Introduction: Emricasan (IDS-6556, PF-04314016) is a potent irreversible pan-caspase inhibitor. To date, emricasan has been studied in more than 650 subjects and has exhibited a safety profile similar to placebo. Emricasan is currently in three Phase 2 clinical trials. Here, we report the effects of emricasan in patients with acute-on-chronic liver failure (ACLF).

Background: Caspases play 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.

ACLF is a syndrome characterized by the acute deterioration of liver function in patients with compensated or decompensated, but stable cirrhosis. It is commonly precipitated by an acute event and associated with failure of the function of extra-hepatic organs. The lack of liver detoxification, and metabolic and regulatory dysfunction together with an altered immune response, lead to life-threatening complications, such as renal failure, increased susceptibility to infection, hepatic coma, and multiorgan failure. In recent years, the recognition of clinically different patterns of liver failure associated with cirrhosis has led to the concept of ACLF. ACLF is an 'acute-on-chronic' liver failure.

Although substantial overlap exists between these entities in terms of clinical presentation, the main differences between them are the potential for recovery, the presence or absence of a precipitating event, and the substantial variability in outcomes.

Current goals of treatment for ACLF are to prevent further deterioration in liver function, reverse precipitating factors, and support failing organs. Liver transplantation is required in selected subjects. Left untreated, the hospital mortality of these subjects is reported to be greater than 50%, and mean length of hospital stay is 21 days, with hospitalizations for ACLF reaching even higher rates of mortality.

An almost constant feature in cirrhotic subjects with ACLF is the rapid and substantial evolution towards multi-organ failure. This further reflected the complexity of the patient population compared with previous patient populations described in the literature.

Methods: This placebo-controlled, multicentre study (UK and US) enrolled subjects with compensated or stable cirrhosis. Eligibility criteria were defined for ACLF defined as a decompensating event or illness (including but not limited to alcohol use, GI haemorrhage, cholangitis, or hypoxic hepatitis) in patients with chronic liver disease. The primary outcome was to evaluate the pharmacokinetics and pharmacodynamics of emricasan 5, 25, and 50 mg BID orally administered for 28 days. Secondary objectives included assessment of safety, evaluation of clinical outcomes and recommendation of a dose(s) of emricasan for a follow-on phase 3 trial.

Randomization was stratified based on presence or absence of alcohol use. If a prior steroid use or not to ensure that subjects were proportionally distributed among treatment groups.

Serial (pre-dose, 0.5, 1, 2, 3, 4, 5 and 8 hr.) pharmacokinetic (PK) samples were taken at Day 1 and Day 4. A single PK sample was taken at Day 28/48 end of treatment. In selected subjects, a 12 hour PK sample was also collected on Day 1 and Day 2. The PK parameters assessed were commensurate with Cmax, AUCC, AUC0-τ, AUC0-τ, and t1/2. Serum biomarker variables assessed included (IDN1830, ROX1830, and Caspase 3).

Conclusions: Of the 21 subjects who received study treatment, 7 subjects achieved a clinical response to treatment. A total of 10 deaths occurred across all treatment groups (2, 3 and 1 respectively). Of these, 5, 25 and 50 mg BID groups, respectively, occurred prior to last known follow-up. By Day 28 there were a total Baseline: 0 (25 mg BID groups), 1 (5 mg BID groups), 5, 25 and 50 mg BID groups, respectively. In the 21 subjects randomised experienced adverse events, of which 13 reported serious adverse events. None of these events were considered to be treatment related by the investigator. No serious adverse events at all doses studied were increased in subjects with ACLF compared to previous patient populations studied.