image acquisition software and associated version that is appropriate for what we are proposing. This is supported by positive evidence for our COU for MRE and MaRIA in CD in the literature across vendor/make/model/software combination.

Biomarker Measurement (Clinical)

Biomarker study and data considerations;

- **Clinical study data supporting the biomarker:** Yes.
- **Non-clinical study data supporting the biomarker:** Not applicable.
- **Type(s) of data available to support the proposed COU of the biomarker:** Retrospective data, prospective data, observational data.
- **Planned future studies:** Yes.
- **Statistician participating in biomarker qualification effort:** Yes.
- **Previous Qualification/Scientific advice received:** None.

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