Clinical pharmacokinetics of INI-822, a small molecule inhibitor of HSD17B13

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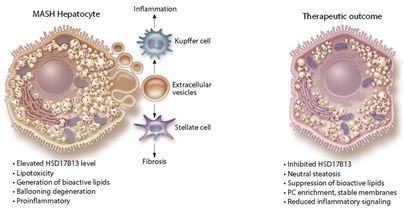
Introduction

Inactive alleles of HSD17B13 are associated with
- Decreased rates of NASH and cirrhosis[1]
- Decreased ballooning, inflammation and fibrosis[2]
- Increased hepatic phosphatidylcholine (PC) content[3,4]

HSD17B13 is a lipid droplet protein capable of oxidizing bioactive lipids[1]
HSD17B13 interacts with lipid metabolizing enzymes on the mitochondria and endoplasmic reticulum[5]
Suggesting a role for HSD17B13 in bioactive lipid flux mediating lipotoxicity



Background

- INI-822 decreases fibrotic proteins in NASH-like Liver on a chip studies[6]
- INI-822 increased circulating HSD17B13 substrates and decreased products in nonclinical models of liver injury with an ED_{50} of 5.4± 2.2 mg/kg in rats and an EC50 for C_{trough} of 56 ng/mL.[7]

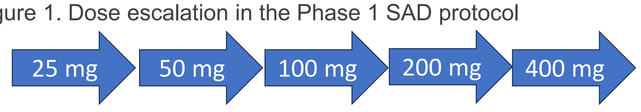
INI-822 is potent and selective
Well tolerated and stable

B13 Ki 15-HETE (nM)	22.7
Selectivity of HSD17B2, B3, B11, B14 over HSD17B13	>100
Safety44/hERG	No significant off target
HepG2 and Hepatocyte cytotoxicity (µM)	>30
CYP phenotyping	Moderate metabolism by multiple CYPs

Methods and Materials

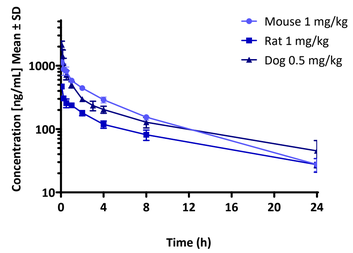
INI-822 was orally administered to mice (10 mg/kg, n=3/group, sparse sampling), rats (30 mg/kg, n=3) and dogs (10 mg (~1 mg/kg), n=6). Blood was collected, processed to plasma at timed intervals and INI-822 plasma concentrations were determined by LC/MS-MS. In a first-in-human study, PK was determined in a Phase 1, placebo-controlled study of INI-822 in healthy volunteers (n=6/cohort) following a single oral dose of INI-822. Noncompartmental PK parameters were calculated. Data presented as mean+/-SD. Steady state QD model was built using geometric mean plasma concentration values with iterative additions encompassing >20 fold the terminal half life while maintaining terminal phase through 3 half lives.

Figure 1. Dose escalation in the Phase 1 SAD protocol



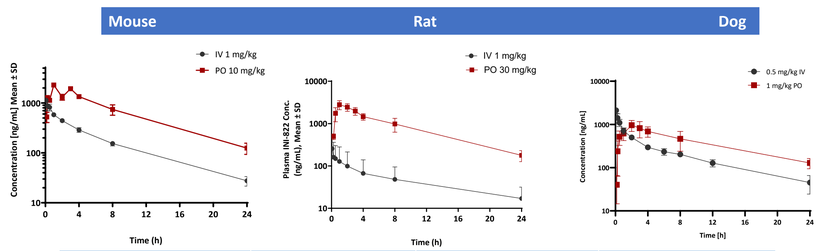
Results

IV Pharmacokinetics in Nonclinical Species



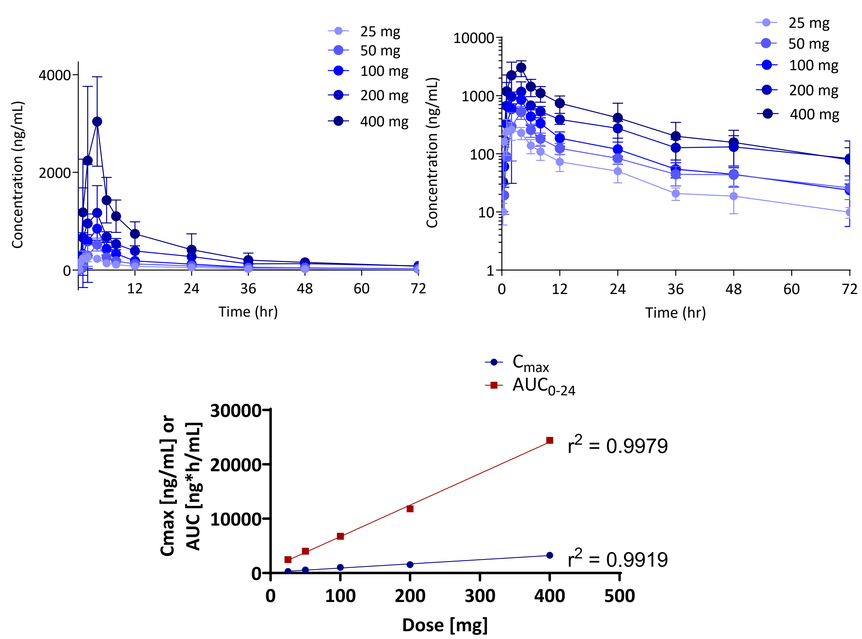
	Mouse	Rat	Dog
Cl [mL/min/kg]	3.6	6.8	1.4
V_d [mL/kg]	1.9	5.7	0.92
$t_{1/2}$ [h]	6.0	9.8	7.6

PO Pharmacokinetics in Nonclinical Species



	Mouse	Rat	Dog
Dose [mg/kg]	10	30	~1 (10 mg total)
AUC_{0-24} [ng*h/mL]	17,500	22,200 ± 5480	10,600 ± 3390
C_{max} [ng/mL]	2,290	3,030 ± 550	765 ± 375
$t_{1/2}$ [h]	5.9	6.5 ± 0.2	8.9 ± 1.8
F%	39%	36%	97%

Single Ascending Dose Pharmacokinetics Healthy Volunteers

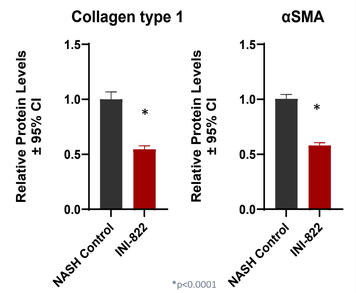


Background (Continued)

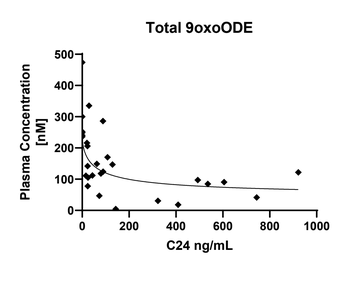
Nonclinical Pharmacology[6,7]

Liver on a chip efficacious free concentration	24 ng/mL
EC50 trough oxylipin	56 ng/mL

MPC/Liver on a chip

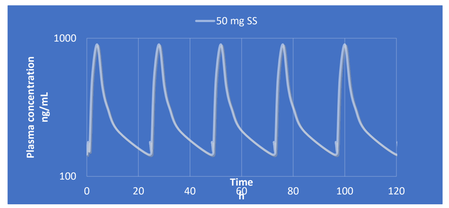


Rat Target Engagement



Results (Continued)

Geometric Steady State Model



	Estimated C_{minSS} ng/mL
25 mg	86
50 mg	140
100 mg	210

- Estimated trough values are in excess of EC50 in rat target engagement model

Conclusions

- INI-822 is a low clearance molecule with good oral bioavailability in preclinical species
- INI-822 achieved clinical plasma exposures that exceeded concentrations projected to inhibit HSD17B13 based on preclinical models
- Single ascending dose PK in healthy subjects achieved approximately dose-proportional linear increases in AUC_{0-24} and C^{max}
- INI-822 represents the first small molecule inhibitor of HSD17B13 with PK characteristics suitable for once daily oral dosing in the clinic.
- A Phase 1 study, to include evaluation of multiple doses of INI-822 in healthy volunteers and patients with liver disease, is ongoing.

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