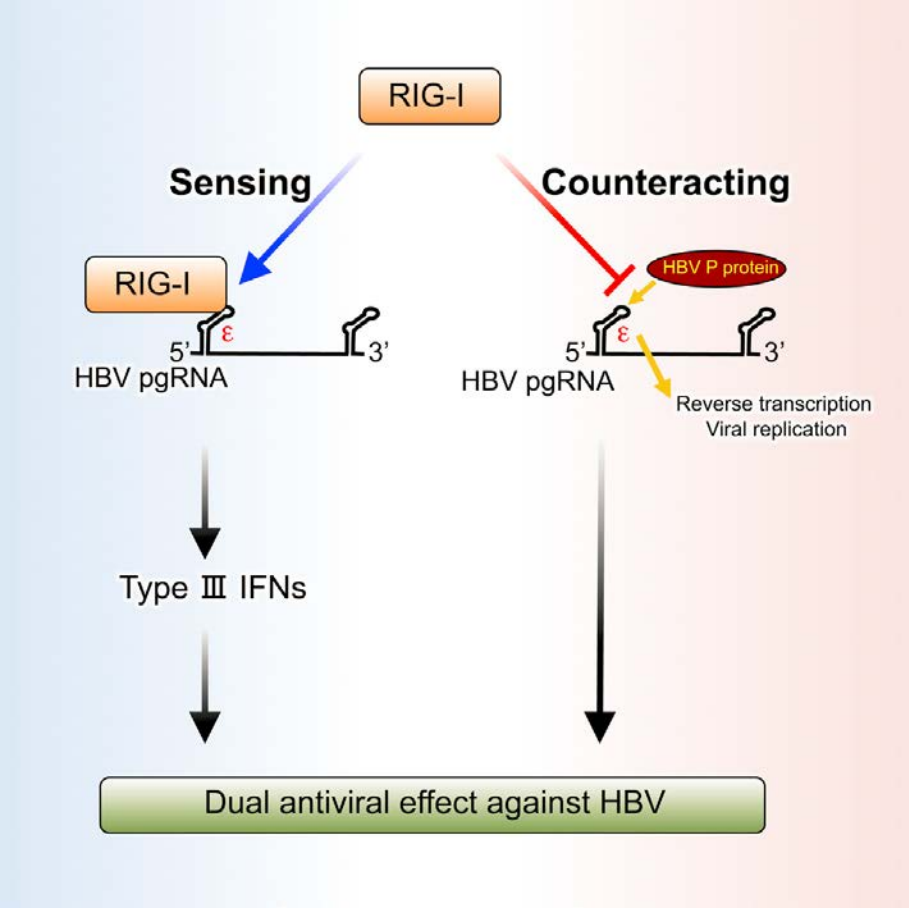
Inarigivir: A novel RIG-I agonist for chronic hepatitis B

Stephen Locarnini, Danny Wong, Kathy Jackson, Renae Walsh, Ros Edwards, Rachel Hammond, Carla S. Coffin, Magdy Elkhashab, Susan Greenbloom, Alnoor Ramji, Henry LY-Yuen Chan, Won Kim, Chelsea Macfarlane, Radhakrishnan P. Iyer, Nezam H. Afdhal, Man-Fung Yuen

On behalf of the ACHIEVE STUDY GROUP

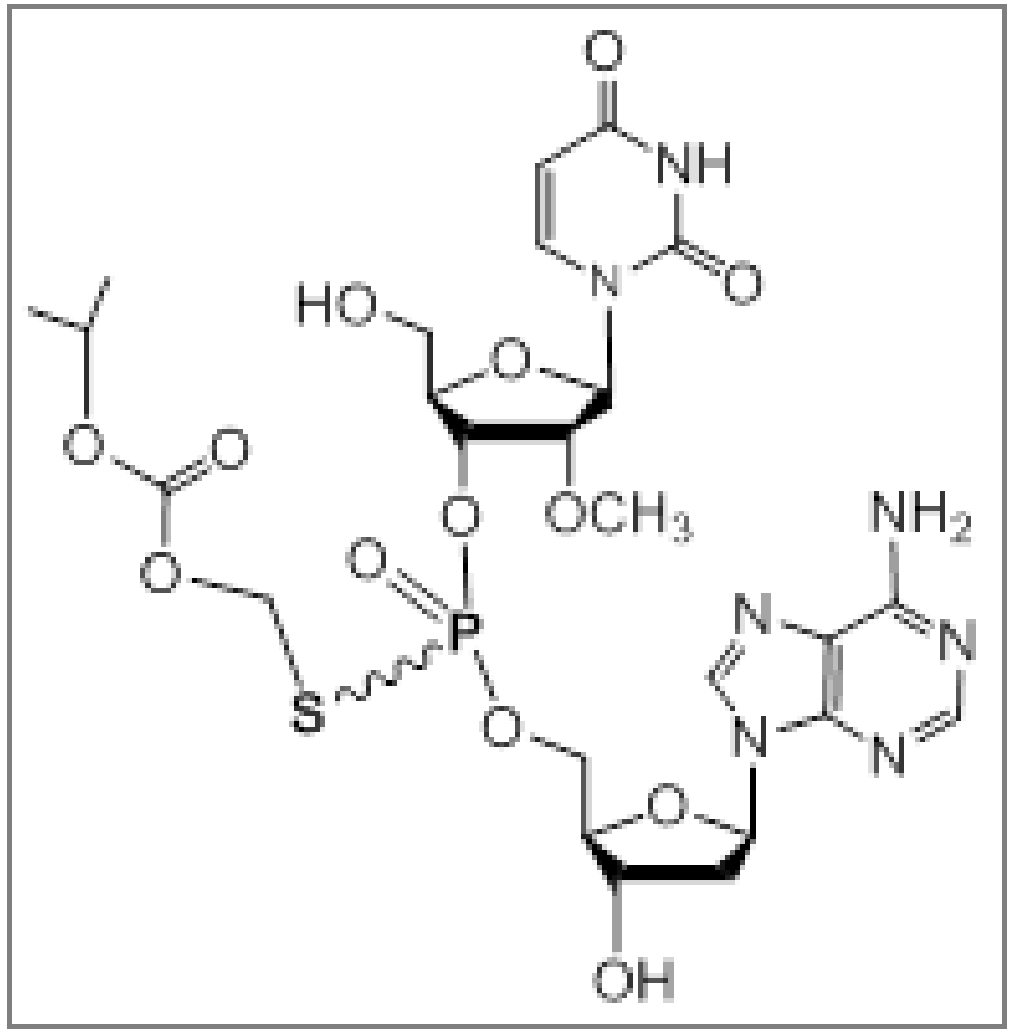
The RNA Sensor RIG-I Dually Functions as an Innate Sensor and Direct Antiviral Factor for Hepatitis B Virus



- RIG-I senses the HBV genotype A, B, and C for the induction of type I and III IFNs
- The 5'-ε region of HBV pgRNA is a key element for the RIG-I mediated recognition
- Type I and III IFNs are predominantly induced in human hepatocytes during HBV infection
- RIG-I binding to pgRNA can suppress encapsidation (Locarnini AASLD 2017)

Sato et al., 2015, Cell Immunity 42, 123–132

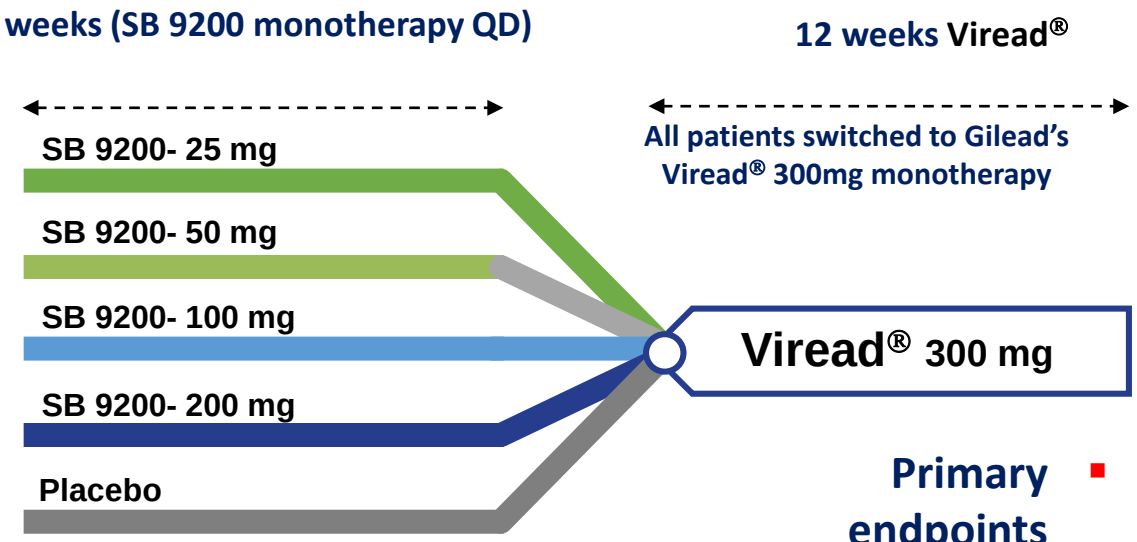
Inarigivir (SB 9200)



- Small molecule nucleic acid hybrid (SMNH)
- RIG-I activator
- Orally bioavailable prodrug
- Active metabolite SB 9000
- Actively transported into hepatocytes via OATP1
- 30:1 liver to plasma ratio
- Not metabolized, not phosphorylated.
- No direct activity against DNA polymerase

STUDY DESIGN Achieve Trial – Part A

20 non-cirrhotic HBV subjects per cohort, randomized 4:1 between SB 9200 and placebo



Primary endpoints

- Safety and antiviral activity at 12 weeks

Other Endpoints

- PK, change in serum HBV DNA, HBsAg, HBeAg, HBV RNA and HBcrAg from baseline to weeks 6, 12, 14, 16 and 24

Key Criteria

INCLUSION

- HBsAg positive for > 6 months
- Treatment naïve for > 6 months
- HBV DNA > 2000 IU/ml for HBeAg –ve and > 20,000 IU/ml for HBeAg +ve
- ALT > ULN but < 150 IU/ml
- FibroScan < 8kPa

EXCLUSION

- F3 or F4 fibrosis
- Evidence of HCC by imaging
- Co-infection with HCV, HIV or HDV
- Creatinine > 1.2mg/dL

Baseline Demographics Cohort 1 and 2

	Placebo	Inarigivir 25mg HBeAg +ve	Inarigivir 25mg HBeAg -ve	Inarigivir 50mg HBeAg +ve	Inarigivir 50mg HBeAg -ve
Number	8	9	7	11	5
Age	38	37	43	36	47
Gender M:F	6 : 2	5 : 4	3 : 4	9 : 2	5
Baseline ALT	74	82	75	75	65
Baseline HBV DNA log_{10}	6.36	7.86	5.69	7.79	4.55
Genotype A	1		1		
B	5	4	3	2	3
C	2	5	1	6	1
D			2	1	

In cohort 2, two patients – 1 HbeAg +ve; 1 HBeAg –ve withdrew at day 1 and day 14 from patient choice

Anti-viral efficacy cohort 1 and 2: Baseline to week 12

MEAN	Placebo	Inarigivir 25mg HBeAg +ve	Inarigivir 25mg HBeAg -ve	Inarigivir 50mg HBeAg +ve	Inarigivir 50mg HBeAg -ve
Baseline HBV DNA log_{10}	6.36	7.86	5.69	7.79	4.55
Change in DNA (BL to week 12) log_{10}	+0.33	-0.37*	-0.86	-0.61#	-1.05
Baseline HBsAg log_{10}	3.75	4.31	3.17	4.12	2.96
Change in HBsAg log_{10}	-0.18	-0.08	-0.34	-0.07	0
Baseline HBV RNA log_{10}	4.23	6.36	4.20	6.58	3.15
Change in HBV RNA	+0.99	-0.32	-1.84$	-0.46	-3.15&

t-test vs placebo

- *P < 0.03
- # p < 0.005
- $ p < 0.01
- & p < 0.01

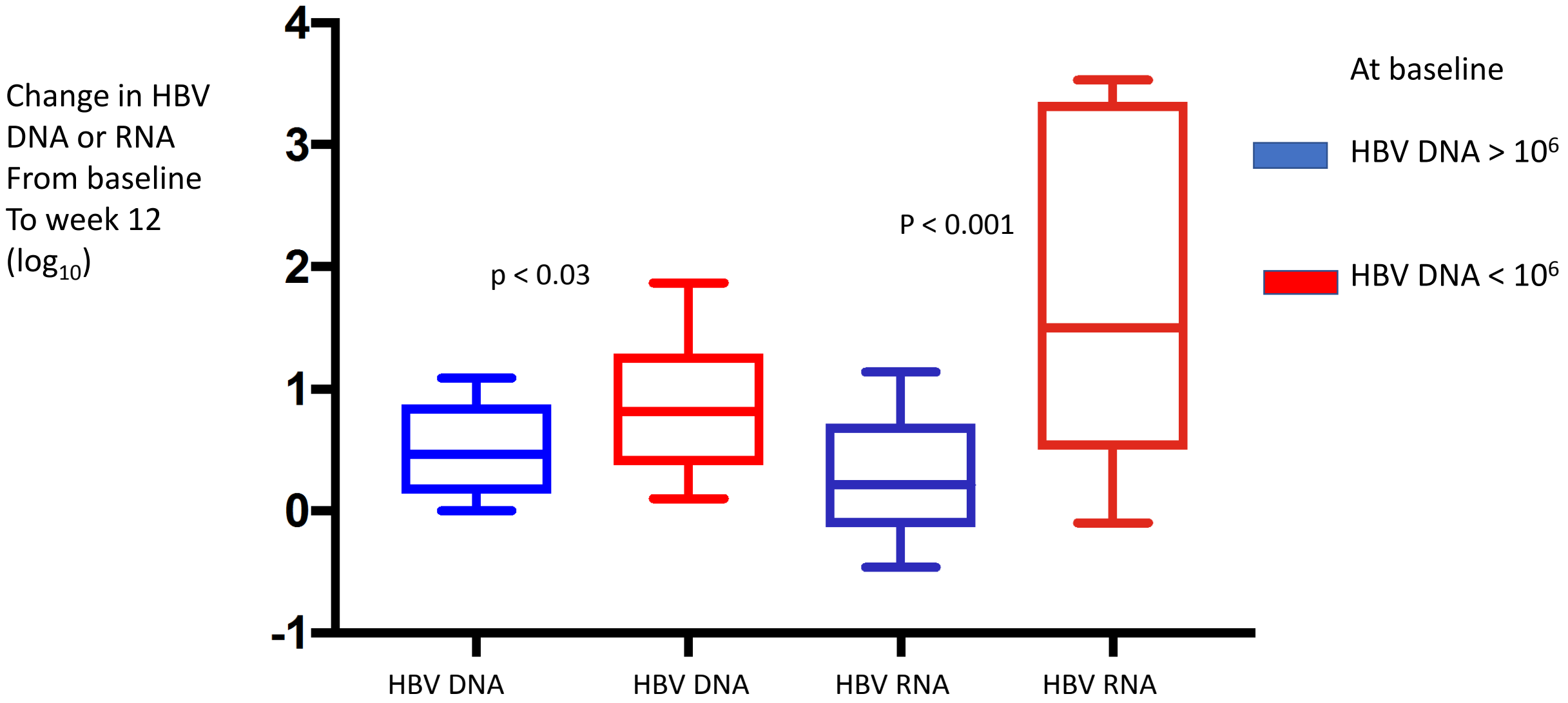
SB9200 Combined 25mg and 50mg Monotherapy Change from baseline to week 12

Virology Decline	HBeAg NEG* (n = 11)	HBeAg POS (n = 19)	PL (n = 8)
HBV DNA > 1log	6	2	0
HBV DNA >0.5 <1log	5	5	1
qHBsAg > 0.5log	4	1	1
qHBeAg > 0.5log	N/A	2	1
HBV RNA > 3log	5	0	0
HBV RNA >1log	1	3	0
HBV RNA > 0.5log	3	4	2

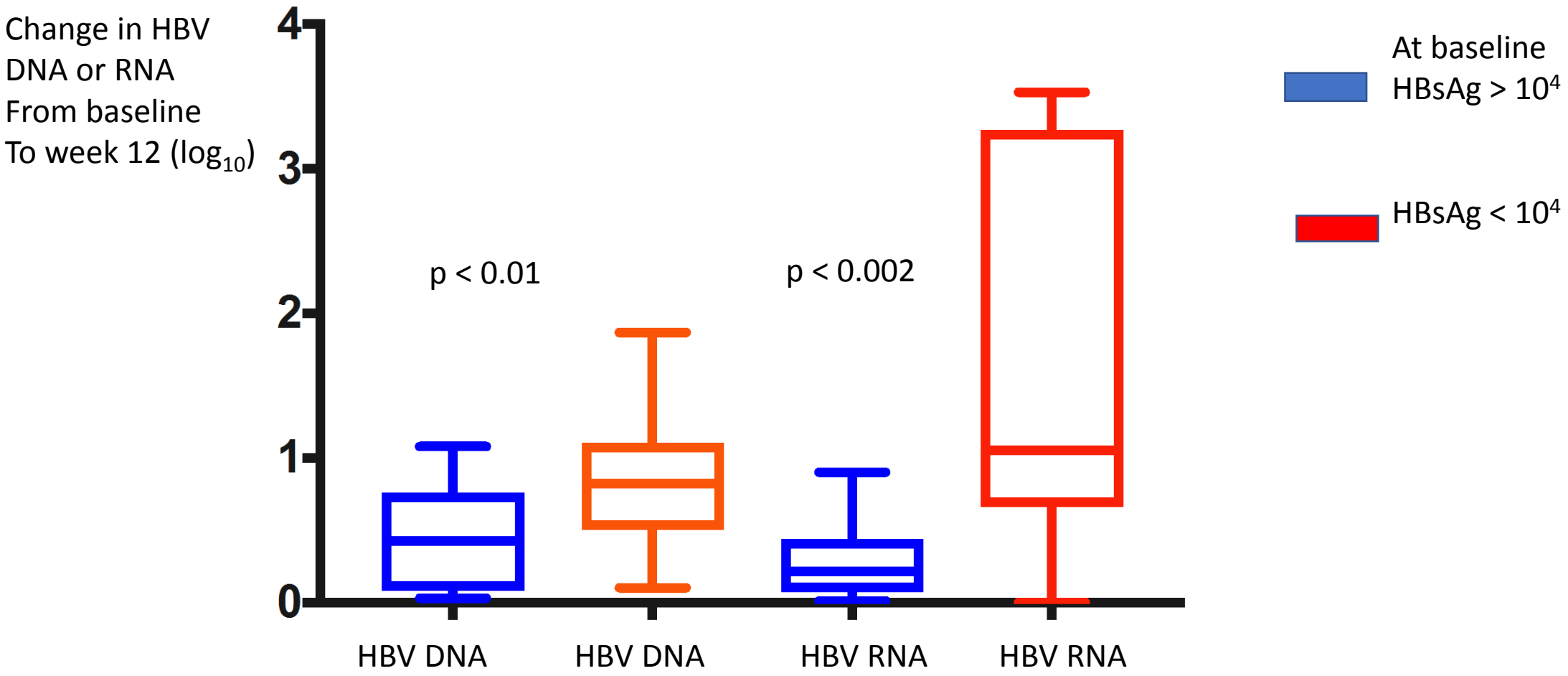
NA = Not Applicablle

*2 HBeAg NEG HBV RNA not detected at baseline

Baseline HBV DNA < 10^6 is a strong predictor of response to low dose Inarigivir



Baseline HBsAg $< 10^4$ is a strong predictor of response to low dose Inarigivir



Anti-viral efficacy cohort 1 and 2: Week 12 to 24 on TDF 300mg

MEAN	Placebo (n=8)	Inarigivir 25mg HBeAg +ve (n=9)	Inarigivir 25mg HBeAg –ve (n=7)	Inarigivir 50mg HBeAg +ve (n=10)	Inarigivir 50mg HBeAg –ve (n=4)
Week 12 HBV DNA log_{10}	6.69	7.49	4.828	7.24	3.5
Change in DNA (week 12 o week 24) log_{10}	-4.14	-4.11	-4.198	-3.84	-3.1
Week 12 HBV RNA log_{10}	5.233	6.04	2.27	6.126	All LLOQ
Change in HBV RNA (week 12 - 24) log_{10}	-1.36	-0.55 # (1 < LLOQ)	-0.92 (5 < LLOQ)	+0.1 * (1 < LLOQ)	N/A
HBeAg + Change in HBV RNA (week 12 - 24) log_{10}	+0.245				
HBeAg- Change in HBV RNA (week 12 - 24) log_{10}	-2.96				

- 8 of 9 increased mean +0.6 log_{10}
- # Excluding responder + 0.1 log_{10} increase

SB9200 Combined 25mg and 50mg Monotherapy
Change from baseline to week 24 after switch to TDF 300mg

Virology Decline	HBeAg NEG (n = 11)	HBeAg POS (n = 19)	PL (n = 8)
HBV DNA Undetctable	9	1	1
qHBsAg > 0.5log	4	5	1
HBV RNA < LLOQ	9	2	3*
HBV RNA >1log	0	1	0

* All HBeAg NEG patients

SAFETY

- No SAE’s
- No AE’s clinical or laboratory grade 3 or greater except ALT
- All clinical AE’s mild to moderate
  - > 10%: URTIs, fatigue, headache, GI symptoms
- 5 ALT flares > 200 IU/ml
  - 2 on placebo; 3 on active drug
  - 1 active on Inarigivir 50mg ALT > 400 IU/ml, discontinued at week 4 and switched to TDF
- 3 dose reductions for ALT flare as per protocol

Most Common Adverse Events in Cohort 1 and 2 Day 1-Wk 12

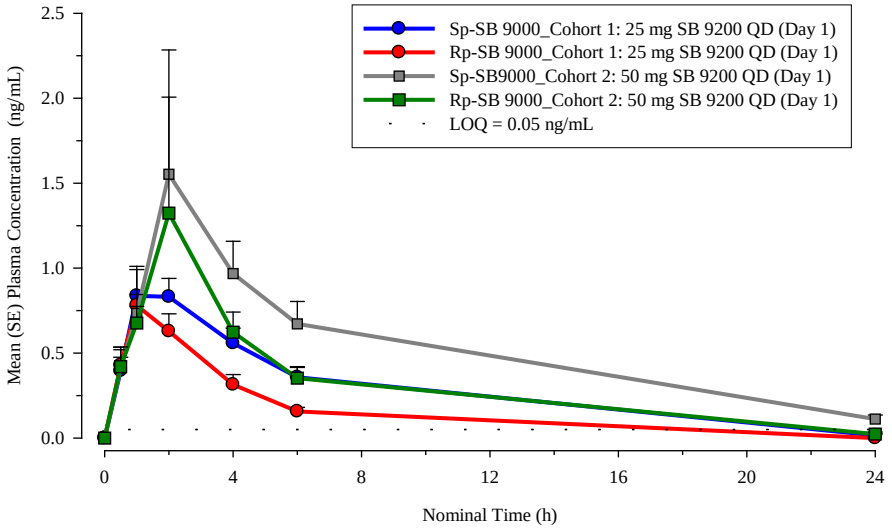
Event	Active (n = 32)	Placebo (n = 8)
URTI	9	1
Fatigue	6	0
ALT elevation	3	2
AST elevation	3	2
Headache	5	0
Appetite Change	2	0

No lab abnormalities > Grade 3 except ALT
Mild increase Uric acid and triglycerides on Inarigivir

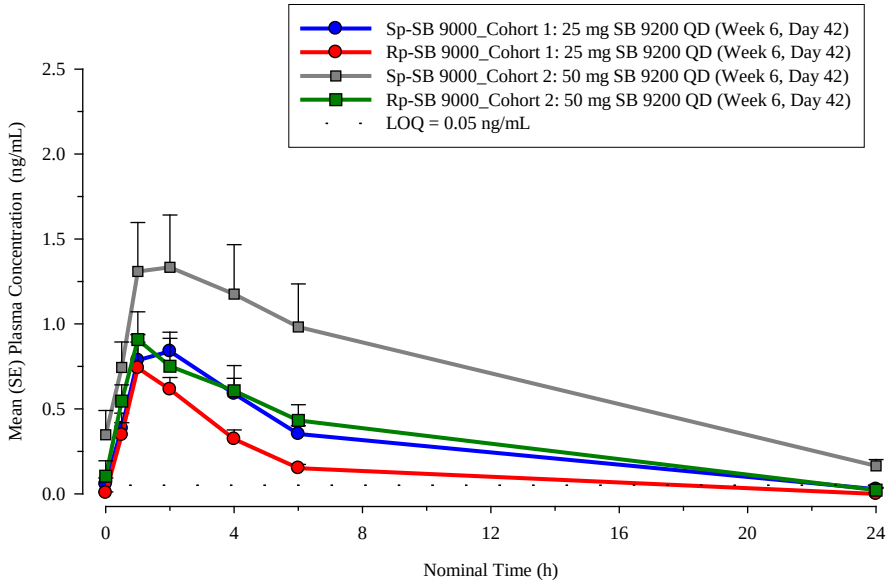
In patients with ALT flares no change in bilirubin, INR or albumin

Mean (+SE) Plasma Concentrations of Sp-SB 9000 and Rp-SB 9000 vs. Time Following Oral Administration of 25 and 50 mg SB 9200 – Day 1 vs. Day 42 - Linear Scales

Day 1



Day 42

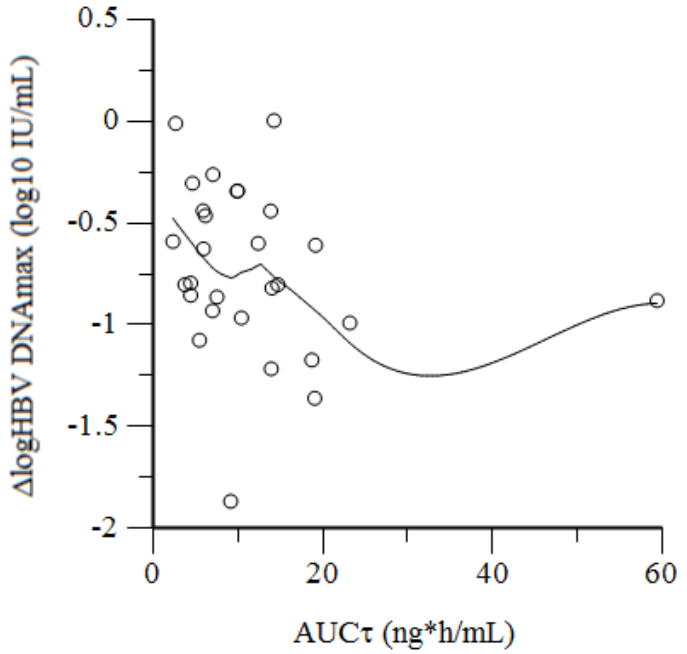


No accumulation was observed following multiple once daily dosing of 25 mg SB 9200.

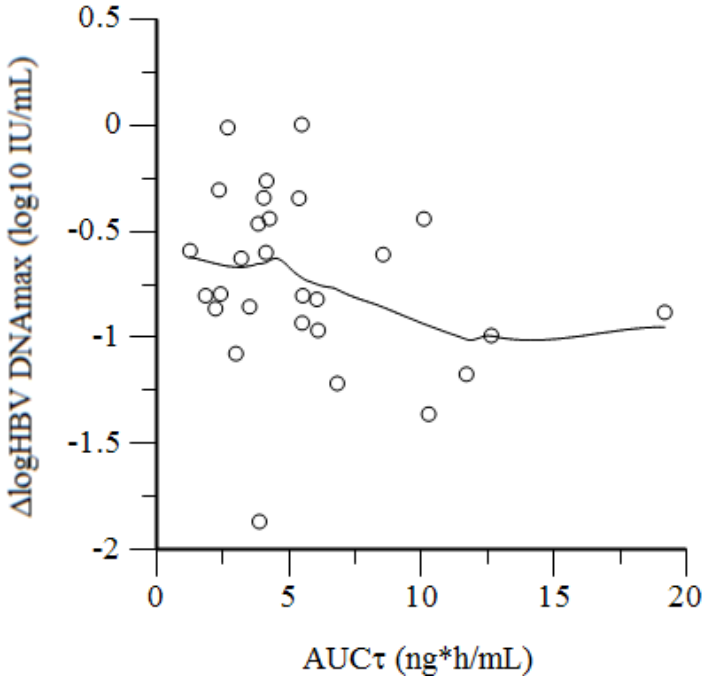
Minimal accumulation was observed following multiple once daily dosing of 50 mg SB 9200.

Maximum Suppression of HBV DNA (Δlog HBV DNA_{max}) vs. Plasma SB 9200 Metabolites Steady-State Exposure (Week 6)

Sp-SB 9000



Rp-SB 9000



White circles= observed; trend line= LOESS

Placebo (AUC=0) not included.

The maximum decrease from baseline in HBV DNA demonstrates a strong trend with increasing metabolite exposure.

Summary

Excellent tolerability and safety at 25mg and 50mg daily

High anti-viral efficacy with reduction of > $1\log_{10}$ HBV DNA and > $3\log_{10}$ HBV RNA in HbeAg negative patients and HBeAg positive patients with low viral burden

HBsAg reduction of > 0.5log in 9 patients (30%) at either week 12 or week 24 in (5 HBeAg +ve and 4 HBeAg –ve patients).

Anti-viral response correlates to PK at low dose inarigivir

Further confirmation of a dual mechanism of action of inarigivir as a direct acting anti-viral and an immune-modulator via activation of RIG-I