SB 9200, a novel immunomodulator for patients with viral hepatitis: Phase I MAD study in patients with hepatitis C Virus (HCV) infection

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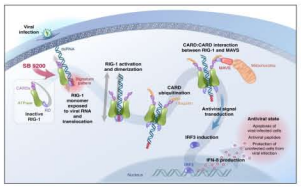
BACKGROUND

The immune response plays an important role in the clearance of HCV, even in the era of highly potent direct acting antivirals (DAA's), particularly as shorter durations of therapy are explored. SB 9200 is a pangenotypic anti-HCV agent. It is an oral dinucleotide prodrug that is enzymatically converted to the active Rp-, Sp-SB 9000 isomers *in vivo*.

Figure 1. SB 9200 Mechanism of Action



- *Binds to RIG-I and NOD2, sentinel proteins in the body's innate defense system, triggering interferon production.*
- *Binding to RIG-I also has a direct antiviral effect by preventing the NS5B polymerase from binding, blocking its progression or displacing it from HCV RNA replicative intermediates.*
- *Synergistic with other drugs, active against resistant strains.*
- *Activates "host" targets instead of viral targets.*

OBJECTIVES

To evaluate and compare the safety and tolerability, pharmacokinetics (PK), pharmacodynamics (PD) and antiviral activity of SB 9200 in patients with chronic hepatitis C infection (CHC) as multiple ascending doses for seven days.

MATERIALS & METHODS

Phase I, first in man, randomized, placebo-controlled study of multiple ascending doses of SB 9200, given as a monotherapy for 7 days in patients with CHC.

Healthy treatment naïve adults of non-childbearing potential, aged 18 to 60 years, with CHC who did not have advanced fibrosis or cirrhosis were enrolled.

Subjects were randomized 6:2 to receive a daily oral dose of SB 9200 or placebo for 7 days under fasted conditions. Doses evaluated were: 200 mg (N=8), 400 mg (N=8), and 900 mg (N=8 HCV-1, N=6 HCV-3).

RESULTS

Demography: Patient characteristics were well matched between treatment groups (**Table 1**).

Table 1. Subject Demography

		200 mg (N=6)	400 mg (N=6)	900 mg HCV1 (N=6)	900 mg HCV3 (N=4)	Placebo (N=8)
Age, years	Mean (SD)	46.0 (6.1)	49.7 (6.9)	47.5 (7.6)	51.8 (6.0)	46.4 (12.5)
Sex, n (%)	Male	6 (100.0%)	4 (66.7%)	4 (66.7%)	3 (75.0%)	5 (62.5%)
	Female	0 (0.0%)	2 (33.3%)	2 (33.3%)	1 (25.0%)	3 (37.5%)
Race, n (%)	White	5 (83.3%)	6 (100.0%)	6 (100.0%)	4 (100.0%)	8 (100.0%)
	Native Hawaiian/ Pacific islander	1 (16.7%)	-	-	-	-
HCV Genotype n (%)	1	-	1 (16.7%)	-	-	-
	1a	5 (83.3%)	5 (83.3%)	6 (100.0%)	-	6 (75.0%)
	1b	1 (16.7%)	-	-	-	1 (12.5%)
	3a	-	-	-	4 (100.0%)	1 (12.5%)
Weight, kg	Mean (SD)	80.68 (10.16)	87.15 (15.68)	74.62 (12.81)	74.28 (14.48)	77.46 (9.31)
Height, cm	Mean (SD)	174.0 (8.7)	173.8 (10.0)	173.8 (12.4)	169.5 (8.9)	171.4 (9.4)
BMI, kg/m^2	Mean (SD)	26.60 (1.84)	28.67 (3.56)	24.80 (4.09)	25.63 (2.72)	26.49 (3.27)

PK: Where comparison was possible, a low to moderate accumulation of SB 9200, Sp-SB 9000 and Rp-SB 9000 was observed following repeated once-daily dosing for 7 days. Increases in SB 9200 $AUC_{0\text{-}t}$ and C_{max} were dose-proportional. PK Parameters are summarized in **Table 2**.

Table 2. Arithmetic Mean (CV%) Day 7 PK Parameters

		200mg (N=6)	400 mg (N=6)	900 mg (N=6)
$AUC_{0\text{-}t}$ (ng*h/mL)	SB 9200	1.41 (129.5)	3.10 (43.3)	9.39 (185.2)
	Sp-SB 9000	60.5 (56.0)	129.1 (47.4)	253 (51.5)
	Rp-SB 9000	25.8 (42.2)	60.3 (57.6)	120.0 (59.2)
C_{max} (ng/mL)	SB 9200	0.885 (85.4)	2.52 (54.8)	6.66 (219.6)
	Sp-SB 9000	7.76 (53.2)	12.0 (58.1)	22.0 (68.4)
	Rp-SB 9000	4.85 (56.0)	7.58 (46.2)	14.7 (82.7)
$t_{1/2}$ (h)	SB 9200	NC	0.684 (40.1)	1.07 (44.2)
	Sp-SB 9000	4.94 (20.3)	8.55 (38.1)	4.65 (15.5)
	Rp-SB 9000	4.98 (78.4)	5.94 (12.3)	4.31 (32.2)

Safety: AEs are summarized by SB 9200 dose in **Table 3**. **Table 3. Adverse Events Reported**

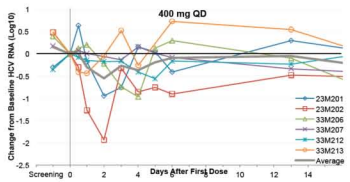
	200 mg (N=6)	400 mg (N=6)	900 mg HCV 1 (N=6)	900 mg HCV3 (N=4)	Placebo (N=8)
Subjects with at least one AE	6	4	5	3	7
Subjects with a Dose Limiting Toxicity	0	0	0	0	0
Subjects with severe or life-threatening AEs	0	0	0	0	0
Subjects with drug-related AEs	4	4	4	3	7
Subjects with serious AEs	0	0	0	0	0

The most frequently reported related AEs Headache (7 events reported by 6 subjects), Nausea (3 events reported by 2 subjects), Elevated ALT (2 subjects with baseline elevated ALT had a less than 3 fold increase on treatment).

There was no relationship between incidence, severity or relationship of AEs and dose of SB 9200 received, or placebo. Further, no systemic interferon-like side effects were observed.

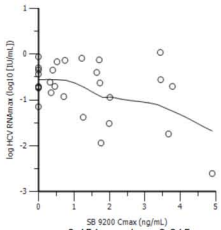
PD: Inter-individual variability in antiviral response was observed, therefore individual data are presented rather than mean data. Overall, peak individual viral load drop improved from 1.5 to 1.9 log_{10} when the SB 9200 dose increased from 200 to 400 mg (**Figure 2**). Further dose increases did not result in response increases.

Figure 2. Individual Viral Load over Time



The data were carefully reviewed for the relationship between PK parameters and maximum HCV RNA suppression. A significant relationship between SB 9200 C_{max} and maximum suppression of HCV RNA on Day 7 was observed (p=0.015), after exclusion of two subjects with extreme C_{max} values (**Figure 3**).

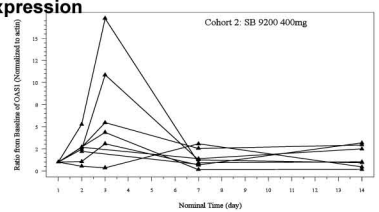
Figure 3. Maximum Suppression of HCV RNA vs. SB 9200 C_{max}



Note: Subjects 21M401 and 33M306 were excluded due extreme C_{max} values.

Innate immune gene induction: The longitudinal expression of canonical interferon-stimulated (ISGs) and pro-inflammatory genes in the peripheral blood of patients was evaluated (OAS-1, RIG-I, MX-1, IP-10, TNF-α and IL-6) using RT-PCR. Preliminary analysis identified induction of ISGs that peaked at 24-48hrs (**Figure 4**).

Figure 4. Peripheral blood OAS1 mRNA Expression



SUMMARY

SB 9200 is a novel oral agent that activates intracellular cytoplasmic viral sensors RIG-1 and NOD2. Therapeutic concentrations of the drug are achieved with once daily administration. In this multiple ascending dose study, peak individual viral load reduction of 1.9 log_{10} was observed at a dose of 400 mg. Peripheral induction of ISGs was observed. SB 9200 was well tolerated.

CONCLUSIONS

SB 9200 is a novel oral agonist of innate immunity. Results of this study suggest a possible anti-viral effect similar to IFN, but without systemic side effects. SB 9200 is a novel anti-HCV agent that merits further evaluation in combination trials with DAAs, as well as HBV.

REFERENCES

Yoneyama M et al. The RNA helicase RIG-I has an essential function in double-stranded RNA-induced innate antiviral responses. Nat Immunol 2004;5:730-737.

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