Liver Selective Acetyl-CoA Carboxylase Inhibition by ND-654 Improves Survival in Cirrhotic Rats with Hepatocellular Carcinoma

Abstract #4452

Omeed Moaven1, Lan Wei1, Geraldine Harriman2, Jeremy Greenwood3, Omid Farokhzad4, Srinivas Viswanath1

1. Overview

- Current treatment options for HCC are limited, and as such, prognosis is extremely poor with a 5-year survival less than 12%.
- Metabolic attenuation is a promising approach to cancer therapy, and rate-limiting steps in key biosynthetic pathways are particularly attractive targets. HepaSpecific ND-654 demonstrates excellent PK/PD relationships in the target tissue, the liver (exposure vs Malonyl-CoA reduction) and is effective at modifying cirrhotic and HCC markers in vivo.

2. Nimbus Solves ACC Druggability Challenge by Targeting Allosteric Site in Biotin Carbamoyl Domain

- Challenges in Drugging ACC
  - ACC is a druggable target with a large active site
  - ACC is associated with severe side effects
  - ACC inhibitors are not selective
  - ACC inhibitors induce stress

- Nimbus ACC structure

3. ND-654: Hepatic-Selective ACC Inhibitor

- ND-654 is a Selective ACC inhibitor
- ND-654 is highly selective across a broad panel (>1000x)

4. ND-654 Demonstrates Liver Tissue Specific Target Engagement and Pharmacology

- ND-654 preferentially biodistributes to the liver where it inhibited ACC activity but did not increase liver toxicity.

5. ND-654 is well tolerated in rats administered DEN animals on drug appear healthy.

6. Liver Directed ND-654 Improves Markers of Liver Health in DEN Treated Rats

- ND-654 reduces serum levels of total bilirubin.

7. Treatment with 10 mg/kg ND-654 QO Results in Marked Reduction of Tumor Nodules

- ND-654 decreases PCNA expression in tumors and results in reduced tumor burden.

8. ND-654 Decreases PCNA Expression in Tumors and Results in Reduced Tumor Nodules

- ND-654 significantly improved survival in the aggressive DEN HCC model.

9. ND-654 Significantly Improved Survival in the Aggressive DEN HCC Model

- ND-654 shows improvements in fibrosis, stellate cell activation and inflammation markers in the liver.

10. ND-654 Shows Improvements in Fibrosis, Stellate Cell Activation and Inflammation Markers in the Rat DEN Model

- ND-654 decreases serum levels of total bilirubin.

11. Quantitative Liver Adipokine Array From ND-654 treated DEN Rats Demonstrates Modulation of Fibrosis, Inflammation and Tumor Markers in the Liver

CONCLUSION

- ND-654 preferentially biodistributes to the liver where it inhibited ACC activity but did not increase liver toxicity.
- ND-654 inhibits HCC development by decreasing tumor proliferation and causing tumor necrosis.
- ND-654 reduces markers of inflammation and fibrosis and improves overall survival in the DEN rat model.
- Our results therefore provide further evidence that de novo lipogenesis is an important mediator of hepatic carcinogenesis.
- Selective inhibition of hepatic ACC is a potential therapeutic strategy for HCC.