Concomitant Zonal Quantification of qSteatosis and qFibrosis in a Sub-study from EMMINENCE, a 12-month Phase 2b NASH study of MSDC-0602K

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Background/Aim

MSDC-0602K is a second-generation insulin sensitizer designed to selectively modulate the mitochondrial pyruvate carrier (MPC), which at the cellular level mediates the effects of overnutrition, a major cause of NASH and other metabolic disorders. The 12-month analysis conducted in 328 patients demonstrated that MSDC-0602K treated patients had significant and durable dose-dependent improvements in liver enzymes, glycemic control and improvement in biomarkers of liver injury. Standard single read biopsy demonstrated a dose dependent reduction in NAS score and steatosis, with a trend for a dose-dependent improvement in NASH resolution and fibrosis improvement. Re-reads of the qualifying biopsy, however, revealed poor intra-reader agreement and imprecision of NASH CRN biopsy reads. Using a non-randomized subset of 100 patients in a retrospective study, we assessed the association between steatosis reduction and fibrosis reduction when measured as a continuous variable using second harmonic generation (SHG) / two-photon excited fluorescence (TPEF) microscopy imaging of paired liver biopsy samples.

Methods

100 non-randomized paired liver biopsies from sites with unstained slides available in the EMMINENCE (NCT02784444) study were examined. Some sites did not retain unstained slides, so a random selection for this post-hoc analysis could not be performed. Qualifying biopsy confirmed NASH (NAS≥4, F1-F3, with at least 50% F2/F3). Fibrosis and steatosis changes were measured in a subset of paired liver biopsies using SHG/TPEF by readers blinded to treatment code. qSteatosis was quantified overall; and in periportal (Zone 1), pericentral (Zone 3), and in between (Zone 2). Fibrosis changes around the fat vacuoles were measured concomitantly.

Results

In patients with reduced qSteatosis score, MSDC-0602K treated patients (n = 24; 125mg and 250mg cohorts combined) showed significant decrease in qSteatosis across all three zones; as compared to the placebo (n = 13), which only showed significant qSteatosis reduction in Zone 2. Concomitant zonal analysis of fibrosis around the steatosis revealed that there was no significant reduction in fibrosis in all three zones for the placebo treatment patients, but MSDC-0602K treated patients clearly indicated a significant reduction in fibrosis in Zone 2. Using exploratory qSteatosis and qFibrosis, a clear difference is observed in the pattern of co-localization in treated versus placebo cohorts. More samples would be needed for further analysis to maximize this assessment.

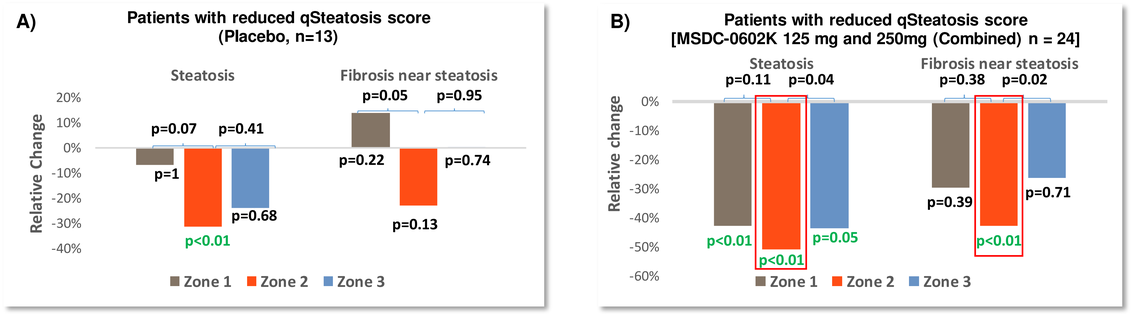

Figure 1. A) No significant reduction in fibrosis observed in all three zones for the placebo-treated patients. **B)** A relative decrease of 51% in qSteatosis in Zone 2 was associated with a relative decrease of 43% in qFibrosis in Zone 2.

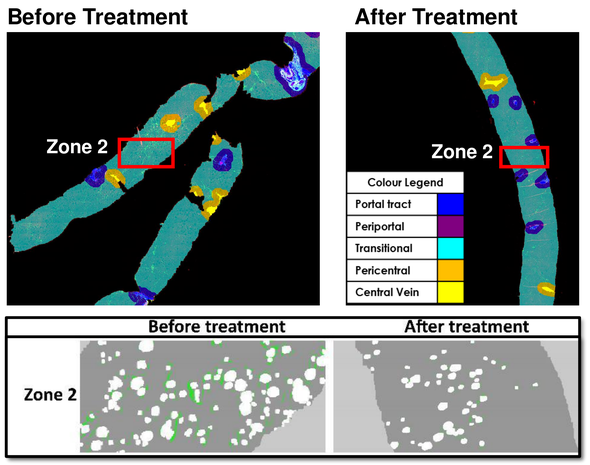

Figure 2. Quantification of collagen near steatosis by overlapping image analysis of SHG/TPE scanned images. Zone 2 fibrosis reduction around reduction in steatosis is clearly demonstrated in the post-treatment sample.

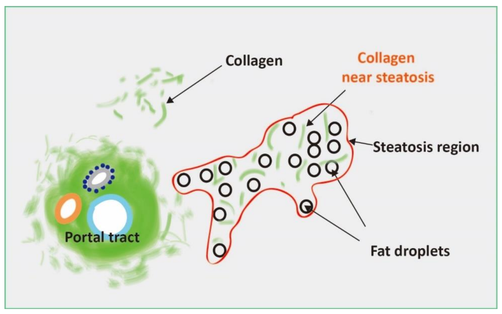

Figure 3. An illustration of how co-localization can reveal steatosis and concomitant fibrosis changes in specific regions of the liver biopsy.

Additional Information

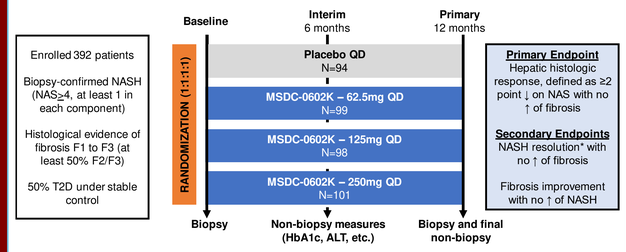

Figure 4. EMMINENCE Study – Phase II, randomized, double-blind, placebo-controlled, 12-month, multiple-dose study to evaluate the safety, tolerability and efficacy of three dose levels of MSDC-0602K in patients with NASH (Information provided from Cirius Therapeutics)

Conclusions

- MSDC-0602K treated patients demonstrated a **greater reduction in qSteatosis and qFibrosis across all zones** as compared to placebo treatment.
- Use of a continuous variable in liver biopsy assessment provides **quantitation of zonal changes in steatosis and fibrosis,** which cannot be captured using the NASH CRN system
- **Concomitant qSteatosis and qFibrosis analyses** on the same biopsy reveals mechanism of action (MOA) and is vital for the assessment of therapeutic efficacy.

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