SB 9200 Shows Antiviral Activity Against HCV-RNA by Targeting Host Cytosolic Sensor Proteins RIG-I and NOD-2 to activate IFN signaling pathways

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BACKGROUND

Hepatitis C virus (HCV) infects approximately 170 million people worldwide and four million new infections each year. SB 9200, an oral prodrug developed by Spring Bank, activates the host-cellular cytosolic sensors RIG-I and NOD2 which results in the production of type I and III IFNs and subsequent induction of ISGs and antiviral immune cells (Sato S, et al. 2015). SB 9200 has been shown to maximally reduce HCV RNA by 1.9 log_{10} in HCV patients (Thompson EASL 2015).

OBJECTIVES

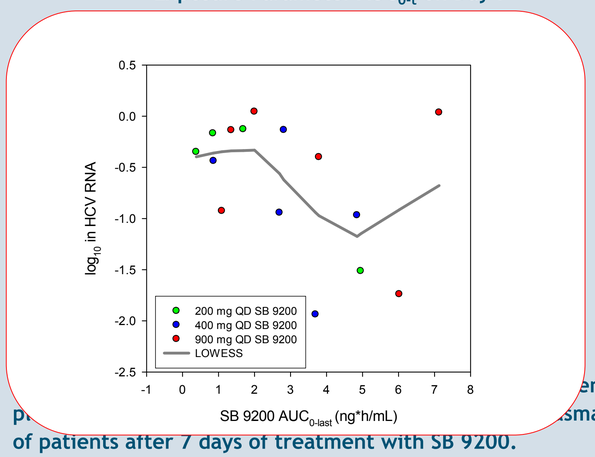
To evaluate the relationship between the pharmacokinetics of SB 9200, and the induction of innate immunity and antiviral response.

METHODOLOGY

HCV patients, GT1 and 3, received 200-900 mg of SB 9200 PO daily for 7 days. Early antiviral kinetics were measured from baseline through 7 days after the first dose of SB 9200. Patients were null responders (NR, < 0.5 log_{10} reduction in HCV RNA, n=11) or responders (R, >0.9 log_{10}, n=6). Plasma IFNα was measured on day 1, 7, 14 by ELISA. Interferon stimulating genes ISG-15 and OAS-1 were measured on Day 1, 2, 3, 7, 14 in peripheral blood via RT-PCR.

RESULTS

Figure 1* : Relationship between Maximum Suppression of HCV RNA (Δlog HCV RNA_{max}) vs. Plasma SB 9200 Exposure Parameter $AUC_{0\text{-}t}$ on Day 7



- …en p… …sma of patients after 7 days of treatment with SB 9200.

*Without 2 subjects (21M401 and 33M306) with extreme plasma SB 9200 and metabolites exposures on Day 7.

RESULTS

Table 1. Baseline Clinical Characteristics for R vs. NR

	Mean (CV%) Median [Min; Max]	
Variables	*Responders (R) (N=6)*	*Null Responders (NR)*
Baseline HCV RNA Viral Load (log_{10} (IU/mL))	*5.63 (17.4) 5.60 [4.31; 6.81]*	*5.81 (12.1) 6.04 [4.55; 6.53]*
ALT (U/L)	*41.8 (40.7)[a] 51 [14; 55]*	*56.4 (58.7) 43 [19; 123]*
AST (U/L)	*27.0 (33.4)[a] 23 [17; 38]*	*44.5 (50.2) 36 [18; 88]*
FibroScan[b]	*6.1 (17.8) 6.1 [4.8; 7.9]*	*5.81 (27.3) 5.2 [4.2; 9.3]*
Platelets (x10⁹/L)	*250 (14.9) 250 [204; 314]*	*190 (34.1) 195 [85; 289]*
Total Bilirubin (μmol/L)	*7.6 (71.2)[a] 6 [4; 17]*	*8.5 (64.6) 7 [4; 23]*
White Blood Cells (x10⁹/L)	*7.1 (33.6) 6.3 [5.1; 11.1]*	*5.5 (29.5) 5.5 [3.0; 8.0]*

[a]N=5 ;[b]Screening values. All data are not signifiant.

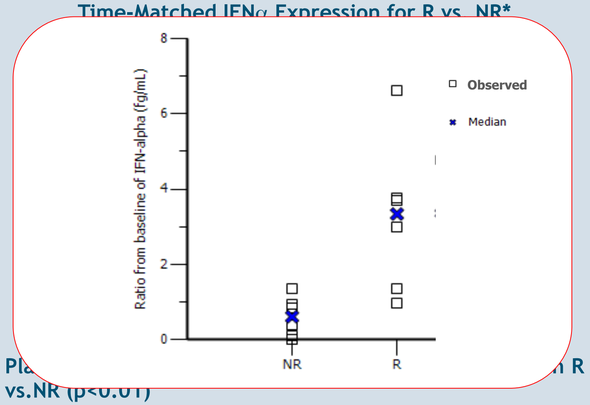
Table 2. Summary of Viral Decrease from Baseline (R vs. NR)

	Mean (CV%) Median [Min; Max]	
Variables	*Responders (R)*	*Null Responders (NR)*
Max. HCV RNA Viral Load Decrease from Baseline (log_{10} (IU/mL))	*-1.3 (33.6) -1.24 [-1.94; -0.93]*	*-0.1 (145.1) -0.14 [-0.44; 0.11]*
Day of Max. HCV RNA Viral Load Decrease from Baseline	*4.2 (38.4) 4 [3; 7]*	*3.5 (59.3) 4 [1; 7]*

All data are not signifiant.

SB 9200 Stimulates the Expression of IFNα

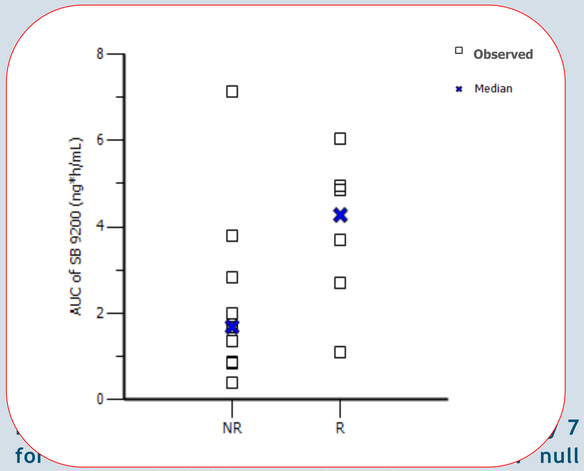
Figure 3* Maximum Suppression HCV RNA (Δlog HCV RNA_{max}) Time-Matched IFNα Expression for R vs. NR*



- Pl… …n R vs.NR (p<0.01)

SB 9200 Exposure is Greater for R vs. NR

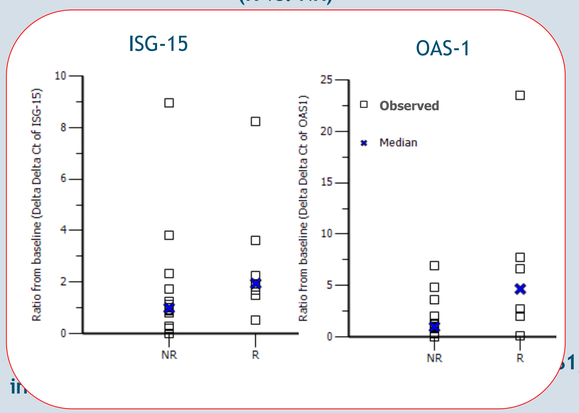
Figure 2*: Day 7 SB 9200 $AUC_{0\text{-}last}$ in Plasma of R vs. NR*



- … 7 fo… … null responders, which did not reach significance in the small sample size (p-value = 0.4386).

SB 9200 Activates Gene Expression of IFNα responsive genes : ISG-15 and OAS-1

Figure 4*: Maximum Suppression HCV RNA (Δlog HCV RNA_{max}) Time-Matched OAS-1 and ISG-15 Expression (R vs. NR)



- … 1, in…
- Increased expression of OAS1 and ISG-15 was observed in R vs. NR, which did not reach significance in the small sample size (p=0.2253)

SUMMARY

Following 7-days of daily treatment with SB 9200 (200 mg-900 mg) :

- Viral Load decreased when plasma SB 9200 exposure ($AUC_{0\text{-}t}$) increased in the plasma of patients
- SB 9200 plasma exposure ($AUC_{0\text{-}t}$) was greater in responders vs. null responders.
- Plasma IFNα statistically significantly increased following SB 9200 treatment and the peripheral IFNα levels are greater in responders vs null responders.
- The expression of IFNα downstream genes, ISG-15 and OAS-1, increased following SB 9200 administration and the gene expression is greater in responders vs null responders, however did not reach significance in the small sample size.

CONCLUSION

SB 9200 is a novel, first-in-class, oral agonist of innate immunity which upregulates IFN responsive gene expression. The data support a mechanism of antiviral action of SB 9200 involving modulation of innate immunity, meriting further evaluation in combination with direct-acting antiviral agents in HCV patients.

REFERENCES

A. J. Thompson et al. SB 9200, A Novel Immuno-Modulator for Patients with Viral Hepatitis: Phase I MAD Study in Patients with Hepatitis C Virus (HCV) Infection. 2015 EASL.

DISCLOSURES

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