# A NOVEL, HOST-DIRECTED, SMALL MOLECULE INHIBITOR OF HCV DISPLAYS 60 SUSTAINED PHARMACOLOGICAL INHIBITION OF LIVER FATTY ACID SYNTHASE

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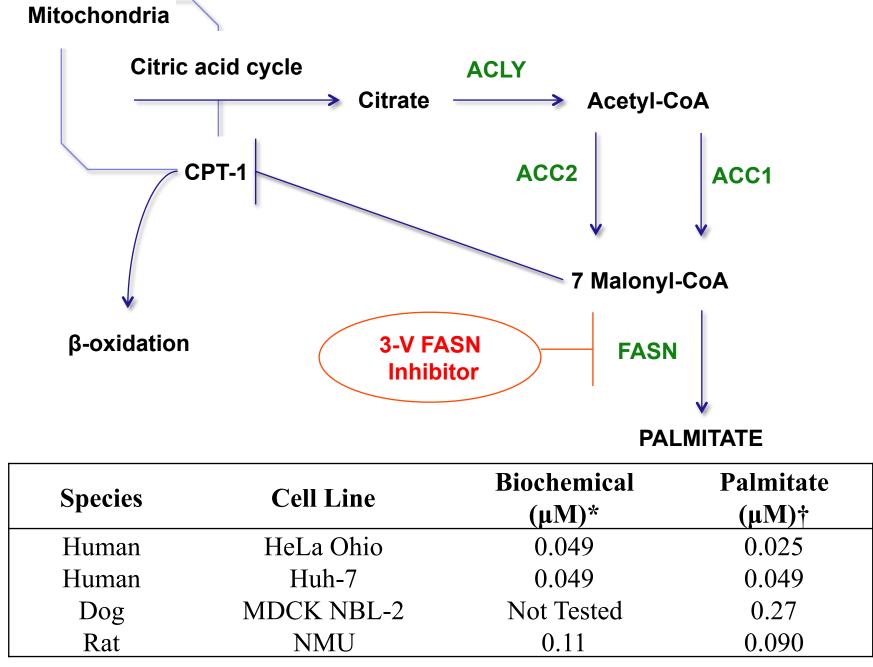
### Abstract

**BACKGROUND:** Optimized new therapies for HCV are needed that have pan genotypic activity and a high barrier to viral resistance. To meet these challenges, 3-V Biosciences has developed a small molecule inhibitor of HCV that targets the host's fatty acid synthase (FASN) enzyme (Abstract 88). HCV infection increases the expression of FASN, the host enzyme responsible for the production of palmitate, and down regulation of FASN inhibits critical viral processes including entry into cells, RNA replication, and particle assembly. FASN inhibitors are expected to have pangenotypic activity and pose a high barrier to viral resistance due to interference with multiple stages of the HCV lifecycle.

**<u>OBJECTIVE</u>**: The objective of this study is to characterize the pharmaceutical properties of a novel, small molecule inhibitor of FASN as a treatment for chronic HCV infection.

**<u>RESULTS</u>**: 3-V Bioscience's FASN small molecule inhibits the human FASN enzyme in biochemical and cell based assays with an IC<sub>50</sub> of 0.049  $\mu$ M and 0.025  $\mu$ M, respectively. Activity against the HCV Gt1b replicon parallels FASN inhibition with an EC<sub>50</sub> of 0.060  $\mu$ M and no observed cytotoxicity. A 10 mpk oral dose of this compound is rapidly absorbed and highly bioavailable ( $\sim 60\%$ ) in rats and dogs with an apparent half-life of 3.2 h and 3.9 h, respectively. Pharmacodynamic activity in rats is exposure-dependent: a 60 mpk dose causes complete inhibition of palmitate synthesis 12h after administration while a single 30 mpk oral dose causes >50 % inhibition at 12h. Palmitate synthesis remains suppressed by  $\sim 60\%$  at 24 hours following a 60 mpk dose, consistent with a once-daily oral dosing regimen. The results of this current work demonstrate that 3-V Bioscience's FASN inhibitor can inhibit de novo fatty acid synthesis in vivo and has pharmaceutical properties necessary for clinical development.

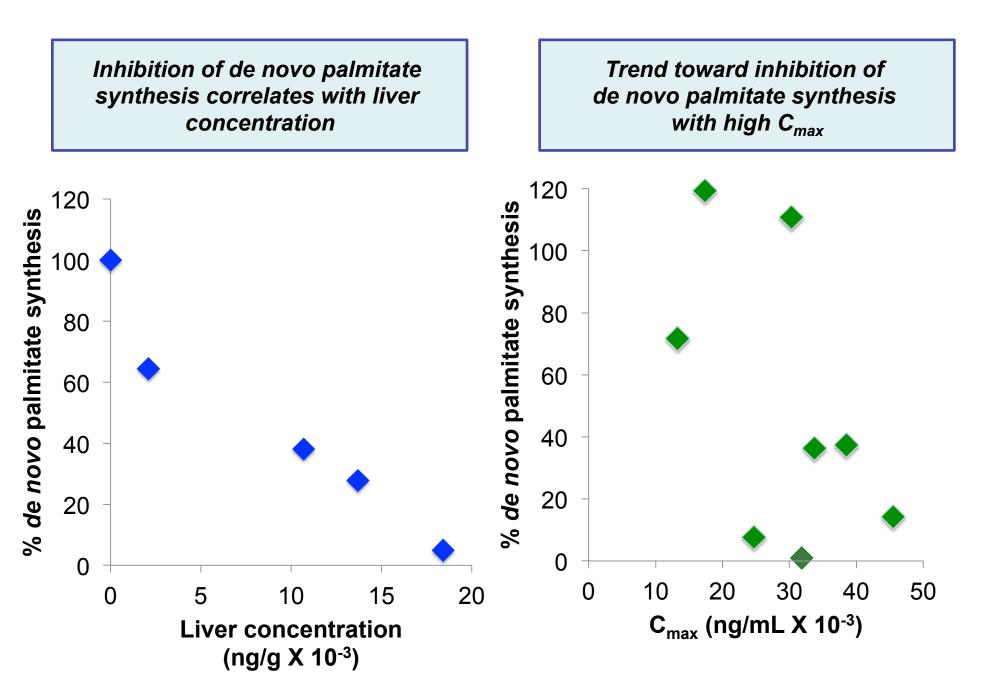
# In Vitro Activity Against Human, Rat, and Dog FASN



\* Biochemical assay: measures the activity of human (crude extract from SKBr3 cells) or rat (purified from rat liver) FASN by measuring the release of coenzyme A with the dye CPM <sup>†</sup> Palmitate assay: To measure *de novo* synthesis of palmitate by FASN, a stable labeled substrate  $({}^{13}C_2 \text{ acetate})$  was added to cells and  ${}^{13}C_2$  labeled palmitate was measured by LC-MS.

Species	R
Dose (mpk)	1
Half-life (hr)	3
T <sub>max</sub> (hr)	1
C <sub>max</sub> (ng/mL)	17
AUC <sub>last</sub> (hr*ng/mL)	11.
% F	59

### **Dose and Exposure Relationships to Inhibition of** de novo Palmitate Synthesis In Vivo

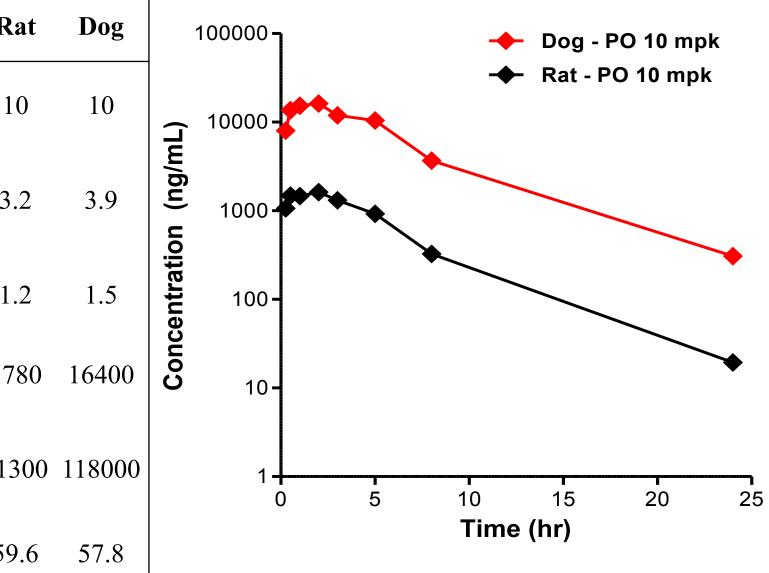


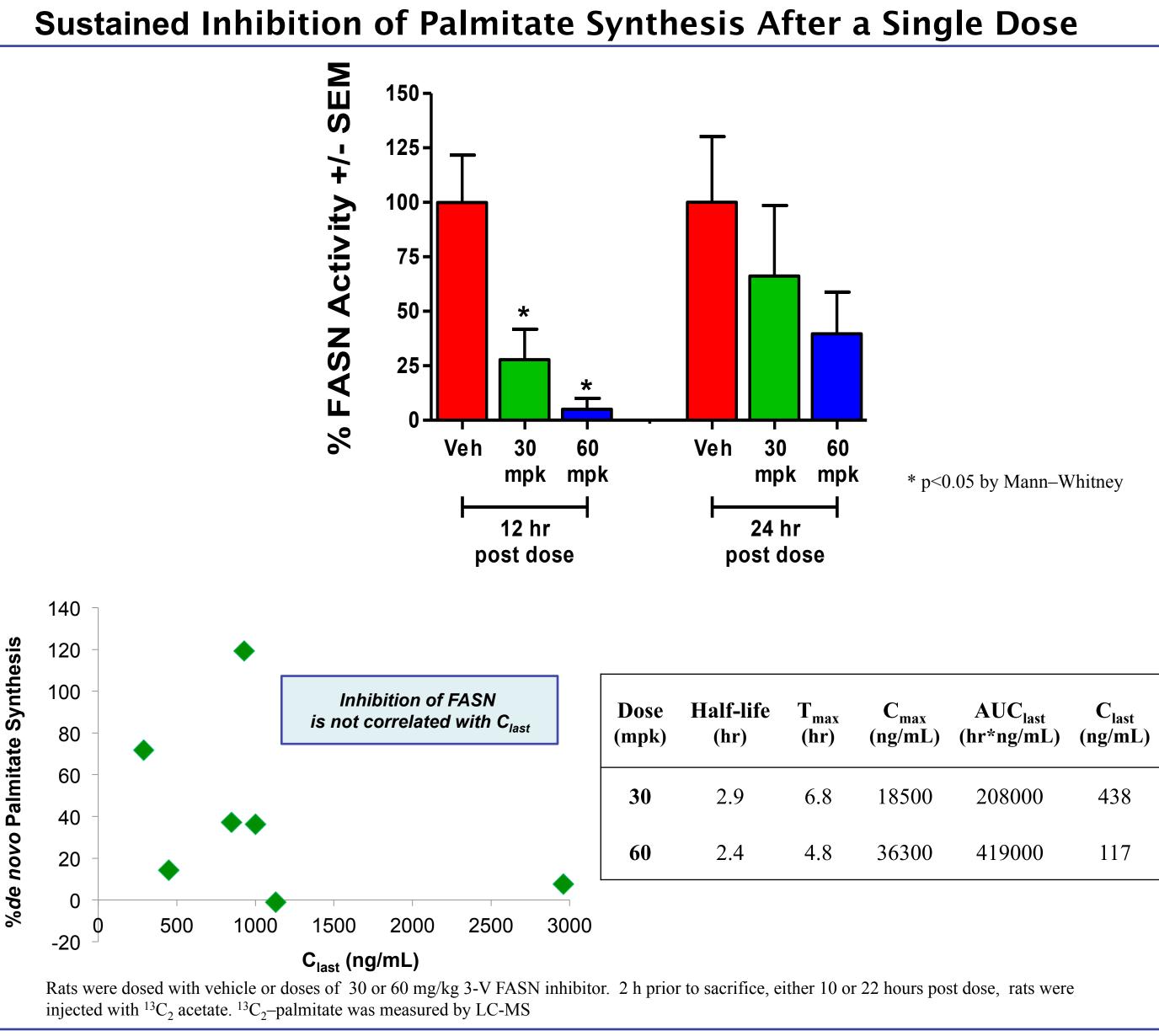
Rats were dosed with vehicle or doses of 3-V FASN inhibitor between 10 and 90mpk. 2 h prior to sacrifice, rats were injected with  ${}^{13}C_2$  acetate tracer.  ${}^{13}C_2$ -palmitate was measured by LC-MS.

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### **Oral Pharmacokinetics in Rats and Dogs**

Dogs and rats display similar apparent half-lives after oral doses of 10 mg/kg, however exposures are 10 X higher in dogs





- Inhibition is reversible in vivo

# Conclusions

3-V's small molecule FASN inhibitor is a potent inhibitor of human fatty acid synthase

• A single oral dose can inhibit *de novo* palmitate synthesis up to 24 hours *in vivo* 

Reduction of *de novo* palmitate synthesis correlates with liver concentration of the drug

The drug's profile meets the criteria to advance into Phase 1 clinical studies in 2013

Disclosure: All authors are current or former employees of 3-V Biosciences, Inc.

