Pharmacokinetics and Safety of VIR-2218 Monotherapy in Adult Cirrhotic Participants with Moderate Hepatic Impairment

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Background: VIR-2218 is an investigational, N-acetylgalactosamine (GalNAc)–conjugated, double-stranded RNA interference (RNAi) therapeutic that targets a region of the hepatitis B virus (HBV) genome that is common to all HBV viral RNA transcripts. VIR-2218 is in clinical development for the treatment of chronic HBV and HDV infection. We have previously demonstrated that VIR-2218 administered every 4 weeks at 200 mg subcutaneously (SC) results in sustained reductions in HBsAg. Here, we report the pharmacokinetics (PK) and safety of VIR-2218 in cirrhotic participants who have hepatic impairment (HI) with Childs-Pugh-Turcotte Class-B (CPT-B) score.

Methods: VIR-2218-V107 (NCT05484206) is a Phase 1, open-label, single-dose parallel-group study. Adult participants with CPT-B HI and healthy participants (HV) were demographically matched. Participants received a single SC dose of VIR-2218 at 200 mg. Blood samples were collected up to 8 weeks and pooled urine samples were collected over 72 hours post-dose to measure the concentrations of VIR-2218 and its major metabolite, AS(N-1)3’VIR-2218. PK parameters were estimated using non-compartmental analysis in WinNonlin®. Safety and tolerability were monitored throughout the study.

Results: Eight (8) cirrhotic participants with CPT-B HI and 8 HV were enrolled. The geometric mean ratios (GMR) of Cmax, AUClast and AUCinf of VIR-2218 in CPT-B participants (test) vs. HV (reference) were 1.7, 2.1 and 1.9, respectively. Similarly, the GMR of Cmax and AUClast of VIR-2218 major metabolite AS(N-1)3’VIR-2218 in CPT-B participants vs. HV were 2.1 and 2.4, respectively. Accordingly, fraction of VIR-2218 and metabolite excreted in urine were higher in CPT-B participants vs. HV. Two SAEs of thrombocytopenia (Grade 4) in 1 participant were reported and resolved within 7 days with platelet transfusion. They were consistent with underlying cirrhosis and were considered unrelated to VIR-2218. There were no clinical cardiovascular events.

Conclusion: A single dose of VIR-2218 at 200 mg was generally well tolerated in participants with moderate CPT-B HI. VIR-2218 exposures were higher in CPT-B participants vs HV. However, based on collective PK and safety data, no dose adjustment is warranted for VIR-2218 in CPT-A and CPT-B participants. PK and safety from a single dose of VIR-2218 support continued evaluation of 200 mg VIR-2218 in participants with HBV and HDV infection with up to moderate CPT-B HI.