Efficacy, safety, tolerability, and immunogenicity of JNJ-0535 following a reduction of viral antigen levels through administration of siRNA JNJ-3989 in patients with chronic HBeAg negative hepatitis B - interim data of the OSPREY study

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Background and Aims: JNJ-64300535 (JNJ-0535), a DNA vaccine with two plasmids encoding HBV core and polymerase (pol) proteins, delivered through electroporation-mediated intramuscular injection, has previously shown to induce strong to modest T-cell responses in healthy adults and weak responses in patients with chronic hepatitis B (CHB). The OSPREY study (NCT05123599) was designed to assess whether a reduction of viral antigens by siRNA JNJ-73763989 (JNJ-3989) prior to JNJ-0535 vaccination, can enhance HBV-specific T cell responses and improve HBsAg kinetics in CHB patients.

Method: OSPREY is a phase 1b, open-label, single-arm, multicenter study in virologically suppressed patients with HBeAg-negative CHB receiving daily doses of nucleos(t)ide analogs (NA) for 36 weeks (W), 7 JNJ-3989 injections (Q4W) until W24, and 4 doses of JNJ-0535 (Q4W) from W14 to W28. NA stopping criteria (HBsAg <10 IU/mL, DNA <LLOQ and ALT <ULN) are assessed based on W36 results and patients are followed up (FU) with or without NA treatment for 48W, accordingly. Changes in virologic markers are assessed in serum and peripheral blood mononuclear cells (PBMCs) are evaluated for T cell responses against core, pol, and surface using ex vivo intracellular cytokine staining (ICS). Intrahepatic changes in immunology markers are assessed from fine needle aspirates (FNA) at baseline (BL) (n=22), W14 (n=19) and W28 (n=14) by single-cell RNA-sequencing. We report interim data with all patients at FUW24.

Results: Of the 23 patients who completed dosing, 11 achieved the primary endpoint of ≥2 log10 IU/mL reduction in HBsAg from baseline (BL) at W36. NA treatment was stopped in 7 patients based on W36 results and was restarted in 2 following an HBV DNA flare. Mean change in HBsAg in log10 IU/mL (SE) from W28 to FUW24 was 0.41 (0.148; n=22) with -0.29 (0.248) in 7 patients who stopped NA (NA completers) versus 0.73 (0.113) in 15 NA non-completers. Among the 7 NA completers, polypositive CD4 T cells (PP CD4) to ≥2 HBV antigens was enhanced at W28 in 4, detected at pre-vaccination and W28 in 1 and not in the 2 NA completers who re-started NA during FU. Among the 14 non-completers with available data, 3 had enhanced PP CD4 at W28 and 1 had PP CD4 at pre-vaccination and W28 with no further enhancement. NA completers had higher proportions of intrahepatic mucosal-associated invariant T cells (MAIT), at all timepoints with FNAs available. Except
1 grade 3 injection site reaction, no grade 3 or 4 adverse events (AE) or serious AEs were reported until FUW24.

**Conclusion:** Treatment with JNJ-3989, JNJ-0535 and NA, continued or stopped was generally safe and well tolerated. HBsAg lowering, followed by vaccination in OSPREY, showed more favourable HBsAg kinetics during FU in patients that were able to stop NA treatment versus patients who continued NA treatment. A potential role of HBV specific polypositive CD4 T cells needs further elucidation.