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A proof-of-concept Phase IIa clinical trial to treat chronic HBV/HDV with the entry inhibitor myrcludex B

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Introduction: Novel therapeutic options to cure chronic Hepatitis B and D (HBV/HDV) are needed to improve health outcome in these patients. Myrcludex B is a first-in-class entry inhibitor, which blocked the receptor function of the HBV/HDV receptor sodium taurocholate cotransporting polypeptide (NTCP) *in vitro* and *in vivo*. Interims results of a clinical trial of myrcludex B in chronic HBV/HDV co-infected patients showed promising antiviral effects, we now present the final results. Aim: To evaluate safety, tolerability, and antiviral effects of myrcludex B as monotherapy and in combination with pegylated interferon. Methodology: 24 patients with chronic HBV/HDV co-infection were scheduled for 48 weeks of pegylated interferon alpha (PEG-IFNa) therapy. 8 patients received pre-treatment with 2mg myrcludex B alone for 24 weeks (A1); myrcludex B was administered concurrently with (PEG-IFNa) for the first 24 weeks to another 8 patients (A2) while 8 patients were treated with PEG-IFNa only (A3). Results: Myrcludex B was well tolerated, with only 4 mild AEs (lab abnormalities) attributed to myrcludex B. 6/7 and 7/7 of patients with data available experienced >1log10 HDV RNA decline at week 24 during myrcludex B monotherapy (A1) or combination therapy (A2) while this occurred in 7/7 of A3 patients. HDV RNA became negative in 2 (A1), 5 (A2) and 2 (A3) patients at week 24. A rebound of HDV RNA occurred in the majority of patients after the end of myrcludex therapy, despite the introduction/continuation of PEG-IFNα. In patients evaluable at the end of 24 weeks treatment free follow up, 1/6 (A1), 2/6 (A2), and 2/5 (A3) patients were HDV RNA negative. At week 24 a trend to ALT normalization was observed in A1 (6/8 patients), which was not maintained after introduction of interferon. There was a significant mean reduction of $\log10^{1.28}$ (p=0.04) at week 24 for HBV DNA in A2, followed by an incline after myrcludex B withdrawal. At the end of treatment, HBsAg levels declined >1log10 in 4/7 patients in A1, 1/7 in A2, and 2/6 in A3, whereas 1 patient from A2 and A3 each experienced HBsAg loss. HBsAg levels inclined in patients without HBsAg loss at the end of follow up. Myrcludex B treatment induced preS-specific antibodies and clinically insignificant bile acid elevation. Conclusion: Myrcludex B was safe and well tolerated and antiviral efficacy of the drug was confirmed. The tendency to ALT increase after the introduction of interferon after myrcludex B lead-in was accompanied by HBV DNA and HBsAg decline, suggesting myrcludex lead-in regimens for HBV cure.

Disclosures:

Pavel Bogomolov - Advisory Committees or Review Panels: R-farm; Grant/Research Support: MYR Gmbh, Johnson, Roche, Abbvie, BMS, Abbott, Biokad

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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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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 $\log_{10}$IU/mL (range 4.43-8.31 $\log_{10}$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 $\log_{10}$IU/mL (range 0.88-3.13 $\log_{10}$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