Physiologically normal levels of apoptosis in healthy volunteers are not reduced by the pan-caspase inhibitor, emricasan.

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Introduction: Emricasan (DN-6556, PF-03491390) is a potent irreversible pan-caspase inhibitor that has demonstrated the ability to reduce elevated levels of serum ALT and AST in HCV infected patients in Phase 1 and Phase 2 clinical trials. These effects were durable throughout the duration of dosing and emricasan has been well-tolerated in all clinical trials. Emricasan also rapidly reduced markers of cellular activity, including caspase enzymatic activity and caspase 3/7 mediated cleavage of cytokeratin-18, a well-accepted specific marker of apoptosis.3 Emricasan dosing and emricasan has been well-tolerated in all clinical trials.1,2 These effects were durable throughout the dosing period of this study in HCV patients. We also reported that regardless of dose, caspase cleaved cytokeratin-18 levels were reduced to within ranges typically observed in healthy volunteers. In addition of cytokeratin-18, caspase 3/7 activity was reduced but not abolished. Together, these observations demonstrate that emricasan can rapidly and predictably reduce both caspase enzymatic activity and apoptosis but, regardless of dose, does not abolish either.

Methods: We previously reported that emricasan rapidly reduced levels of both caspase 3/7 enzymatic activity and caspase cleaved CK-18 in chronic HCV patients. Statistically significant reductions from baseline values were very rapidly achieved for both analyses at 3 hours following the first dose of emricasan on Day 1. Figure 2 and in addition the effect on both analyses was durable throughout the dosing period of this study in HCV patients. We also reported that regardless of dose, caspase cleaved cytokeratin-18 levels were reduced to within ranges typically observed in healthy volunteers. In addition of cytokeratin-18, caspase 3/7 activity was reduced but not abolished. Together, these observations demonstrate that emricasan can rapidly and predictably reduce both caspase enzymatic activity and apoptosis but, regardless of dose, does not abolish either.

Results: The mean pre-dose serum titer of caspase-cleaved cytokeratin-18 on study Day 1 in this cohort of healthy male and female volunteers was 275 U/L. Pre-dose levels and serial monitoring of serum titers of caspase-cleaved cytokeratin-18 following administration of emricasan was conducted on study Days 1, 17 and 24. Figure 4. As can be seen, emricasan had no significant effect on serum titers of caspase cleaved cytokeratin-18 at any time point in these healthy volunteers. This is in sharp contrast to the rapid and statistically significant reduction of serum levels of caspase-cleaved cytokeratin-18 at this dose in chronic HCV patients.

Conclusions: In healthy volunteers, the potent small molecule pan-caspase inhibitor emricasan does not reduce serum levels of caspase-cleaved cytokeratin-18 below the normal range of caspase activity and apoptosis. This further suggests that the on-going caspase dependent processes in healthy individuals are largely unaffected by emricasan. These results suggest that normal levels of apoptosis and caspase activity may be a healthy marker of caspase activity and apoptosis.

The data and observations presented above suggest that the pan-caspase inhibitor emricasan, can effectively reduce elevated levels of caspase activity and apoptosis in patients with liver disease, but appears to have minimal, if any, impact on homeostatic levels of apoptosis as measured in healthy volunteers. This may have important implications about the potential of chronic dosing and long-term safety of emricasan.

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References:


