Viral sequence analysis of chronic hepatitis B (CHB) patients treated with the silencing RNA (siRNA) JNJ-3989 in the REEF-1 and REEF-2 clinical studies

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Background and Aims: JNJ-3989 is an siRNA composed of 2 triggers targeting the HBsAg and HBx protein open reading frame. Baseline (BL) polymorphisms in the target region complementary to positions 2-18 of the S- and X-trigger, considered potentially relevant for binding and activity, were present in 10% and 2.4% of not currently treated (NCT) REEF-1 patients, respectively, with no impact on JNJ-3989 induced HBsAg decline. Here, viral sequence changes in the S-/X-trigger target regions were evaluated in patients with virologic relapse (VR; at least transient off-treatment increase in HBV DNA to >200 IU/mL from <LLOQ) after discontinuation of all treatment in REEF-1 (NCT03982186) and REEF-2 (NCT0412954).

Method: HBV DNA/RNA was extracted from on- and off-treatment plasma samples with sufficiently high HBV DNA/RNA levels and HBV genome was sequenced using Illumina sequencing. Nucleotide (nt) variants were defined as changes versus the universal HBV reference sequence (sequence read frequency >15%).

Results: In REEF-1, VR occurred in 30/37 (81%) JNJ-3989 treated virologically suppressed (VS) patients stopping all treatment - in REEF-2, in 54/77 (70%) JNJ-3989 treated and 39/40 (98%) NA-control arm patients, respectively. Across both studies 114/123 (93%) VS patients with VR had off-treatment HBV sequence data available. Variants at X-trigger target region positions of interest (POI) were more frequently observed off-treatment in JNJ-3989 treated VS patients than in NA-control arm VS patients with VR (56% and 5.7%, respectively). Variants at X-trigger target region POI 1794, 1785, and 1784 were observed off-treatment with a prevalence of 43%, 18% and 6.5%, respectively, which is higher than the prevalence of these variants off-treatment in either NA-only treated patients with VR (range: 0%-2.9%) or observed at baseline in REEF-1 NCT patients (range: 0%-1.2%). Variants at S-trigger target region POI were present off-treatment in 33% of JNJ-3989- and 19% of NA-only treated VS patients with VR and majority had variant at S-trigger POI 273, also frequently (10%) observed as at baseline in REEF-1 NCT patients. To assess if these variants observed during off-treatment follow-up were selected on-treatment, EOT samples from 30 NCT JNJ 3989-treated patients were evaluated using HBV RNA based sequencing and no emerging variants at S- or X-trigger target POI were detected. Off-treatment HBsAg kinetics did not differ between JNJ-3989 treated patients with and without variants in S-/X-trigger target POI observed during VR.

Conclusion: In JNJ-3989-treated patients who discontinued all treatment and experienced VR, variants within the X-trigger target region were frequently observed during VR but were not selected on-treatment, suggesting that these X-trigger variants developed off-treatment in JNJ-3989 treated patients. Presence of these variants did not impact off-treatment HBsAg kinetics.