A Phase 2 Study Of Titrating-Dose Lonafarnib Plus Ritonavir In Patients With Chronic Hepatitis D: Interim Results From The Lonafarnib With Ritonavir In HDV-4 (LOWR HDV-4) Study
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Abstract Body
Background/Aim: Globally 15-20 million people are coinfected with the hepatitis delta (HDV) and hepatitis B (HBV) viruses. Lonafarnib (LNF) is an oral prenylation inhibitor that has been shown to reduce levels of HDV RNA in short-term studies in a dose-dependent manner. Prenylation inhibitors are associated with gastrointestinal (GI) adverse effects (AE) at higher doses (anorexia, nausea, diarrhea, weight loss), but step-wise increase in dose has been shown to be well-tolerated in a pediatric population. Previous data in HDV patients demonstrated that co-administering LNF + ritonavir (RTV), a CYP3A4 inhibitor, increases the post-absorption levels of LNF with lower GI exposure. LOWR HDV-4 is an open-label, phase 2 dose-titration study of LNF+RTV in patients with HDV to investigate if rapid step-wise increases in LNF dose can allow more patients to achieve higher doses.

Methods: Key inclusion criteria: positive HDV RNA by qPCR, ALT <10xULN, compensated liver disease, platelet counts >90,000/µl. All patients were started on LNF+RTV (50mg/100mg bid). If well tolerated, LNF could be increased to 75mg bid after a minimum of 4 weeks, and next to 100mg bid after a minimum of 2 weeks since the last dose escalation. RTV was kept at 100mg bid regardless of the LNF dose. Safety, HDV RNA, HBV DNA, HBsAg and ALT were assessed at each visit. Here we present the interim data at Week 8 of treatment.

Results: 15 patients (11 male) were enrolled. At baseline (BL), mean HDV RNA was 6.53 log10 IU/mL (range 4.43-8.31 log10 IU/mL); mean ALT 111 IU/mL (range 53-362 IU/mL), mean Fibroscan 14.4 kPA (range 6.3-24.5 kPA). Two patients were cirrhotic on biopsy. By Week 8, 10/15 (66%) patients were able to be dose-escalated to LNF 100mg bid + RTV, 6 of which still remain at this dose. All patients had HDV RNA declines with a mean decline from BL to Week 8 of 1.87 log10 IU/mL (range 0.88-3.13 log10 IU/mL). Three patients had HBV DNA rebound associated with HDV RNA decline, two of which were started on tenofovir. 11 patients were on a nucleos(t)ide (NUC) at BL. AE were mostly grade 1-2 intermittent diarrhea; 3 patients had grade 3 AE (2 diarrhea; 1 asthenia), all transient and non-recurring; none had grade 4 AE. Conclusion: Dose-escalation of LNF+RTV was feasible, and led to early decline in HDV RNA in all patients. HDV RNA decline was associated with a rebound of HBV DNA in patients not receiving a NUC, suggesting a suppressive effect of HDV on HBV replication. These interim data support longer durations of therapy. The Week 24 end of treatment data will be presented.