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 downstream of cytochrome-18 in HCV infected patients. To date, emricasan has been studied in more than 550 patients with liver cirrhosis. Here we report the effect of the emricasan on patients with liver cirrhosis. Here we report the effect of the emricasan on patients.

Elevated serum levels of cCK18 have been associated with severity in a wide variety of liver diseases. Full-length CK18 is released following cell wall rupture, and microparticles that promote disease progression, Figure 1.

Background: Caspase-mediated cell death plays a central role in the processes of apoptosis and inflammation. As such, caspases are attractive targets for the treatment of a variety of liver diseases. In liver disease, chronically elevated apoptosis is reported to increase progressively with disease severity and is considered a mechanism of liver disease. Full-length CK18 is released following cell wall rupture, and microparticles that promote disease progression, Figure 1.

Methods: A total of 28 subjects with hepatic impairment and 8 matched healthy controls were enrolled in an open label study to evaluate the pharmacokinetics and pharmacodynamics effect of emricasan. Twelve subjects classified as mild (Child-Pugh A), eight as moderate (Child-Pugh B) and eight as severe (Child-Pugh C) were enrolled in the study. Eight healthy control subjects were matched to severe subjects based on demographic characteristics.

On Study Day 1, a pre-dose blood sample was collected followed by administration of a single 50 mg dose of emricasan to all subjects. Eight blood samples were then collected over a 12 hour period post-dose with further samples collected at 24 and 48 hours post-dose.

Results: Consistent with literature reports, baseline serum levels of cCK18 were elevated in subjects with advanced liver disease. In addition, serum levels of cCK18 increased along with the progression of disease stage, Figure 2. These data suggest that elevated levels of apoptosis in these subjects may contribute to disease progression and pathology in patients with advanced liver disease.

Summary: Emricasan means liver and median levels.

Serum levels of cCK18 were rapidly reduced in all subjects with liver disease following a single 50 mg oral dose of emricasan, Figure 3. A maximal response was observed approximately 4 hours post-dose. Importantly, cCK18 activity quickly approached levels observed in the cohort of matched healthy subjects.

Serum levels of cCK18 were rapidly reduced in all subjects with liver disease following a single 50 mg oral dose of emricasan, suggesting that, in addition to decreasing levels of caspase 3/7, emricasan can be expected to effectively reduce apoptosis in these subjects. It is particularly noteworthy that this marker was reduced in all subjects with hepatic impairment while no effect was observed in any healthy subject, Figure 4.

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Conclusions: Caspase activity and apoptosis are elevated in subjects with advanced liver disease and may play a role in disease pathology and progression. Following a single 50 mg oral dose, emricasan rapidly reduced caspase enzymatic activity, serum markers of apoptosis (M30) and overall cell death (M65) in all subjects with hepatic impairment.

Caspase activity and apoptosis are elevated in subjects with advanced liver disease and may play a role in disease pathology and progression. Following a single 50 mg oral dose, emricasan rapidly reduced caspase enzymatic activity, serum markers of apoptosis (M30) and overall cell death (M65) in all subjects with hepatic impairment.

These reductions were statistically significant. Emricasan may provide clinical benefit to patients with advanced stages of liver disease.

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References:


The collective data and observations presented above suggest that the pan-caspase inhibitor, emricasan, can significantly and effectively reduce serum levels of caspase 3/7, emricasan can effectively reduce the levellcaspase activity, apoptosis and, more generally, cell death in patients with advanced liver disease. These attributes may translate into clinical benefit in patients with advanced stages of liver disease.

Summary statistics of these data are presented in Table 1.

Table 1: Effect of emricasan on caspase activity and biomers of cell death and apoptosis in subjects with hepatic impairment and matched healthy controls.

The pharmacokinetic information derived from this trial was used to support the design of ongoing trials in patients with cirrhosis. These data will be presented, along with pharmacokinetic data from additional trials in patients with organ impairment.

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