SB 9200 is a small orally bioavailable dinucleotide that activates the cellular transcription factor IFN-α and NOZD causing the induction of IFN signaling cascade for antiviral defense (1, 2). In preclinical studies, SB 9200 has shown to be a potent agent against hepatitis B virus (HBV) (1, 2). In woodchucks chronically infected with woodchuck hepatitis virus (WHV), SB 9200 monotherapy for 12 weeks at two select doses resulted in potent antiviral activity (4).

**RESULTS**

Two groups of five woodchucks were treated orally with SB 9200 (30 mg/kg/day) and ETV (0.5 mg/kg/day). Group 1 received ETV for 4 weeks followed by SB 9200 for 12 weeks. Group 2 received SB 9200 for 12 weeks followed by ETV for 4 weeks. Both groups were monitored for 8 weeks post-treatment. Endpoints included viral load, tolerability and antiviral efficacy. Safety parameters included hematology, clinical chemistry, body weights, and temperatures.

Viral load was determined by a rapid test and hybridization and samples below the limit of detection were further evaluated by PCR. Serum surface antigen (WHsAg), hepatitis B DNA, and total bilirubin assay was performed. Hepatitis C virions were quantified using real-time PCR. WHV DNA in sera was assayed by real-time PCR. Induction of innate immune response to SB 9200 treatment was assessed by measuring mRNA levels of genes encoding NK92, IFN-α, and IL-10.

At the end of treatment in **Group 2**, average reductions of 6.4 log_{10} in serum WHV DNA and 3.3 log_{10} in WHsAg were observed whereas in **Group 1**, average reductions of 4.2 log_{10} in WHV DNA and 1.1 log_{10} in serum WHsAg and WHV DNA were seen compared to pretreatment levels. Treatment demonstrated significant reductions of WHV DNA RNA, cccDNA, and RNA in Group 2 (78%, 49%, and 51%) and Group 1 (57%, 39%, and 41%). Following cessation of treatment and the 8-week follow-up period, recurrence of WHV replication was observed in Group 1, whereas recurrence in Group 2 was much delayed with viremia and antigenemia staying at 1.7 and 0.7 log_{10} below pretreatment levels. Overall, both treatment regimens slightly reduced hepatic WHV antigen expression and slowed liver disease progression. Serconversion to anti-WHs antibody was not observed. The antiviral effects were also associated with the induction of IFN-α, IFNβ, OAS-1, CCL10, ISGs, and IL-6 in blood and liver, which were more pronounced in Group 2 compared to Group 1.

The mean score for hepatic steatosis is plotted on the right y-axis. Induction of host innate immune response by pretreatment with SB 9200 followed by ETV in woodchucks resulted in significant declines in viral DNA, RNA, and antigens that was superior to that seen using the strategy of viral reduction with ETV followed by immune modulation. These data support the planned Phase II clinical trial of SB 9200 alone and in combination with a nucleoside in the treatment of chronic HBV.