Robust reduction of HBsAg and HDV RNA levels with low risk for ALT elevations in JNJ-73763989 treated patients with chronic hepatitis D (CHD) and baseline HBsAg levels below 10,000 IU/mL: part 2 of the REEF-D study

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Background and Aims: The siRNA JNJ-73763989 (JNJ-3989) profoundly reduced HBsAg in patients with chronic hepatitis B. In Part-1 of the REEF-D study, this reduction was associated with serum HDV RNA decline in patients with chronic hepatitis D (CHD). Treatment discontinuation due to relevant ALT elevations was primarily seen in patients with high HBsAg and HDV RNA levels at screening. Based on predefined virologic response criteria in Part-1, the confirmatory Part-2 was initiated with modified inclusion and stopping criteria for ALT elevations.

Method: In REEF-D, a phase 2, multicenter, randomized, double-blind, placebo-controlled study, adult participants with CHD were enrolled. After observing ALT elevations in Part-1, Part-2 excluded patients with liver cirrhosis and those with a combination of HBsAg >10,000 IU/mL and HDV RNA >100,000 IU/mL. Patients were randomized 4:1 to receive JNJ-3989 (100 mg sc. Q4W) + NA for 144 weeks (immediate active) or placebo + NA for 52 weeks followed by JNJ-3989 + NA for 96 weeks (deferred active). Changes in serum viral markers and safety were assessed. For Part-2, the primary composite endpoint reported here is the proportion of patients with HDV RNA decline from baseline (BL) of ≥2 log10 IU/mL (or undetectable) and normal ALT at treatment week (TW) 48.

Results: Of 30 patients enrolled in Part-2, 24 and 6 were randomized to the immediate and deferred treatment arms and 15 and 6 completed the double-blind phase up until TW48, respectively. The primary endpoint was met by 7/15 completers (47%) and 7/24 overall (29%) versus 0 in the deferred arm. Among 15 completers in the immediate active arm 10 (67%) reached an HDV RNA decline from BL of ≥2 log10 IU/mL and 7 (47%) had HDV RNA <LLOQ at TW48 and mean (SE) reductions of HBsAg and HDV RNA from BL were 2.44 (0.238)/2.09 (0.294) log10 IU/mL in the immediate arm versus 0.02 (0.026)/0.19 (0.199) log10 IU/mL in the deferred arm. Nine of 24 (37.5%) patients in the immediate arm had treatment-emergent ALT elevations (≥3× upper limit of normal and ≥2× nadir), which resulted in early discontinuation of JNJ-3989 in 7 patients. Six of those 7 patients had HBsAg levels at screening of >10,000 IU/mL. In contrast, only one of 16 (6%) patients with HBsAg <10,000 IU/mL at screening had an on-treatment ALT elevation leading to discontinuation. In general, ALT elevations returned to BL values after treatment discontinuation and no cases of liver decompensation occurred. Besides ALT elevations, no other safety issues were observed including four participants from Part-1 who continued treatment with JNJ-3989 for up to 144 weeks.
**Conclusion:** Patients with screening HBsAg <10,000 IU/mL had a low risk for ALT flares and showed a profound and sustained on-treatment suppression of HBsAg and HDV RNA. ALT elevations seen in patients with HBsAg ≥10,000 IU/ml were safely managed with strict stopping criteria for JNJ-3989.