17 September 2019
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Executive Director

Letter of support for cT1

Corrected T1 (cT1) is an MRI-based diagnostic imaging biomarker of the liver, developed in order to facilitate, by enriching, patient recruitment for clinical trials in NASH. cT1 is intended to be used as a proxy for inflammation and fibrosis 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 NASH. 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:

There are currently several phase 2 and phase 3 clinical investigations ongoing which have fatty liver disease as the condition under investigation. Despite the high prevalence of steatosis, defined as a liver fat > 5%, recruitment for these trials is inefficient as only a subset of participants with steatosis will have steatohepatitis. Non-alcoholic steatohepatitis (NASH), the more aggressive form of non-alcoholic fatty liver disease (NAFLD), may progress to cirrhosis and hepatocellular carcinoma (HCC). NASH is estimated to overtake hepatitis C virus infection as the leading cause of liver transplantation, and there are currently no approved medicines for this disease. Prior to enrolment into late stage studies for new therapeutics in NASH, a biopsy is required to confirm the presence of the disease. However, a significant number of potential participants will not have the pathological hallmarks of NASH (ballooning, inflammation) or fibrosis as to be confirmed by a histopathological analysis (required by current regulatory guidance). Clinical trials thus run the risk that subjects who do not have NASH will undergo an unnecessary and risky procedure. cT1 is thus proposed as an add-on diagnostic for the purpose of reducing unnecessary biopsy of potential participants that will ultimately not meet the enrolment criteria for clinical trials based on histopathology.

The proposed context of use:

Magnetic Resonance Imaging Iron-corrected T1 (cT1) of liver tissue is a diagnostic enrichment biomarker that can be used for the recruitment of patients into clinical trials, in conjunction with clinical risk factors, to identify participants who are more likely to have NASH (at high risk of developing cirrhosis) based on liver histopathologic confirmation of fibrosis, inflammation and ballooning.

Description of the biomarker:

Iron-corrected T1 (cT1) is an imaging biomarker based on T1 mapping technology which takes

advantage of the increase in extracellular tissue fluid that occurs in response to inflammation and fibrosis. The corrected T1 (longitudinal relaxation time) takes the measurement of T2* (transverse relaxation time) into account which itself determines the iron content of a tissue. This is necessary due to the relative iron overload found in many liver diseases.

Iron corrected T1 is computed as per the published algorithm [1] and is quantified using post-processing software.

<u>Current and future research:</u>

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 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 overall satisfactory results.

Clinical Validation

The rationale for the cT1 biomarker and support for its use within the proposed Context of Use has partially been demonstrated in two independent cohorts:

- A training cohort, a UK-based population in which the proposed cT1 cut-off was systematically derived (RIAL-NICOLA and CALM trials)
- the proposed cT1 cut-off threshold was applied to an independent validation dataset (BAMC study) for validation purposes.

A further independent multi-centre *validation* study is currently being planned to evaluate, in 225 patients with suspected NASH referred for liver biopsy, the diagnostic performance of cT1 at discriminating those with NAS ≥4 & F≥2 from those without.

<u>Summary:</u>

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 cT1 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

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[1] Tunnicliffe, E.M., et al., A model for hepatic fibrosis: the competing effects of cell loss and Iron on shortened modified Look-Locker inversion recovery T1 (shMOLLI-T1) in the liver. J Mag Reson Imaging, 2017. 45(2): p. 450-462.