Establishing the foundation for a novel, first-in-class, fatty acid synthase inhibitor, TVB-2640, for NASH treatment

INTRODUCTION
Increased hepatic de novo lipogenesis (DNL) drives liver fat deposits and inflammation in non-alcoholic fatty liver disease and plays a role in developing non-alcoholic steatohepatitis (NASH). Targeting fatty acid synthase (FASN), a key enzyme of DNL, could treat liver diseases. We have reported that FASN inhibition prevents diet induced liver steatosis in mice and blunts inflammatory responses. A clinical trial of TVB-2640, an oral, selective FASN inhibitor, in >130 cancer patients showed this drug was generally well tolerated, absorbed efficiently through the gut and inhibited DNL in the skin.

CONCLUSIONS & NEXT STEPS
FASN inhibition reduces diet induced liver damage in mice & inhibits lipogenesis in humans
Preclinical – diet induced obese mice show FASN inhibition:
• Reversed steatosis
• Reduced inflammatory cytokines and the adipokine leptin
• Reduced fibrosis
• Decreased liver triglycerides & cholesterol
• Decreased plasma ALT & AST levels
• Effective at very low doses
Clinical – TVB-2640, a once-daily oral FASN inhibitor
• Inhibited lipogenesis in solid tumor patients
• Exhibited excellent absorption and PK
TVB-2640: potential backbone NASH therapy
• Treatment inhibits multiple pathogenic drivers of NASH
• Currently evaluating inhibition of hepatic lipogenesis in humans to identify doses for NASH clinical development

METHODS
• FASN inhibitor (TVB-3664) was dosed daily by oral gavage in mice.
• TVB-3646: close analog of TVB-2640 with better murine PK & potency
• Results left panel - Male C57BL/6J mice were fed high fat/sugar diet (Research Diets #D12492) (CARE LLC, Fort Collins, CO)
• Results top middle panel - Male C57BL/6J mice were fed high fat/sugar diet (Research Diets #D14120701) (CARE LLC, Fort Collins, CO)
• Results lower middle panel - Male C57BL/6J mice were fed high fat/sugar diet (Research Diets #D12492) (CARE LLC, Fort Collins, CO)
• Quantitative serum fatty acid analysis was performed on Substrate® Patches collected for biomarker analysis during the TVB-2640 Phase 1 trial, CLIN-002. Analysis was performed at Metabolon, Inc. using GC-MS after lipid hydrolysis and derivatization.

RESULTS
FASN inhibition prevents development of steatosis, inflammation & fibrosis in mice on a high fat/sugar diet

FASN inhibition treats liver damage in mice with established steatohepatitis and fibrosis

TVB-2640 inhibits lipogenesis in humans: non-invasive skin assay in solid tumor patients

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