EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Executive Director

Letter of support for MRI-PDFF

Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) is a MRI-based diagnostic imaging biomarker of the liver, developed in order to facilitate, by enriching, patient recruitment for clinical trials in NASH. MRI-PDFF is a measure to assess liver fat content and is proposed to be used as non-invasive method to limit unnecessary liver biopsies by avoiding biopsies in those patients with a low likelihood of fatty liver. It is intended to be used as a pre-screening strategy in an adult population having clinical signs or risk factors suggesting non-alcoholic fatty liver disease (NAFLD).

Drug development need:

Non-alcoholic fatty liver disease (NAFLD) is currently the most common cause of chronic liver disease worldwide. Furthermore, the progressive form of NAFLD, non-alcoholic steatohepatitis (NASH), is one of the leading indications for liver transplantation. In spite of the burden posed by fatty liver diseases, neither the FDA nor the EMA have yet approved any medicines for treatment of NASH. A major burden in clinical trials remains the need for liver biopsy for selection of eligible participants. Liver biopsy is expensive and invasive, carrying with it risks of abdominal pain, bleeding and death. As such, there is a need for non-invasive enrichment biomarkers to reduce the number of unnecessary liver biopsies for enrolment into clinical trials. MRI-PDFF is a non-invasive, quantitative biomarker to assess liver fat content. The applicant claims that MRI-PDFF is an accurate quantitative imaging biomarker with high repeatability and reproducibility and has provided results from test and validation datasets with MRI-PDFF compared to liver histology to show optimal MRI-PDFF cut-offs in order to reduce the number of unnecessary biopsies prior to enrolment in clinical trials and identify candidates who are most likely to meet the criteria for enrolment in NASH clinical trials.

The proposed context of use:

MRI-PDFF is a diagnostic enrichment biomarker that can be used in the recruitment of patients for clinical trials, in conjunction with clinical risk factors, to identify participants who are more likely to have steatosis and presence of NAS≥4 appropriate for inclusion in clinical trials. Such participants will undergo liver biopsy to confirm eligibility for clinical trial enrolment.

Description of the biomarker:

Magnetic Resonance Imaging Proton Density Fat Fraction (MRI-PDFF) of liver tissue is an imaging biomarker derived from the fat and water component images acquired during an MR examination, and computed as the ratio: MRI-PDFF = $\frac{fat}{fat+water} \times 100\,\%$

Current and future research:

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Technical validation

A technical evaluation of different MR scanners, across multiple manufacturers (GE, Siemens and Philips) and models has been performed. Similarly, an evaluation and comparison between the different quantitative post-processing devices have been performed, both in-vivo and using phantom data, as well as a reliability assessment of operator performance with satisfactory results.

Clinical Validation

The rationale for the PDFF biomarker and support for its use within the proposed COU was partially demonstrated in two independent cohorts:

- A training cohort, a UK-based population in which the proposed MRI-PDFF cut-off will be systematically derived (RIAL-NICOLA and CALM trials).
- In order to validate the proposed MRI-PDFF, cut-off threshold will be applied to an independent validation dataset (BAMC study).

A further independent multi-centre *validation* study is currently being planned to evaluate, in patients with suspected NASH referred for liver biopsy, the diagnostic performance of MRI-PDFF to discriminate candidates with NAS ≥4 from those without, and those with Brunt Steatosis ≥2 from those without.

Summary:

The CHMP agrees there is an unmet need in avoiding unnecessary biopsies during recruitment for clinical trials and also agrees that development of the proposed biomarker would potentially enable identifying patients within the context of use as mentioned above. In addition to the qualification effort, we encourage further study of the PDFF biomarker including collection of specified information from the proposed clinical trials.

Data sharing and the capability to integrate data across trials can enhance biomarker development and utilization. Any groups that would like to join in this effort or have information or data that may be useful can contact Dr. Jaco Jacobs, PhD (jaco.jacobs@perspectum-diagnostics.com) or Dr. Andrea Dennis, PhD (andrea.dennis@perspectum-diagnostics.com).

Yours sincerely,

Guido Rasi
Executive Director