A PLACEBO-CONTROLLED, MULTICENTER, DOUBLE-BLIND, RANDOMISED TRIAL OF EMRICASAN (IDN-6556) IN SUBJECTS WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD) AND RAISED TRANSAMINASES

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Introduction:

Emricasan (IDN-6556, PF-03491390) is a potent irreversible pan-caspase inhibitor with the ability to rapidly reduce elevated levels of serum ALT, AST and caspase mediated cleavage of cytokeratin-18 in HCV infected patients.[1,2,3] To date, emricasan has been studied in more than 550 individuals and has exhibited a safety profile similar to placebo.

Emricasan is currently in three Phase 2 clinical trials, including two trials in patients with liver cirrhosis. Here we report the effect of emricasan in subjects with NAFLD and raised transaminases.

Background:

Caspases are attractive targets for the treatment of a variety of liver diseases[4] and play a central role in the processes of apoptosis and inflammation. They are enzymes responsible for executing apoptotic pathways, or programmed cell death, and for activation of cytokines such as IL-1β and IL-18. Both caspase-mediated apoptosis and inflammation have been shown to play important roles in the development and progression of NASH and NAFLD, leading to the hypothesis that inhibition of caspases may have significant therapeutic benefit for the treatment of NAFLD/NASH[5,6]. Emricasan has shown specificity in assays measuring caspase inhibition and prevented apoptosis in a variety of cellular assays. It also demonstrated efficacy in a number of animal models of liver disease, as well as in models of damage to other organ systems. Emricasan was also protective in models of NAFLD/NASH where it reduced steatosis, inflammation, apoptosis and fibrosis.

Human studies have demonstrated that emricasan can lower serum transaminases after intravenous or oral administration to a limited number of NAFLD/NASH subjects. Treatment of subjects with a variety of liver diseases with emricasan was also associated with statistically significant reductions in activated serum caspases and cleaved CK18 (cCK18), a caspase-cleaved substrate, indicating that emricasan works by the presumed mechanism of action of inhibiting apoptosis of liver cells. In addition, emricasan inhibits a subgroup of caspases involved in the maturation of proinflammatory cytokines, IL-1β and IL-18.

Methods:

The primary objective of this placebo-controlled, multicentre study (USA only) was to evaluate the effect of emricasan 25 mg BID orally for 28 days in subjects with NAFLD and elevated ALT (defined as ALT levels ≥1.5 x ULN on at least two occasions, seven or more days apart, during the Screening period).

The secondary objectives of this study were as follows:

- To assess the efficacy and pharmacodynamics of emricasan (25 mg BID) in subjects with NAFLD and raised transaminases using serum markers of mechanism of action, apoptosis, inflammation and fibrosis.
- To assess the safety and tolerability of emricasan (25 mg BID) in subjects with NAFLD and raised transaminases.

Subjects were randomized in a 1:1 ratio (19 emricasan treated subjects and 19 placebo subjects) to the following:

- Emricasan 25 mg BID for 28 days
- Placebo BID for 28 days

Subjects on statins, fibrates, sulfonylureas and/or metformin were required to be on stable doses of drug for 3 months prior to study entry and for the study duration. Laboratory and serum biomarker samples were collected at each study visit (Day 1 (Baseline), Day 7, Day 28 and Day 56 (Follow-up). The serum biomarker variables assessed included ALT, cCK18/M30, fICK18/M65, and Caspase 3/7.

We report on the primary endpoint in the study (change from Baseline in ALT at Day 28 compared to Placebo) and key secondary endpoints (change from Baseline in cCK18, fICK18, caspase 3/7).

Results:

All 38 subjects randomized were dosed. Baseline characteristics were well matched between treatment groups as presented in in Table 1.

Table 1: Subject Demographics and Baseline Characteristics

		Placebo	IDN-6556 25 mg BID
n		19	19
Gender	(Male/Female)	12/7	12/7
Ethnicity	Hispanic or Latino/Other	1/18	3/16
Race	(American Indian or Alaska native/Black or African American/White)	0/2/17	1/1/17
Mean Age (years)		53.7 (34-70)	45.7 (23-76)
Mean BMI (kg/m²)		32.6 (22.6-41.5)	35.0 (26.5-47.5)

All 38 subjects had a Day 28/ET visit. Three subjects in the placebo group prematurely discontinued the study prior to Day 28. Reasons for discontinuation were given as lost to follow-up (1 subject), continuation would have been in violation of the inclusion/exclusion criteria (1 subject) and other (1 subject). Five subjects (3 placebo and 2 active) were excluded for the pre-specified per-protocol (PP) population.

The study was designed to estimate the treatment effect of emricasan on ALT. The median absolute reduction in ALT from Baseline was greater for emricasan 25mg BID than for placebo at Day 7 (36.65 vs 8.65 U/L) and at Day 28 (25.80 vs 9.40 U/L). This change from Baseline in the emricasan group vs the placebo group was also statistically significant ($p<0.05$).

Figure 1: Absolute Change from Baseline in ALT

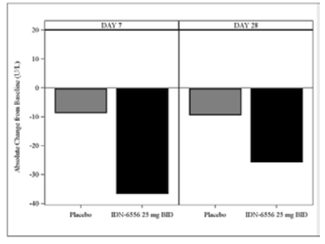
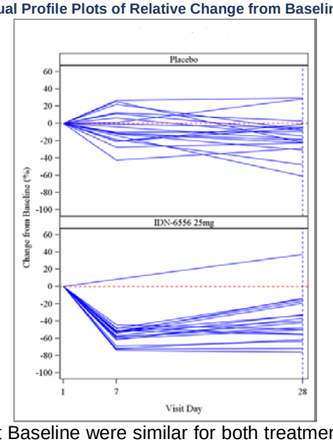


Figure 2: Individual Profile Plots of Relative Change from Baseline in ALT



AST values at Baseline were similar for both treatment groups with median values of approximately 44 U/L. The median change from Baseline in AST was similar at Day 28 (-6.7 vs -5.2 U/L decreases for emricasan 25 mg BID and placebo respectively). Median relative changes from Baseline in AST were a -22% vs -10% reduction at Day 28 for emricasan 25 mg BID and placebo respectively.

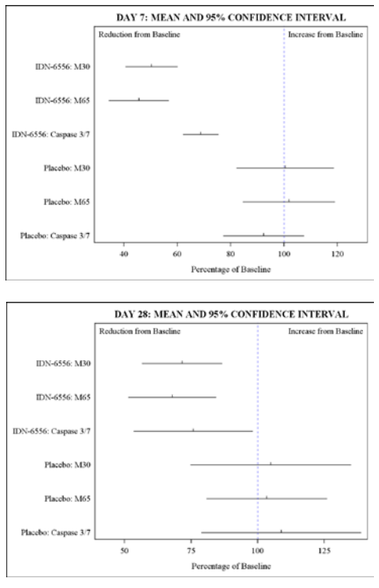
Consistent with literature reports, Baseline serum levels of cCK18 were elevated in subjects with NAFLD and median Baseline values of cCK18/M30, fICK18/M65 and Caspase 3/7 were similar across the groups (Table 3).

Table 3: Baseline Values of Biomarkers – Serum cCK18/M30, fICK18/M65 and Caspase 3/7

Parameter	Treatment Group	Baseline Characteristics			
		Mean	SD	Median	Min/Max
cCK18/M30 (U/L)	Placebo (n=19)	759	886	416	152/3811
	IDN-6556 25 mg BID (n=19)	605	225	586	281/1140
fICK18/M65 (U/L)	Placebo (n=19)	1334	1259	879	431/5547
	IDN-6556 25 mg BID (n=19)	876	315	812	317/1708
Caspase 3/7 (RLU)	Placebo (n=19)	1138	569	1356	300/2138
	IDN-6556 25 mg BID (n=19)	1138	709	1190	316/2478

Mean relative changes from Baseline in cCK18/M30 were a -28% reduction vs 5% increase at Day 28 for emricasan 25 mg BID and placebo respectively. Mean relative changes from Baseline of fICK18/M65 at Day 28 were -32% and 3% for 25mg BID and placebo respectively and mean relative changes from Baseline in Caspase 3/7 were
-24% vs 9% increase for placebo.

Figure 3: Relative Change from Baseline in Caspase Biomarkers



Emricasan was generally well tolerated in the study and adverse events were typical of what has been previously reported. Eighteen of the 38 subjects randomized experienced adverse events, of which 2 subjects reported serious adverse events. One subject on emricasan 25 mg BID reported cellulitis of the lower limb and one subject on placebo reported acute GI haemorrhage. Neither were deemed treatment related by the investigator. No deaths were reported in the study. Of the 19 placebo subjects, 8 subjects reported 20 adverse events. In the emricasan 25 mg BID group (n=19) there were 23 adverse events reported by 10 subjects.

Importantly no changes in total cholesterol, HDL, LDL or triglycerides were reported in the study.

Conclusions:

- Of the 38 subjects who received study treatment, 35 subjects completed the study (Day 28). Of these subjects, 19 received placebo, and 19 were in the emricasan 25 mg BID treatment group.
- cCK18/M30 was raised in subjects with NAFLD.
- Clinically relevant and statistically significant reductions were seen in ALT at Day 28 compared to Baseline in subjects randomised to emricasan compared to placebo.
- Emricasan treatment caused mean reductions in cCK18/M30 compared to placebo at Day 28 of approximately 30%, consistent with the reductions reported in other studies.
- Similar magnitudes of reductions were also reported in the Caspase 3/7 and fICK18/M65 biomarkers.
- Emricasan treatment caused statistically significant decreases from baseline in cCK18, fICK18 and caspase 3/7, on both Days 7 and 28.
- No changes were reported in weight, cholesterol, HDL, LDL or trigycerides in the study in either the emricasan or placebo arms.
- Emricasan was generally well tolerated in the study and the adverse event profile was similar to that already reported in previous studies.
- The study achieved its objectives and the results suggest that emricasan may have utility in the treatment of NAFLD/NASH although larger confirmatory studies will be required.

References:

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Disclosure of Interest: M. Shiffman: Grant: Conflict with: Abbvie, Achillion, Beckman-Colter, Bristol Myers-Sqibb, Boehringer-Ingelheim, Conatus, Gilead, Hologic, Intercept, Lumena, Merck, Novartis, Sponsored Lectures : Conflict with: Roche/Genentech, Vertex, Bayer, Janssen; B. Freilich: Grant: Conflict with: Conatus; R. Vuppalanchi: None Declared; K. Watt: Grant: Conflict with: Gilead, Conatus; G. Burgess: Stockholder: Conflict with Conatus, Employee: Conflict with: Conatus; M. Morris: Stockholder: Conflict with: Conatus, Employee: Conflict with: Conatus; B. Sheedy: Employee: Conflict with: Conatus; E. Schiff: Grant: Conflict with: Abbott, Bristol Myers Squibb, Gilead, Merck, Orasure Technologies, Roche, Janssen, Discovery Life Sciences, Beckman Coulter, Siemens, MedMira, Conatus, Consultant: Conflict with: Acorda, Other: Conflict with: Pfizer, Arrowhead

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