Proton-density fat fraction-derived R2* liver iron concentration – an exploratory study of Revita-2 phase II trial data

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Declaration of Financial Interests or Relationships

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Have the following financial interest or relationship(s) to disclose with regard to the subject matter of this presentation:

- Employment: full-time employees of Fractyl Laboratories Inc and may hold Fractyl stock and/or stock options.

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Have no financial interests or relationships to disclose with regard to the subject matter of this presentation.
▪ Use of MRI-based proton density fat fraction (PDFF) measurements of liver fat for clinical trial primary endpoints is well established.

▪ Accuracy of PDFF liver fat fraction measurements is reliant on correction for T2/T2* related signal decay
Signal Intensity

out-of-phase (OP)  in-phase (IP)

Echo time (TE)

(adapted from Sirlin CB, ‘Hepatic Steatosis - Liver MR Imaging: Quantitative Approaches to Liver Disease’, ISMRM Hawaii, 2017.)
Multi-echo data can be modelled to generate T2* maps, for FF map correction:

T2* maps are generated as part of the PDFF measurements and can be used to estimate liver iron concentration (LIC).

(from Henninger B et al. RöFo. 2015;187(06):472-479, for measurements at 1.5T.)
Dysregulation of iron homeostasis has been associated with:

- non-alcoholic fatty liver disease (NAFLD)
- and type 2 diabetes mellitus (T2DM)

The value of PDFF-derived T2*/R2* for quantification of LIC across varying siderosis/steatosis is under ongoing investigation.


DMR is an endoscopic treatment designed to reduce insulin resistance and hyperinsulinemia.\(^1,2\)

Prior studies (Revita-1) showed a single DMR procedure improves hepatic and glycemic parameters through 2 years in patients with T2DM, indicating potential benefit in T2DM ± NAFLD/NASH.\(^3-6\)

Revita-2 is a blinded, sham-controlled international multi-site multi-scanner vendor cross-over trial (NCT02879383).

Investigation of the effect of DMR on hepatic and glycaemic parameters in patients with poorly controlled T2DM

Trial endpoints include absolute and relative change in liver MRI-PDFF from baseline at 12 weeks (in patients with MRI-PDFF >5% at baseline)
1. To explore the association between PDFF-derived R2* LIC measurements and liver FF

2. To determine if there is a difference in the strength of association between relative change in FF and LIC at 12 weeks:

   *in DMR and sham-treatment cohorts*

   *to support the presence of any treatment-induced mechanistic differences in hepatic iron metabolism*
Patients recruited at 8 EU sites

Data were acquired at 7 sites (4 Philips & 1 GE 3T system, 1 Philips & 1 GE 1.5T system).

Vendor-derived PDFF sequences (e.g. Philips mDixonQuant, GE IDEAL-IQ) were used.
Baseline and 12-week post-treatment liver MRI scans

- Initial open-label training (n=17) cohort
- DMR (n=39) cohort
- Sham (n=23) cohort
Methods – Image analysis

- Custom-developed online platform (Ambra Health, New York, USA)

- Circular ROIs measuring up to 20mm diameter

- Colocalised on PDFF maps and T2* maps

- LIC (μmol/g) estimated from T2* data using previously reported methods

Linear regression with calculation of Pearson’s correlation coefficient

Relationship assessed:

a) Between baseline absolute liver FF and LIC measurements

b) Between relative (%) change in liver FF and LIC at 12 weeks post-treatment
Results – Baseline correlation

$r = 0.6097, P<0.0001$
Results – Training case cohort

$r = 0.7025, P=0.0024$
Results – DMR vs Sham cohort

DMR

Sham

$r = 0.4943, P=0.0016$

$r = 0.3235, P=0.1322$
The significant positive correlation demonstrated between PDFF-derived liver FF and LIC is comparable with previously reported results\(^1\).

This finding is important, given that data has been collated from multiple field strengths and patients with normal range LIC levels (<36 μmol/g)\(^2\).

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- Significant linear correlations between post-treatment relative (%) change in liver FF and LIC in both training and DMR cohorts were noted.

- Weaker non-significant correlations in the sham cohort raise the possibility of altered mechanistic effects on hepatic iron metabolism as a result of treatment.

- To better understand this phenomenon, ongoing studies using non-imaging biomarkers of iron metabolism are underway.
Conclusions

- PDFF-derived liver FF and LIC are positively correlated at baseline.

- Relative change in liver FF and LIC at 12 weeks is more strongly correlated post-DMR than in sham-treated patients raising the possibility of altered mechanistic effects on hepatic iron metabolism as a result of DMR.

Questions?
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