Novel Antiviral Activity of SB 9200 (Inarigivir), a RIG-I Agonist: Results from Cohort 1 of the ACHIEVE Trial

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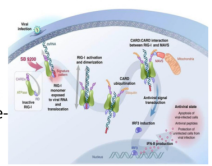
Introduction

SB 9200 is a novel oral prodrug of the dinucleotide SB 9000 which activates the viral sensor proteins retinoic acid-inducible gene I (RIG-I) and the nucleotide-binding oligomerization domain-containing protein 2 (NOD-2), resulting in the induction of both type I and type III interferon (IFN) responses. The 5′-ε region of HBV pregenomic (pg) RNA is a key element for RIG-I-mediated recognition. The binding of SB 9200 to these sensor proteins can also interfere, presumably by steric blocking, the protein-RNA interaction of the HBV polymerase (POL) and the 5′-ε region, thereby inhibiting reverse-transcription and directly suppressing viral replication (see Figure). The ACHIEVE trial is a double-blind, placebo-controlled phase 2 study of SB 9200 in chronic HBV treatment-naïve patients. Cohort 1 received either 12 weeks (week 1-12) of 25mg PO daily SB 9200 monotherapy or placebo (PL), followed by a switch to 300mg Tenofovir (TDF) daily for a further 12 weeks (week 12-24).



Aim

We report here the molecular virological and serological responses of the SB 9200-treated patients compared to PL in ACHIEVE Cohort 1 (week 1-24).

See also Clinical Presentation by Yuen, M.F. et al. Sunday Morning, Parallel 5 Hepatitis B: New Therapies Abstract #39.

Patients and Methods

Twenty treatment-naïve non-cirrhotic patients with chronic hepatitis B were randomised 4:1 to 25mg SB 9200 (16) or placebo (4) for 12 weeks and then all 20 were switched to TDF (300mg) daily from week 12-24. HBV DNA was assayed using the Roche Cobas®/Ampliprep/Taqman HBV test. HBsAg was quantified with the Roche Elecsys® HBsAg II assay. HBeAg was quantified with the LIAISON® HBeAg Assay (Diasorin). HBV RNA was extracted by the QIAamp RNA minikit, reverse transcribed and amplified using the method described by Van Bommel[1]. HBcrAg was assayed with the Lumipulse® G system (Fujirebio). HBsAg epitope mapping was performed on the Bioplex Platform as previously described[2]. Statistical analysis by Fischer's Exact Test (in R).

Patient Characteristics

	HBeAg- (N=7)	HBeAg+ (N=9)	Placebo (N=4)
ALT	75	82	82
AST	45	46	46
Bilirubin (umol)	8.6	8	8
Genotype (n)	A-1; B-3; C-1; D-2	B-4; C-5	A-1; B-2; C-1
HBV DNA $\log_{10}$ IU/ml	5.69	7.86	6.00
HBsAg $\log_{10}$ IU/ml	3.17	4.46	3.70

M 12: F8.; Asian 18: Cauc 2.; Mean Age 40.5 years

1 placebo patient HBeAg positive; 3 HBeAg negative

Results

A. SB 9200 Monotherapy (week 0-12)

Virology Decline	HBeAg-NEG n=7	HBeAg-POS n=9	PL n=4	Rx versus PL
HBV DNA [≥1.0 $\log_{10}$ IU/ml]	3/7	1/9	0/4	25% vs 0%
qHBsAg [≥0.5 $\log_{10}$ IU/ml]	4/7	1/9	0/4	31% vs 0%
qHBeAg [≥0.5 $\log_{10}$ PEIU/ml]	NA	1/9	0/4	11% vs 0%
HBV RNA [≥3.0 $\log_{10}$ copies/ml to undetectable]	3/7	NC	0/4	18% vs 0%
[≥1.0 $\log_{10}$ copies/ml to <3 $\log_{10}$ copies/ml]	1/7	1/9	0/4	12% vs 0%
[≥0.5 $\log_{10}$ copies/ml to <1 $\log_{10}$ copies/ml]	3/7	2/9	1/4	31% vs 25%
HBcrAg [≥1.0 $\log_{10}$ kU/ml]	3/7	NC	0/4	18% vs 0%
[≥0.5 $\log_{10}$ kU/ml to <1 $\log_{10}$ kU/ml]	3/7	1/9	0/4	25% vs 0%

NA = Not Applicable; NC = No Change; PL = Placebo

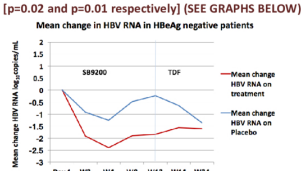
IN THE HBeAg-NEGATIVE COHORT, HBV RNA AND HBcrAg DECLINE COMPARED TO PLACEBO WERE SIGNIFICANT [p=0.02 and p=0.015 respectively] (SEE GRAPHS BELOW)

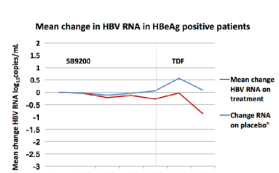
B. TDF Switch (week 12-24)

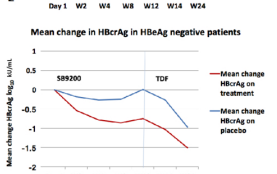
Virology Decline	HBeAg-NEG n=7	HBeAg-POS n=9	PL n=4	Rx versus PL
HBV DNA [>1.0 $\log_{10}$ IU/ml]	7/7	9/9	4/4	100% vs 100%
qHBsAg [>0.5 log IU/ml]	3/7	3/9	2/4	38% vs 50%
qHBeAg [>0.75 log PEIU/ml]	NA	4/9	0/4	44% vs 0%
HBV RNA [>3.0 $\log_{10}$ copies/ml to undetectable]	5/7	1/9	1/4	38% vs 25%
[≥1.0 $\log_{10}$ copies/ml to <3 $\log_{10}$ copies/ml]	1/7	2/9	0/4	18% vs 0%
[≥0.5 $\log_{10}$ copies/ml to <1 $\log_{10}$ copies/ml]	1/7	NC	0/4	6% vs 0%
HBcrAg [>1.0 $\log_{10}$ kU/ml]	5/7	2/9	1/4	44% vs 25%
[≥0.5 $\log_{10}$ kU/ml to <1 $\log_{10}$ kU/ml]	2/7	3/9	0/4	31% vs 0%

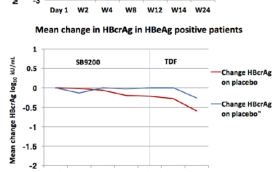
NA = Not Applicable; NC = No Change; PL = Placebo

IN HBeAg-NEGATIVE COHORT, HBV RNA AND HBcrAg DECLINE COMPARED TO PLACEBO WERE SIGNIFICANT [p=0.02 and p=0.01 respectively] (SEE GRAPHS BELOW)









POSSIBLE IMMUNE EFFECTS

In patients who experienced more than a 0.5 $\log_{10}$ IU/ml drop in qHBsAg, epitope changes in the HBsAg that were associated with a clearance profile (p=0.0385) were demonstrated. Anti-HBs complexed to circulating HBsAg was observed in 9/16 (56%) of SB 9200-treated patients compared to only 1/4 (25%) placebo subjects, indicating possible (partial) immune recovery.

SUMMARY

Twelve weeks of SB 9200 monotherapy at 25mg/day resulted in:

- Significant decline in HBV DNA and qHBsAg, more pronounced in the HBeAg-negative patients.
- Dramatic drop in HBV RNA and HBcrAg, more pronounced in the HBeAg-negative patients.
- Possible early immune mediated effects manifested in changes to key HBsAg epitopes.

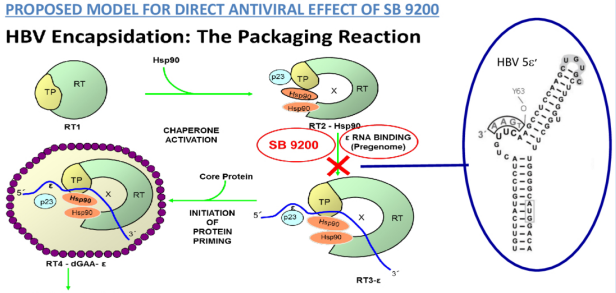
SB 9200 could be acting directly at the level of encapsidation (see Model below) but a moderate effect on transcriptional activity of cccDNA cannot be excluded .

DISCUSSION

At this dose of 25mg/day, there was no evidence of significant activation of systemic innate or adaptive immune responses, which were only seen at doses of 200mg or greater given daily in the SB 9200 Phase 1 studies in HCV patients.

PROPOSED MODEL FOR DIRECT ANTIVIRAL EFFECT OF SB 9200

HBV Encapsidation: The Packaging Reaction



Modified from Seeger C & Mason WS. 2000. MicrobiolMolBiolRev;64:51-68

Conclusions

SB 9200 at a dose of 25mg for 12 weeks resulted in significant antiviral effects on HBV replication. Based on the pattern of the key viral biomarkers affected, SB 9200 appears to be inhibiting HBV directly at the level of RNA packaging and subsequent reverse-transcription. There is also a suggestion of an immune- mediated clearance response, also more pronounced in the HBeAg-neg cohort. Further studies are warranted.

References

1. van Bommel, F et al 2015. Hepatology;61(1):66-76.
2. Walsh, R et al 2016 AASLD. Hepatol;64(Suppl 1):296A

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