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Randomized, double-blind, placebo-controlled trial of Tenofovir Alafenamide in children and adolescents with chronic hepatitis B

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Background and aims: Tenofovir Alafenamide (TAF) is a novel prodrug of tenofovir (TFV) with non-inferior efficacy and greater plasma stability resulting in enhanced delivery of TFV and reduced plasma concentrations leading to an improved bone and renal safety profile over tenofovir disoproxil fumarate (TDF).TAF is approved for use in adult patients with Chronic Hepatitis B (CHB). However, safety and efficacy data in pediatric CHB patients are lacking. In a multicenter, randomized, double-blind, placebo-controlled trial we evaluated the safety and efficacy of TAF in children 6 years and older weighing ≥25 kg.

Method: Males or females aged 12 to <18 years weighing ≥35 kg (Cohort 1), and 6 to <12 years weighing ≥25 kg (Cohort 2, Group 1), with HBV DNA $\geq 2 \times 10^4$ IU/ml, ALT ≥1.5 × ULN, and creatinine clearance (eGFR; Schwartz method) ≥80 ml/min were randomized (2:1) to TAF 25 mg or PBO daily for 24 weeks, after which all patients received open-label TAF for up to Week 240. The co-primary end points were the proportion with HBV DNA <20 IU/ml and safety (treatment-emergent [TE] serious adverse events [SAEs] and all TE adverse events [AEs]) at Week 24; other assessments included serological and biochemical responses, bone mineral density (BMD) (spine and whole body[minus head]), resistance surveillance and pharmacokinetics.

Results: 88 patients were randomized and treated (Cohort 1: TAF 47, PBO 23; Cohort 2 group 1: TAF 12, PBO 6). Baseline (BL) characteristics were similar; overall mean (range) age and mean (SD) weight were 14 (7–17) years and 50.9 (12.9) kg, respectively; 58% were male, 66% Asian, 68% had HBV DNA ≥8 log10 IU/ml and mean (SD) ALT 107 (118) U/L. 99% were HBeAg-positive, with genotypes D (44%), C (24%), and B (23%) being most common. Overall, at Week 24, 11/59 (19%) TAF and 0/29 PBO patients had HBV DNA <20 IU/ml ($p = 0.0137$); mean (SD) HBV DNA change from BL TAF vs PBO was −4.98 (1.52) log10 IU/ml and −0.10 (0.64) log10 IU/ml ($p < 0.0001$), respectively. High BL viral load and genotype D were associated with lower rates of viral suppression. A higher proportion of TAF vs PBO patients had ALT normalization (TAF 67%, PBO 4%; $p < 0.0001$), while the rate of HBeAg seroconversion was similar (TAF 7%, PBO 3%). Grade 3 or 4 AEs and SAEs related to study treatment were similar for TAF vs PBO. Slight fluctuations in eGFR were noted for both treatment groups during double blind treatment; however, no patient had eGFR <90 ml/min/1.73m^2 at Week 24. Mean % increases from BL to Week 24 in BMD were similar in the TAF vs PBO (spine: +1.6% vs. +1.9%; [$p = 0.77$]; whole body: +1.9% vs. +2.0%; [$p = 0.83$]). Viral resistance was not detected through Week 24. TAF and TFV plasma exposures were within range of adult reference cohorts

Conclusion: In pediatric CHB patients, viral suppression and ALT normalization were superior to placebo, while safety results, including changes in BMD, were similar for TAF and PBO at Week 24

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The discovery of AMS-I-1274, a high potent and orally active capsid-assembly modulator against hepatitis B virus

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Background and aims: Hepatitis B virus (HBV) infection leads to a wide spectrum of liver diseases ranging from acute to chronic hepatitis, cirrhosis, and hepatocellular carcinoma. New drugs that inhibit HBV replication are needed to enhance the treatment of chronic hepatitis B resulting in a higher number of durable responses and functional cures. Capsid-assembly modulators (CAM) are a novel class of HBV antivirals and they have been suggested to be effective anti-HBV agents in both preclinical and clinical studies. Here, we describe the discovery of a novel CAM through high-throughput screening. Lead optimization resulted in the identification of the clinical candidate, AMS-I-1274.

Method: HepAD38 cells were used for the investigation of efficacy including serum-shift assay and mechanism of action studies. HBV genotype (Gt), core-, and NA-resistant variants were evaluated in a HepG2/plasmid DNA transfection system. In vitro anti-viral activity and the effect on the cccDNA level were determined in HBV-infected HepG2-hNTCP cells and primary human hepatocytes (PHH). Pharmacokinetic (PK) properties were assessed in rodents and non-human primates. uPA/SCID mice with humanized liver (PXB-mice) were used for in vivo efficacy studies. Human hepatotoxicity was ascertained by in vitro model using Hurel micro liver.

Results: AMS-I-1274 inhibited HBV replication with an EC50 value of 6.2 nM. The presence of 40% of human serum albumin (HAS) caused a slight reduction in potency (EC50 = 15.6 nM, 2.5-fold increase). It also did not show any significant cytotoxicity (CC50 >100 μM). AMS-I-1274's anti-viral activity was 65-fold more potent compared to Novira 3–778 (EC50 = 5, 700 nM at 40% HSA). Capsid formation assay demonstrated that AMS-I-1274 induced the formation of empty capsid particles devoid of pgRNA and rcDNA (Class II capsid inhibitor). In a de novo HBV infection system, AMS-I-1274 inhibited viral replication with an EC50 value of 1.2 nM against HBV DNA, 8.4 nM against HBsAg, 13.8 nM against HBeAg, and 1.6 nM against intracellular HBV RNA, respectively, and reduced the level of cccDNA (EC50 = 772 nM). AMS-I-1274 showed pan-genotypic activity against isolates from Gt A to H. Most core variants showed no or modest decrease in potency; except for T33N (80-fold). NA-resistant variants remained fully susceptible to AMS-I-1274. PK results showed a good systemic exposure and high oral bioavailability in rodent and non-human primates. In HBV-infected PBX-mice, oral administration of AMS-I-1274 at 50 mg/kg twice daily resulted in robust multi-log reduction (-3.49 log10) of serum HBV DNA after 42 days of treatment.