Apoptotic bodies and other subcellular fragments such as microvesicles. \(^4,5\) In liver disease, chronic elevated apoptosis is generally recognized as a specific mechanistic biomarker of apoptosis. Elevated serum levels of cCK18 have been associated with severity in a variety of liver diseases. \(^3,7\) on a wide variety of cellular substrates. One target substrate of the mechanism to disrupt normal homeostatic mechanisms and promote disease pathology.

**Background:**

These cellular end-products of apoptosis, which contain a wide variety of biologically active substances, are engulfed by neighboring tissue and promote disease pathology. Caspase mediated apoptosis is driven by the enzymatic action of caspase 3 and 7 on a wide variety of cellular substrates. One target substrate of caspase 3 is the intermediate filament protein, cCK18. Caspase cleavage of cCK18 yields a protein fragment, cCK18, which is a cross-sectionally recognized as a specific mechanistic biomarker of apoptosis. Elevated serum levels of cCK18 have been associated with severity in a variety of liver diseases including those with advanced stages of liver disease. Elevated serum levels of full-length CK18, (flCK18), are also associated with cirrhosis, cCK18 has been reported to increase progressively with chronic hepatitis C. Elevated serum levels of cCK18 have been associated with severity in a variety of liver diseases including those with advanced stages of liver disease. Elevated serum levels of cCK18 have been associated with severity in a variety of liver diseases including those with advanced stages of liver disease.

**Results:**

Elevated serum levels of cCK18 (cCK18) and flCK18 are associated with liver disease. Full-length CK18 (flCK18) is released into the circulation as a result of necrosis, and as such it is a recognized marker independent, generic biomarker of liver cell death. Serum levels of cCK18 and flCK18 are measured by the specific ELISA based monoclonal antibody assays, M30 and M34, respectively. Caspase 3/7 activity was measured using Caspase-Glo 3/7 Assay Kit (Promega).

Inhibition of caspase activity has long been recognized as a potentially attractive approach for the treatment of a variety of liver diseases. However, a longstanding concern associated with the potential therapeutic of the mechanism to disrupt normal homeostatic mechanisms and promote tumor formation, has understandably hampered development in this field. We show here that emricasan does not affect caspase activity and apoptosis in healthy subjects and is unlikely to affect normal homeostatic processes that may be modulated by caspase enzymes. Additionally, emricasan was found to have no tumorigenic potential in a recently reported carcinogenicity study.

**Methods:**

Emricasan was administered as a single 50 mg oral dose to subjects with mild Child Pugh A (n=2), moderate Child Pugh B (n=8) or severe Child Pugh C (n=8), hepatic impairment and 8 healthy controls matched demographically with subjects in the severe cohort. In a second study, emricasan was administered as a single 50 mg dose to 8 subjects with severe renal impairment and 8 matched healthy controls. In both studies, serial blood samples were collected over a 48 hour period and analyzed for markers of apoptosis, cell death and caspase enzymatic activity.

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 collected over the 48 hour post-dose with further samples collected at 24 and 48 hours post-dose.

**Results:**

Median baseline levels of caspase 3/7 activity in subjects with hepatic impairment were elevated in all subject groups, mild, moderate and severe. These levels were also elevated in all subject groups with severe renal impairment.

In addition, baseline levels of caspase 3/7 enzymatic activity were elevated in subjects with severe renal impairment compared to matched healthy controls. The data for baseline caspase 3/7, cCK18 and flCK18 for respective controls and severe cohorts are presented in Table 1.

**Conclusions:**

Collectively these data provide important new insight and increase our understanding of the effect of a small molecule pan-caspase inhibitor in man. Furthermore these observations are also consistent with the large pre-clinical database of safety information along with the clinical experience with emricasan, both of which are remarkably devoid of theoretically anticipated mechanism-driven side effects.

**References:**

2. Spada A, Contreras P, Burgess G. Inhibition of caspase activity with a pan-caspase inhibitor, emricasan. Inhibition of caspase activity has long been recognized as a potentially attractive approach for the treatment of a variety of liver diseases. In liver disease, chronically elevated apoptosis results in the accumulation of apoptotic cells as well as the release of apoptotic bodies and other subcellular fragments such as microvesicles. These cellular end-products of apoptosis, which contain a wide variety of biologically active substances, are engulfed by neighboring tissue and promote disease pathology.

**Figure 1:** Hepatocyte cell death leads to amplification of disease pathology

**Figure 2:** Median of serum levels of caspase 3/7 enzymatic activity following a single 50 mg oral dose of emricasan to subjects with hepatic impairment and healthy controls.

**Figure 3:** Median of serum levels of caspase 3/7 enzymatic activity following a single 50 mg oral dose of emricasan to subjects with severe renal impairment or healthy control subjects.

Elevated serum levels of full-length CK18, (flCK18), are associated with cirrhosis, cCK18 has been reported to increase progressively with chronic hepatitis C. Elevated serum levels of cCK18 have been associated with severity in a variety of liver diseases including those with advanced stages of liver disease.

**Figure 4:** Median of serum levels of caspase 3/7 enzymatic activity following a single 50 mg oral dose of emricasan to subjects with severe renal impairment or healthy control subjects.

Elevated serum levels of full-length CK18, (flCK18), are associated with cirrhosis, cCK18 has been reported to increase progressively with chronic hepatitis C. Elevated serum levels of cCK18 have been associated with severity in a variety of liver diseases including those with advanced stages of liver disease.

**Figure 5:** Median of serum levels of caspase 3/7 enzymatic activity following a single 50 mg oral dose of emricasan to subjects with severe renal impairment or healthy control subjects.

Elevated serum levels of full-length CK18, (flCK18), are associated with cirrhosis, cCK18 has been reported to increase progressively with chronic hepatitis C. Elevated serum levels of cCK18 have been associated with severity in a variety of liver diseases including those with advanced stages of liver disease.

**Figure 6:** Median of serum levels of caspase 3/7 enzymatic activity following a single 50 mg oral dose of emricasan to subjects with severe renal impairment or healthy control subjects.

Elevated serum levels of full-length CK18, (flCK18), are associated with cirrhosis, cCK18 has been reported to increase progressively with chronic hepatitis C. Elevated serum levels of cCK18 have been associated with severity in a variety of liver diseases including those with advanced stages of liver disease.