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ABSTRACT OF ORAL PRESENTATION TO THE INTERNATIONS SYMPOSIUM ON HEPATITIS C VIRUS AND RELATED VIRUSES - Melbourne (VIC), October 7, 2013

Preclinical Evaluation of TT-034: Safe and Durable Hepatic Expression of Anti-HCV shRNA in a Non-Human Primate Model

The Hepatitis C virus (HCV) chronically infects over 170 million individuals worldwide and, despite the recent addition of DAAs, the current standard of care treatment is limited by long duration and significant side effects, as well as viral escape and incomplete genotype coverage. Because the viral genome is comprised of a single strand of RNA and its replication occurs strictly within the cytoplasm, HCV is an ideal candidate for therapeutics based upon RNA interference (RNAi).

We have developed an RNAi-based therapeutic against HCV, termed TT-034, which uses three independent transcriptional cassettes to express three shRNAs that simultaneously target multiple well-conserved regions of the HCV genome. Intended as a “one-shot cure”, TT-034 uses an Adeno-Associated Virus (AAV) capsid to deliver the recombinant genome preferentially into hepatocytes. We have characterized the therapeutic potential of TT-034 in several *in vitro* studies using replicon systems as well as an infectious tissue culture model of HCV and demonstrated dose-dependent inhibition of HCV activity.

shRNA levels required for complete inhibition of replicon activity were assessed by quantitative PCR and demonstrate the catalytic nature of RNAi based therapeutics as a limited number of shRNA per cell was sufficient to abrogate the HCV activity. Systemic administration via a single intravenous injection in a non-human primate model resulted in complete transduction of hepatocytes, as assessed by in situ hybridization analysis of shRNA and resulted in the persistent expression of shRNA out to 180 days, the duration of the study. Acute toxicity studies performed in non-human primates with clinically relevant doses demonstrate that levels of shRNA in excess of the predicted effective dose could be produced in the absence of hepatocellular toxicity. No other adverse events were noted in the animals. Follow-on IND-enabling, GLP toxicology studies on 520 mice and 80 cynomolgus monkeys, followed over 180 days, showed an excellent safety profile, supporting the safety of a planned Phase I/II clinical study in subjects chronically infected with HCV. An open label phase I/II first-in-man dose escalation safety study in chronic HCV patients that have failed the current Standard of Care is planned to start in 2H 2013.

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