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 agnostic 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 HBV, HCV, RSV, and Norovirus.** Results of a Phase I clinical trial of SB 9200 in HCV-infected patients was recently reported (Thompson et al., EASL 2015, AASLD, 2015).

BACKGROUND

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 HBV-variants in in vitro assays in chronically HBV-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 has also been conducted in rats and monkeys..

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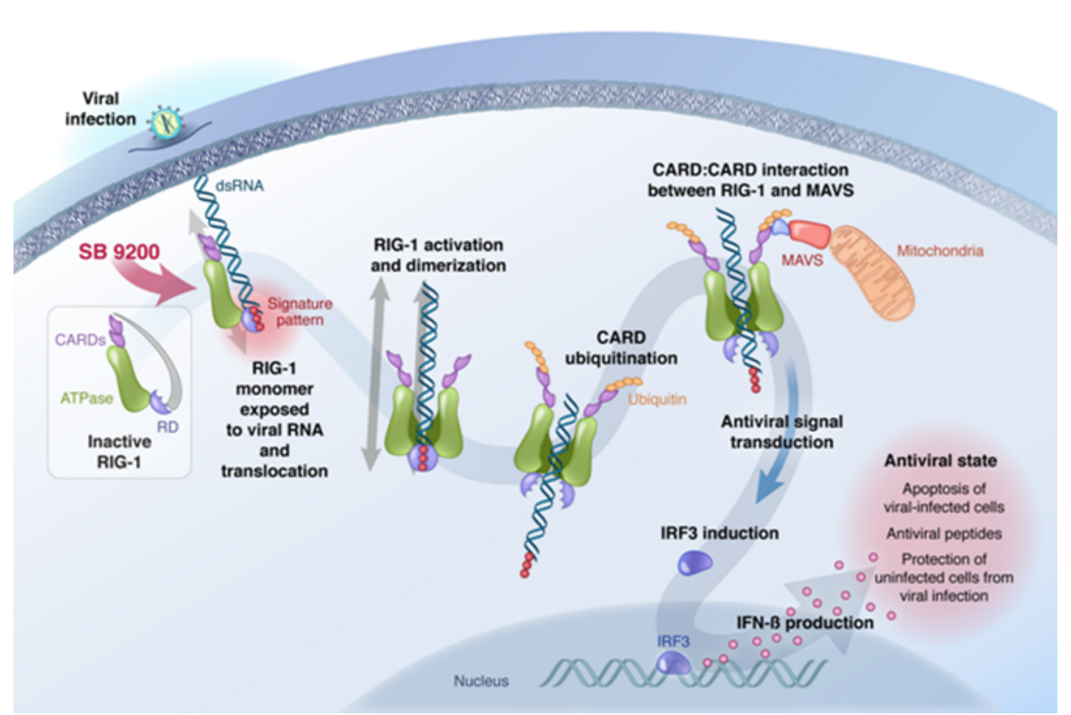
Activation of RIG-I by SB 9200



In Vitro Anti-HBV Activity of SB 9200 [EC50 for Inhibition of Viral Intermediates]

HBV strain	SB 9200, µM	3TC, µM	ADV, µM
Wild type	2.5	0.2	1.5
M204V	2.3	>100	1.8
M204I	3.0	>100	2.0
L180M	2.1	5.3	2.1
L180M/M204V	3.1	>100	2.2
N236T	2.8	0.2	7.5

3TC = Lamivudine; ADV = adefovir dipivoxyl

OBJECTIVE

Determine the concentration and toxicokinetics of SB 9000 and its diastereomers in plasma and liver following oral administration to Sprague Dawley rats after 90 days of repeat dosing and assess potential toxic effects and uptake by the liver.

METHODS

Rats were administered 50, 150 or 250 mg/kg for 90 days QD by oral gavage. On study days 90 and 91, after the last dose, plasma was collected at 0.25, 0.5, 1, 3, 6 and 24 h (6M/6F rats per time-point, a total of 2 time-points for each rat). Rats were sacrificed after the last blood collection at 3, 6 and 24 hours post-dose and livers were collected from 3M/3F rats per time-point. SB 9000 (total, calculated), Rp SB 9000 and Sp SB 9000 concentrations were determined by a validated LC-MS/MS method in both liver and plasma at the end of 90 day dosing.

ACKNOWLEDGEMENTS

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RESULTS

Multiple peak levels of SB 9000 were observed in plasma consistent with enterohepatic cycling.

SB 9000 distributed to the liver with peak levels 10-20 fold higher and exposures 20-40 fold higher than plasma with clearance 24-hr post-dose after 3 months of daily dosing.

However, the plasma bioavailability of SB 9000 was below 3% consistent with a large first-pass uptake of SB 9000 into the liver from the portal blood.

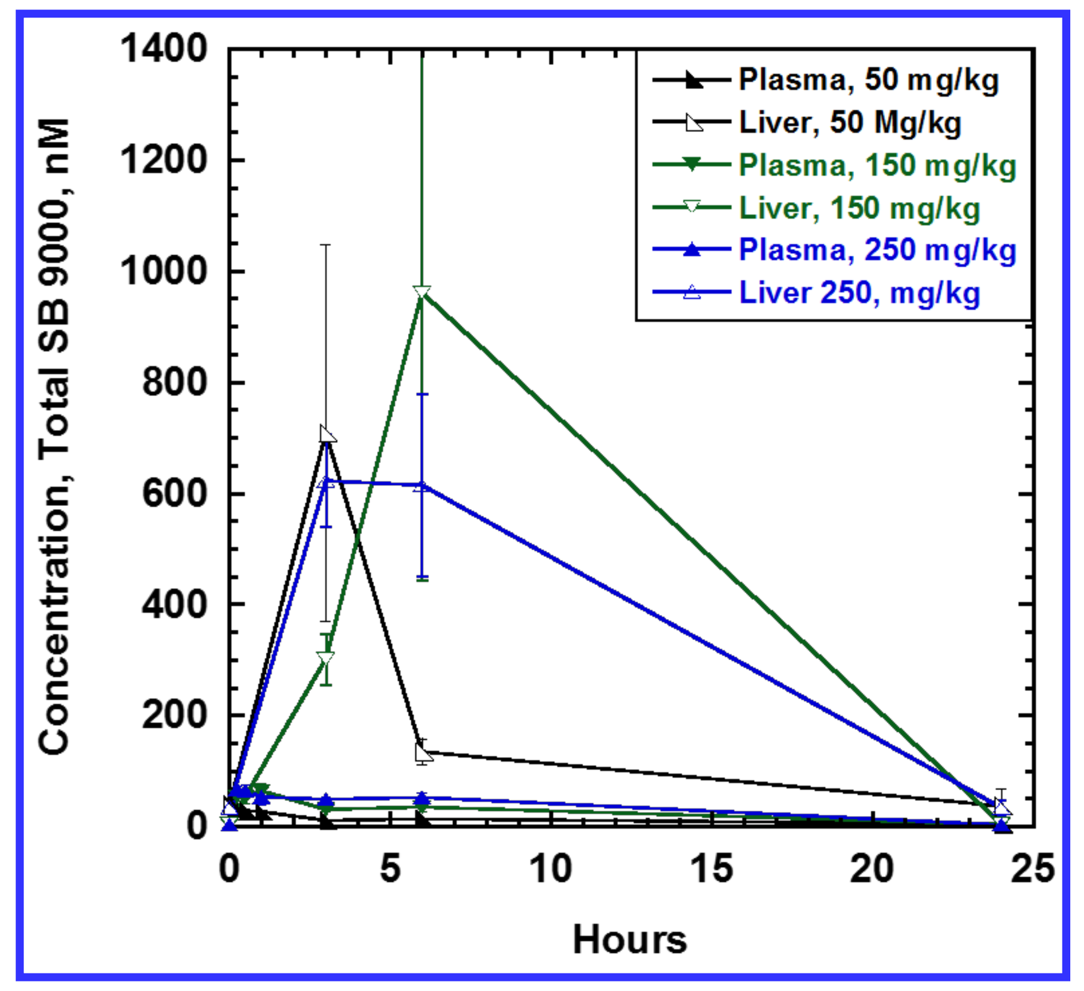

Figure 1. Concentration of total SB 9000 (nM) in plasma and liver from rats administered SB 9200 for 90 days

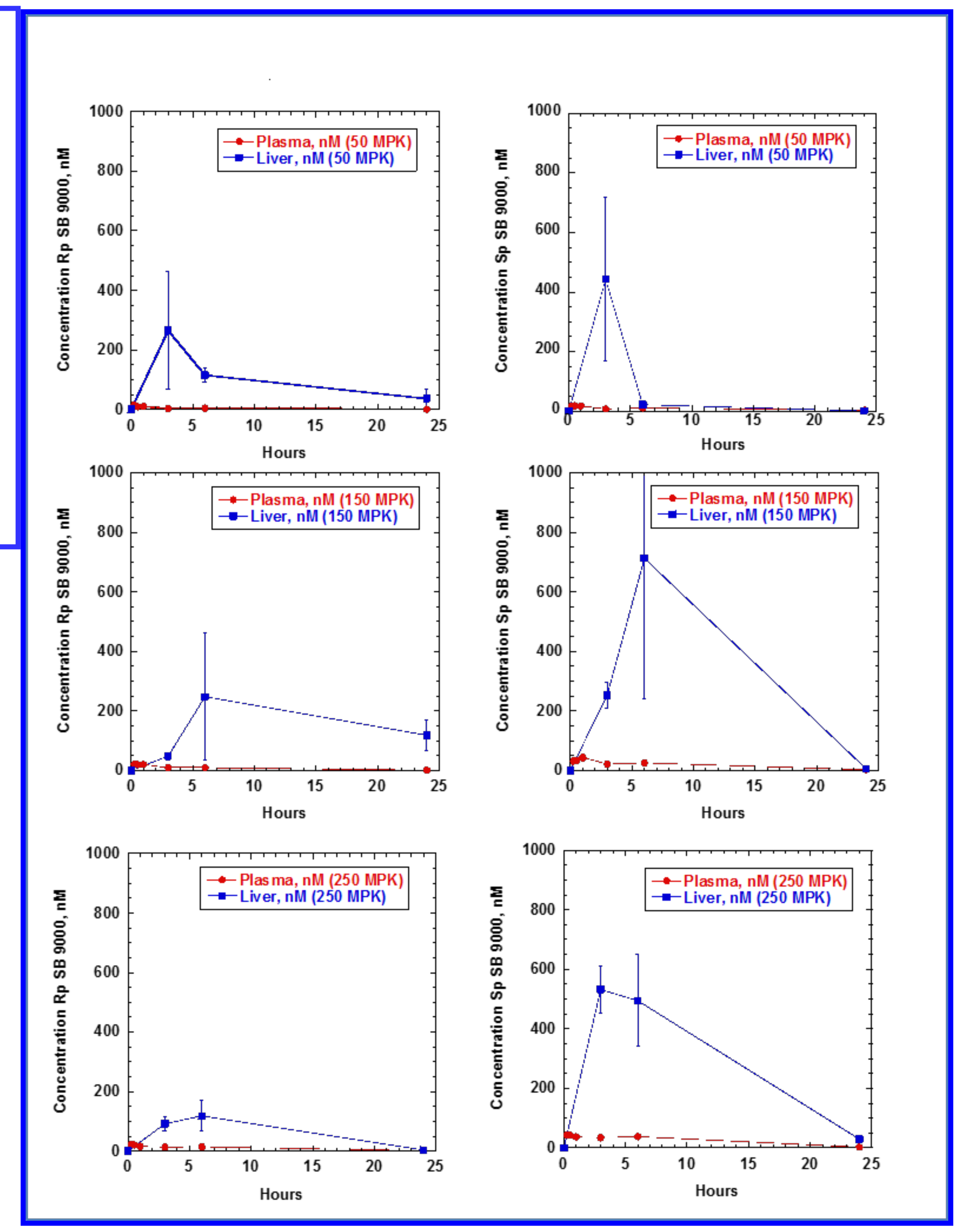

Figure 2. Concentration of Rp SB 9000 and Sp SB 9000 (nM) in plasma and liver from rats administered SB 9200 for 90 days

*Table 1: Liver to Plasma ratios [$AUC_{0-24,}$9hr*nM/mL)] of total SB 9000, Rp SB 9000 and Sp SB 9000 after PO administration of SB 9200 for 90 days to rats*

	Diasteriomer	50 mg/kg	150 mg/kg	250 mg/kg
Plasma	Total SB 9000	197.4	280.1	485.4
Plasma	Rp SB 9000	138.5	102.4	138.3
Plasma	Sp SB 9000	109.1	244.3	347.1
Liver	Total SB 9000	3980	11531	8921
Liver	Rp SB 9000	294.4	2895	1630
Liver	Sp SB 9000	2913	8653	7338
Liver:plasma ratio	Total SB 9000	20	41	19
Liver:plasma ratio	Rp SB 9000	2.1	10.3	12
Liver:plasma ratio	Sp SB 9000	27	35.4	21

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 to rats

	Diasteriomer	50 mg/kg	150 mg/kg	250 mg/kg
Plasma	Total SB 9000	32.3	63.8	67.2
Plasma	Rp SB 9000	14.9	20.7	23.2
Plasma	Sp SB 9000	18.1	43.7	44.0
Liver	Total SB 9000	708	961	623
Liver	Rp SB 9000	265	248	120
Liver	Sp SB 9000	443	713	531
Liver:plasma ratio	Total SB 9000	22	15	9
Liver:plasma ratio	Rp SB 9000	18	12	5
Liver:plasma ratio	Sp SB 9000	25	16	12

RESULTS

Mean (±SEM) concentrations 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 3: The levels (nM) of SB 9000 in plasma and liver from rats administered SB 9200 QD for 90 days

Dose SB9200	50 mg/kg Concentration, nM		150 mg/kg Concentration, nM		250 mg/kg Concentration, nM	
Hours	Plasma	Liver	Plasma	Liver	Plasma	Liver
0.25	32.3±7.5	NC	53.1±6	NC	67.2±6	NC
0.5	27.5±4.5	NC	52.4±10	NC	64±10	NC
1	27.3±2.9	NC	63.8±13	NC	53.2±13.2	NC
3	10.7±1.4	708.3±338	30.9±4	301±46	49±4	623±85
6	14.2±1.8	135±24	35±8.3	961±518	53±8	615±163
24	4.1±1.3	37±31	4.01±0.5	5.7±2	3±0.5	34±13.2

NC = not collected

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

Dose SB9200	50 mg/kg Concentration, nM		150 mg/kg Concentration, nM		250 mg/kg Concentration, nM	
Hours	Plasma	Liver	Plasma	Liver	Plasma	Liver
0.25	14.9±3.2	NC	20.73±3.4	NC	23.2±3.5	NC
0.5	9.4±1.5	NC	19.4±5.5	NC	21.4±2.9	NC
1	10.0±1.8	NC	20.1±6.4	NC	16.2±2.6	NC
3	3.9±0.8	265.3±198	9.9±2.2	48.4±14	14.0±3.0	92±24
6	4.0±0.8	20.0±7	9.9±1.6	248.3±214	14.4±2.0	120±51
24	0.9±0	0	0.81±0.3	0	1.7±0.4	3.7±2

NC = not collected

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

Dose SB9200	50 mg/kg Concentration, nM		150 mg/kg Concentration, nM		250 mg/kg Concentration, nM	
Hours	Plasma	Liver	Plasma	Liver	Plasma	Liver
0.25	17.4±6.8	NC	32.4±5	NC	44.0±6	NC
0.5	18.1±4.2	NC	33.0±8.2	NC	42.8±6	NC
1	17.3±2.3	NC	43.7±11.6	NC	37.0±7.4	NC
3	6.8±1.2	443±274	21.0±3.3	253±44	35.0±6.3	531±80
6	10.2±1.6	115±23	25.1±5.9	713±472	38.1±5.8	495±155
24	3.2±1.3	37±31	3.2±0.4	5.7±2	1.8±0.96	30±13

NC = not collected

CONCLUSIONS

Our studies suggest that SB 9000 is actively transported via organic anion transporters into hepatocytes from the portal blood (see poster number #048, April 20th).Thus, oral administration of SB 9200 could potentially lead to high exposures in the liver with low non-hepatic systemic exposures in patients

- Liver levels were highest at the150 mg/kg dose and did not increase at the 250 mg/kg dose.
- Plasma levels increased in a dose-proportional manner.
- Levels of both diastereomers in the liver were substantially higher than in plasma at all time-points sampled 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 intestine into the portal blood, excreted into the intestine from the liver via bile, and then re-absorbed into the portal vein where it recycles once again through the liver.
- Little or no accumulation of Rp or Sp SB 9000 was observed in the liver or plasma with the 24 hour dosing interval used in this study.