SB 9200, a Novel Antiviral Agent, Targets Liver after Oral Administration to Rats

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INTRODUCTION

Acute and chronic infections caused by RNA and DNA viruses constitute a major public health crisis affecting millions of people. A limited arsenal of antiviral agents exists, mostly directed against a specific viral target such as the polymerase or protease characteristic of each virus. There is also rapid emergence of resistance to direct-acting antiviral drugs and dose-limiting toxicity. Therefore, new anti-viral drugs are urgently needed. Ideally compounds with novel mechanisms of action that have a broader spectrum of antiviral activity and are agonistic to viral genotypes and resistant mutants will be needed. SB 9200, an oral dinucleotide designed to target the liver, is a potent antiviral agent against wild-type and resistant HIV variants in in vitro assays in chronically HIV-infected HepG2.2.15 cell lines. SB 9200 shows potent antiviral activity in chronically WHV-infected woodchucks. The pharmacokinetics, dose-ranging toxicity, and safety pharmacology studies of SB 9200 have also been conducted in rats and monkeys.

RESULTS

SB 9200 has novel mechanisms of action involving the activation/enhancement of cytosolic proteins involved in virus detection, resulting in activation of the IFN signaling cascade and induction of antiviral state in cells. SB 9200 shows potent antiviral activity against wild-type and resistant HIV variants in vitro assays in chronically HIV-infected HepG2.2.15 cell lines. SB 9200 shows potent antiviral activity in chronically WHV-infected woodchucks. The pharmacokinetics, dose-ranging toxicity, and safety pharmacology studies of SB 9200 have also been conducted in rats and monkeys.

Figure 1: Concentration of total SB 9000 (nM) in plasma and liver from rats administered SB 9200 for 90 days

Figure 2: Concentration of Rp SB 9000 and Sp SB 9000 (nM) in plasma and liver from rats administered SB 9200 for 90 days

Table 1: Liver to Plasma ratios [AUC0-24 hr*nM/mL] of total SB 9000, Rp SB 9000 and Sp SB 9000 in the liver and plasma of rats after 90 days of dosing are shown in tables 3-5.

Table 2: Liver to Plasma ratios of the Cmax (nM) of total SB 9000, Rp SB 9000 and Sp SB 9000 after PO administration of SB 9200 for 90 days in rats

Table 3: The levels (nM) of SB 9000, Rp SB 9000 and Sp SB 9000 in plasma and liver from rats administered SB 9200 QD for 90 days

Table 4: The levels (nM) of Rp SB 9000 in plasma and liver from rats administered SB 9200 QD for 90 days

Table 5: The levels (nM) of Sp SB 9000 in plasma and liver from rats administered SB 9200 QD for 90 days

CONCLUSIONS

Our studies suggest that SB 9000 is actively transported via organic anion transporters into hepatocytes from the portal blood (see poster number 8048, April 20th). Thus, oral administration of SB 9000 could potentially lead to high exposures in the liver with low non-hepatic systemic exposures in patients

- Liver levels were highest at the 150 mg/kg dose and did not increase at the 250 mg/kg dose.
- Plasma levels increased in a dose-proportional manner.
- Levels of both dosimeters in the liver were substantially higher than in plasma at all time-points for each rat and the concentrations of SB 9000 in the liver were not directly correlated with plasma levels.
- Liver levels were up to 40-fold higher than the plasma levels and Cmax values did not correlate between liver and plasma, suggesting substantial first-pass extraction of SB 9000 from the portal blood.
- Multiple peak levels were observed in the plasma indicating enterohepatic cycling where drug is absorbed from the liver and plasma, suggesting substantial first pass extraction of SB 9000 from the portal blood.
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