A phase 2 open-label study to evaluate safety, tolerability, efficacy, and pharmacodynamics of JNJ-73763989, nucleos(t)ide analogs, and a low-dose PD-1 inhibitor in patients with chronic hepatitis B – Interim results of the OCTOPUS-1 study

Tarik Asselah¹, Scott K. Fung², Sila Akhan³, Wan-Long Chuang⁴, Maria Buti⁵, Maurizia Brunetto⁶, Kosh Agarwal⁷, Camellia Diba⁸, John Jerzorwski⁹, Thomas Kakuda¹⁰, Catherine Naipas¹¹, Carine Guinand-Azadian¹¹, Thierry Verbiënne⁵, Erkki Lathouwers⁸, An De Creus⁴, Oliver Lenz⁸, Michael Biermer⁸

¹Université de Paris-Cité, INSERM UMR1149, Department of Hepatology, AP-HP Hôpital Beaujon, Clichy, France, ²Toronto General Hospital, Toronto Center for Liver Disease, Toronto, Canada, ³Department of Infectious Diseases and Clinical Microbiology, Kocaeli University Faculty of Medicine, Kocaeli, Turkey, ⁴Hepatobiliary Division, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung City, Taiwan, ⁵Hospital General Universitari Vall d’Hebron , Barcelona, Spain, ⁶Dept of Clinical and Experimental Medicine and H epatit ics Unit, University of Pisa, Pisa, Italy, ⁷Institute of Liver Studies, King’s College Hospital, London, United Kingdom, ⁸Janssen Research & Development, Beerse, Belgium, ⁹Janssen Research & Development, Trenton, United States, ¹⁰Janssen Research & Development, South San Francisco, United States, ¹¹Janssen Research & Development, Issy-les-Moulineaux, France

Email: tarik.asselah@aphp.fr

Background and Aims: Treatment of chronic hepatitis B (CHB) with the small-interfering RNA (siRNA) JNJ-73763989 (JNJ-3989) and nucleos(t)ide analogs (NA) has shown reductions in hepatitis B viral markers. This study aims to assess the efficacy and safety of adding low-dose PD-1 inhibitor nivolumab to JNJ-3989 and NA once HBsAg levels are reduced.

Method: OCTOPUS-1 is a phase 2, randomized, open-label, parallel-group, multicenter study to evaluate safety, efficacy, and pharmacokinetics of JNJ-3989, nivolumab, and NA in hepatitis B e-antigen (HBeAg) negative, virologically suppressed (VS) CHB patients. Patients received daily NA, JNJ-3989 200mg once a week for the first 4 weeks (loading dose), then once every 4 weeks until W24; nivolumab (0.3 mg/kg) was administered IV at W16 for Arm 1 (A1), and at W16, 20, and 24 for Arm 2 (A2) and follow-up with NA treatment is for 48 weeks. Primary endpoint is proportion of patients with HBsAg seroclearance (<0.05 IU/mL) at FU W24. Changes in viral markers (HBsAg, HBcrAg, and HBV DNA) and safety were assessed.

Results: At this W24 data snapshot, all patients have reached the end of treatment. Thirty-seven patients were enrolled, 18 in A1, 19 in A2, and received all doses of JNJ-3989. The protocol was amended and dosing of nivolumab was discontinued prior to the 3rd administration of the last two patients. The mean age (standard deviation: SD) was 44.38 years (7.38), 18.9% were female, 37.8% Asian. Mean (SD) baseline HBsAg levels were 3.25 (0.47) and 3.13 (0.54) in A1 and A2, respectively. Receptor occupancy 2 hrs post nivolumab administration at W16 was >90% in 29/35 (83%) of patients. At W24, mean HBsAg levels decreased by 2.0 (0.40) and 2.1 (0.58) \( \log_{10} \) IU/mL from BL in A1 and A2 with HBsAg reduction >2 \( \log_{10} \) IU/mL in 58.8 % and 55.6%, respectively. 88.2% and 50.0% in A1, 94.4% and 50.0% in A2 achieved HBsAg levels <100 and <10 IU/mL At W24 no patient achieved HBsAg seroclearance. No SAEs or grade 3 or 4 AEs were observed, and no patient discontinued the study prematurely. 48.6% of patients had TEAE, 13.3% were considered related to JNJ-3989 and 5.4% related to Nivolumab. JNJ-3989 loading dose led to mild increases of mean ALT from 23 U/L at BL to 35 U/L at W8 with no further increase until EOT, no patient met flare criteria. 2 cases of TSH suppression 8 weeks post nivolumab in A1 triggered the discontinuation of further nivolumab dosing, both cases resolved rapidly. No other immune-related events or cases of virologic breakthrough were observed.

Conclusion: After 24 weeks of treatment with JNJ-3989 + NA + nivolumab the mean decline of HBsAg from baseline was 2 \( \log_{10} \) IU/mL in both arms. Cross-study analysis of JNJ-3989 with VS, HBeAg- patients in REEF-1 did not show an apparent benefit of JNJ-3989 loading dose or nivolumab. Treatment was generally safe and well tolerated but administration of low-dose nivolumab in the study was terminated due to observed TSH suppression.