The FASN inhibitor TVB-2640 is efficacious in a new 3D human liver microtissue model of NASH

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**Introduction**

- **FASN in NASH**
  - De novo lipogenesis (DNL) is upregulated in NASH and drives steatosis and lipotoxicity
  - Fatty acid synthase (FASN) is the last committed step in the DNL pathway and produces palmitate
  - Palmitate is not only a building block for lipids, but a signaling molecule that activates the inflammasome and TLR pathways, impacting inflammation and fibrosis in NASH

- **TVB-2640**
  - Once-a-day oral small molecule
  - Potent with FASN EC50 approx. 50 nM
  - Excellent and predictable human PK profile
  - Inhibits hepatic DNL up to 90% in human 13C-acetate tracer study
  - First-in-class FASN inhibitor

**TVB-2640 reduced liver fat in NASH patients in Ph2 FASCINATE-1 trial**

- 61% patients treated with 50 mg TVB-2640 had > 30% reduction in liver fat by MRI-PDF, vs 11% in placebo
- Also decreased inflammation and fibrosis markers
- Oral presentation EASL ILC Abstract A5074, Loomba et al., 2020

**Results in liver microtissue (LMT) model**

**TVB-2640 inhibits three hallmarks of NASH; steatosis, inflammation and fibrosis**

- **Primary human cell NASH model**
  - Contains 4 liver cell types
  - Mimics human NASH by culture with glucose, fructose, fatty acids, insulin, LPS
  - Developed and run by InSphero

- Results in liver microtissue (LMT) model
  - LMTs were treated for 10 days with TVB-2640 in full NASH conditions (high sugars, insulin, FFA, LPS). Supernatants were tested for IP-10 levels in the Luminex platform (day 5). LMTs were lysed and assayed for TG levels by 11°C-acetate tracer study. InSphero's OCA (INT747) provided suppression of cellular TG in the LMT model in full NASH conditions.

**Combination Study Cellular TGs**

- **In vitro culture for 10 days**
  - **Hepatic steatosis**
    - **Assay for triglycerides, cytokines, fibrosis markers, gene expression, histology**
  - **Assay for**
    - **High sugars, insulin, FFA, LPS**

- **Inflammation IP-10**
  - **Fibrosis Sirus Red**

**LMTs were treated for 10 days with TVB-2640 and/or other compounds in full NASH conditions (high sugars, FFA, insulin, LPS). LMTs were lysed and assayed for TG levels by 11°C-acetate tracer study. InSphero's OCA (INT747) provided suppression of cellular TG in the LMT model in full NASH conditions.**

**Conclusions**

- TVB-2640 reduced markers of steatosis (cellular TGs), inflammation (IP-10) and fibrosis (Sirius Red) in the human primary cell LMT model.
- Consistent with FASN inhibitor results in mouse NASH DIO and CCl4 models, previously published.
- Decreased cellular TGs by TVB-2640 in the LMT model recapitulates reduced liver fat by TVB-2640 in the recent Ph2 FASCINATE-1 study in NASH patients.
- Other NASH agents tested (Elafibranor, OCA) did not decrease cellular TGs in the LMT full NASH model as single agents, although decreases liver fat or steatosis have been shown in the clinic. These agents do not directly inhibit DNL, while ACC inhibitor GS-9076 had similar effect to TVB-2640 (not shown), consistent with direct DNL inhibition. The LMT full NASH model may not recapitulate the required mechanisms of altered lipid metabolism for other classes, and/or higher concentrations may be required.
- Addition of TVB-2640 to the other NASH agents tested provided suppression of cellular TG in the LMT model in full NASH conditions.
- Lipidomic profiling of supernatants by One Way Liver and assessment of fibrosis readouts such as ProC3 are ongoing.
- The InSphero LMT model provides a usable tractable and non-invasive human model in NASH.

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- Syed-Ahmad et al., 2020, Hepatology 72: 100.
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