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A Placebo-Controlled, Multicenter, Double-Blind, Phase 2 Randomised Trial of the Pan-Caspase Inhibitor Emricasan in Patients with Acutely Decompensated Cirrhosis

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Background: **Cirrhosis and acute-on-chronic liver failure (ACLF) are associated with systemic inflammation, and caspase-mediated hepatocyte cell death. Emricasan is a novel, pan-caspase inhibitor. Aims of this study were to assess the pharmacokinetics, pharmacodynamics, safety and clinical outcomes of emricasan in acute decompensation (AD) of cirrhosis.** ***Methods:*** **This was a phase 2, multicentre, double-blind, randomised trial. The primary objective was to evaluate the pharmacokinetics, pharmacodynamics and safety of emricasan in patients with cirrhosis presenting with AD and organ failure. AD was defined as an acute decompensating event ≤6 weeks' duration. Patients were randomised proportionately to emricasan 5 mg bid, emricasan 25 mg bid, emricasan 50 mg bid or placebo. Treatment was continued to 28 days, or voluntary discontinuation.** ***Results:*** **Twenty-three subjects were randomised, of whom 21 were dosed (placebo $n = 4$; 5 mg $n = 5$; 25 mg $n = 7$; 50 mg $n = 5$). Pharmacokinetic data showed 5 mg dose was associated with low plasma levels (<50 ng/ml), and 25 mg and 50 mg doses showed comparable pharmacokinetic profiles. Therefore, for analysis of secondary endpoints, placebo and 5 mg groups were merged into a 'placebo/low-dose' group, and 25 mg and 50 mg groups were merged into a 'high-dose' group. Five deaths occurred amongst the 21 patients, all due to progression of liver disease (2 in placebo/low-dose, 3 in high-dose). No statistically significant changes from baseline MELD score or CLIF-C ACLF score were noted between placebo/low-dose and high-dose groups at day 7 (MELD −1 vs −1, CLIF-C ACLF 0.7 vs 0.8). An initial reduction in cleaved keratin M30 fragment was noted between placebo/low-dose and high-dose groups (percent relative change: day 2: −11.6 vs −42.6, $P = 0.017$, day 4: −3.5 vs −38.9 $P = 0.017$) although this did not persist to day 7 (−3.1 vs −20.8, $P = 0.342$).** ***Conclusion:*** **This study demonstrates that emricasan is safe and well tolerated in advanced liver disease. However, this study fails to provide proof-of-concept support for caspase inhibition as a treatment strategy for ACLF.** ***Trial registration:*** **EudraCT 2012-004245-33 (J Clin Exp Hepatol 2017;xx:1–11)**

The natural history of cirrhosis is characterised by progression to episodes of acute decompensation (AD) of liver function.[1] Most patients with cirrhosis and AD are treated successfully in the majority of cases. However, about 30% of these patients develop hepatic and/or extra-hepatic organ failure that progresses in about 20% to multi-organ failure and death.[2] When this occurs rapidly, within a period of weeks, the condition is referred to as acute-on-chronic liver failure (ACLF). The 170,000 cirrhosis deaths in Europe each year are largely due to ACLF and the condition costs $3Bn in the USA and £50 K per survivor in the UK.[3] There are as yet no specific therapies for ACLF.

The pathobiology of ACLF is characterised by hepatic and systemic inflammation, and progressive, unrelenting hepatocyte injury and death.[4,5] Approaches targeting systemic inflammation have been tried, such as anti-TNF therapies, although these have led to negative outcomes suggesting that alternative approaches are required.[6]

Apoptosis is a highly regulated form of or programmed cell death. In response to injury or inflammation, hepatocytes can undergo apoptosis via an extrinsic pathway

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Abbreviations: ACLF: acute-on-chronic liver failure; AD: acute decompensation; ALT: alanine aminotransferase; ANCOVA: analysis of covariance; AST: aspartate aminotransferase; Bid: *Bis in die* (twice a day); DL: decilitre; HCV: hepatitis C virus; INR: international normalised ratio; MELD: model for end-stage liver disease; Mg: milligrams; TNF: tumour necrosis factor; TRAIL: tumour necrosis factor-related apoptosis-inducing ligand

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activated by death ligands, Fas, and tumour necrosis factor-related apoptosis-inducing ligand (TRAIL), or an intrinsic pathway activated by intracellular stress of membrane-bound organelles, such as lysosomes, endoplasmic reticulum and mitochondria.[7–10] Both pathways of apoptosis converge on the caspases (cysteine aspartyl proteases), which play an essential role in the initiation, execution and regulation of apoptosis.[11]

Previous work has demonstrated that apoptosis is a key pathway of cell death in patients with ACLF. Fragmented chromatin and caspase-dependent cleaved keratin 18 are both terminal end-products of the apoptotic pathway.[12] Adebayo et al. have shown that serum levels of cleaved keratin 18 (M30 fragment) are significantly elevated in patients with ACLF compared to patients with AD alone, and correlate with disease severity.[13] Immunohistochemistry of liver tissue also demonstrates apoptotic M30-positive hepatocytes in patients with severe ACLF. Similarly, Cao et al. have demonstrated elevated levels of fragmented chromatin in the ACLF compared with the AD group.[14] These data support the central role of hepatocyte apoptosis in the progression of ACLF, and provide the rationale for therapeutic targeting of apoptosis in ACLF.

Caspases provide a druggable target for the inhibition of apoptosis in liver disease. As such, caspase inhibitors have been shown to decrease liver injury in rodent models of acute liver failure, fatty liver disease, cholestatic liver injury and alcohol-induced liver injury.[15–20]

Emricasan (IDN-6556) is a novel, orally active, pan-caspase protease inhibitor. Emricasan has been studied in eight phase 1 studies and eight phase 2 studies involving over 650 patients, providing initial safety data and supporting the dose range of 5–50 mg used in phase 2 studies in patients with chronic liver disease.[21,22] The aims of this study were to assess the pharmacokinetics, pharmacodynamics, safety and clinical outcomes of emricasan in patients with cirrhosis and a rapid deterioration of liver function associated with organ failure.

PATIENTS AND METHODS

Study IDN-6556-02 (ClinicalTrials.gov NCT01937130) was conducted in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all patients before enrolment, in agreement with approved protocols from research ethics committees (North West-Haydock Research Ethics Committee, reference 13/NW/0464).

Study Design

This was a phase 2, multicentre, double-blind, randomised trial was conducted in 10 sites in the United States and United Kingdom. The primary objective was to evaluate the pharmacokinetics, pharmacodynamics and safety of emricasan, orally administered for 28 days in patients with cirrhosis and a rapid deterioration of liver function associated with organ failure (Figure 1).

Selection of Doses

The relationship between emricasan dose and biomarker responses had been thoroughly characterised in subjects with active HCV hepatitis and normal hepatic function.[21,22] However, the dose-biomarker response relationship had not been characterised in subjects with impaired hepatic function. The initial studies in subjects with HCV hepatitis and normal function assessed the effect of emricasan upon a panel of 4 biomarkers (caspase 3/7, M30, ALT and AST) at oral doses ranging from 0.5 mg BID up to 200 mg BID. Doses as low as 0.5 mg BID dose were pharmacodynamically active, decreasing M30 and ALT by nearly 50%, but had less effect upon AST and caspase 3/7. Doses greater than 50 mg BID did not appear to have any greater reduction in the 4 biomarkers compared to the 50 mg BID dose. Thus, doses of 5, 25 and 50 mg BID were selected for this study in patients with severe hepatic impairment.

Sample Size

The sample size was based around a simulation exercise of 1000 simulated outcomes, which were used to predict the dose required for a set target exposure. A sample size of 15 subjects per group (60 total) would have resulted in >80% of simulated outcomes recommending the correct dose to take forward to a follow-on ACLF efficacy study, if the exposure and pharmacodynamic effects in cirrhotic

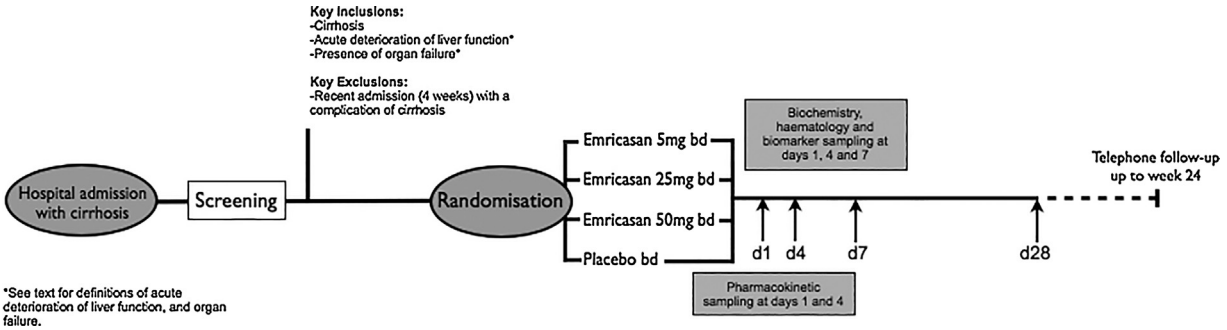

Figure 1 Study design outline.

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