Phase IIa Achieve Clinical Trial of SB 9200: Results from the Tenofovir switch segment of the 25mg cohort.

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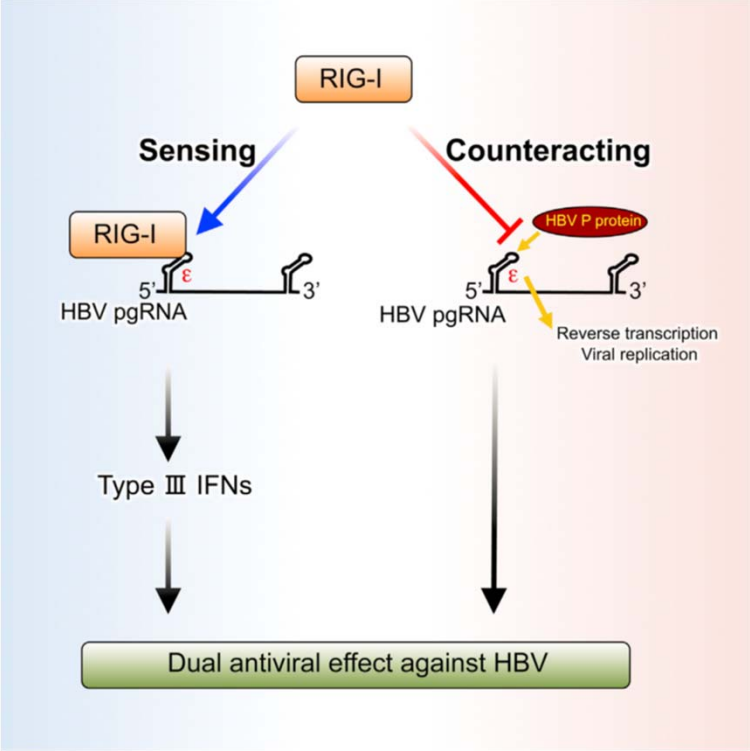
N.H Afdhal.

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
- RIG-I counteracts the interaction of HBV polymerase with pgRNA to suppress viral replication
- Type III IFNs are predominantly induced in human hepatocytes during HBV infection

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

SB 9200

Small molecule nucleic acid hybrid (SMNH)

Orally bioavailable prodrug; active metabolite SB 9000

Actively transported into hepatocytes via OATP1

30:1 liver to plasma ratio

Not metabolized, not phosphorylated

Biliary excretion of intact molecule

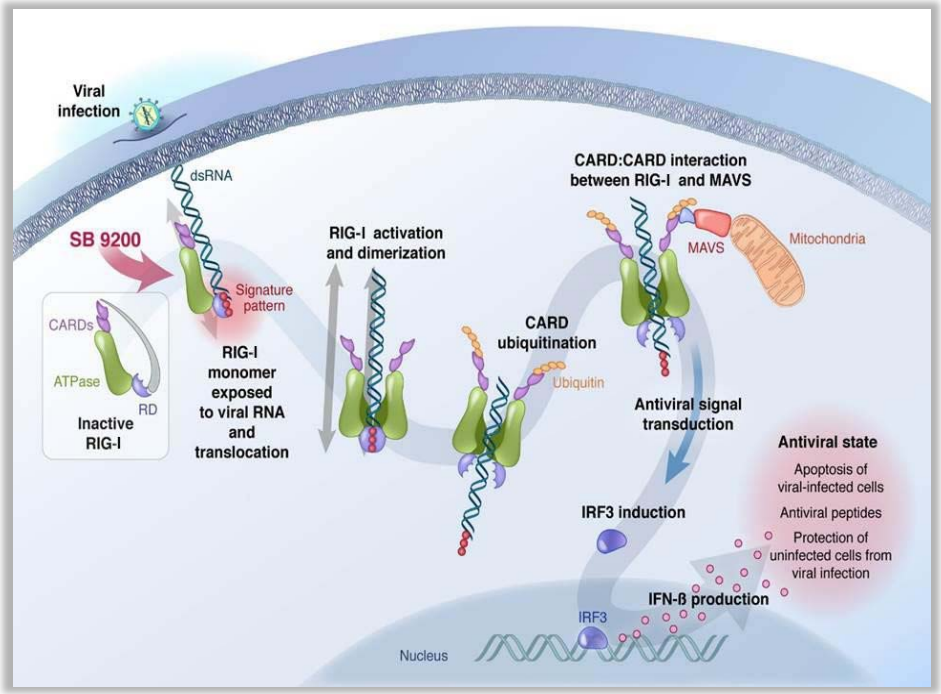
No direct activity against DNA polymerase

SB 9200 Designed to Stimulate Interferon Production and Induce Immune Response via Activation of RIGI and NOD2

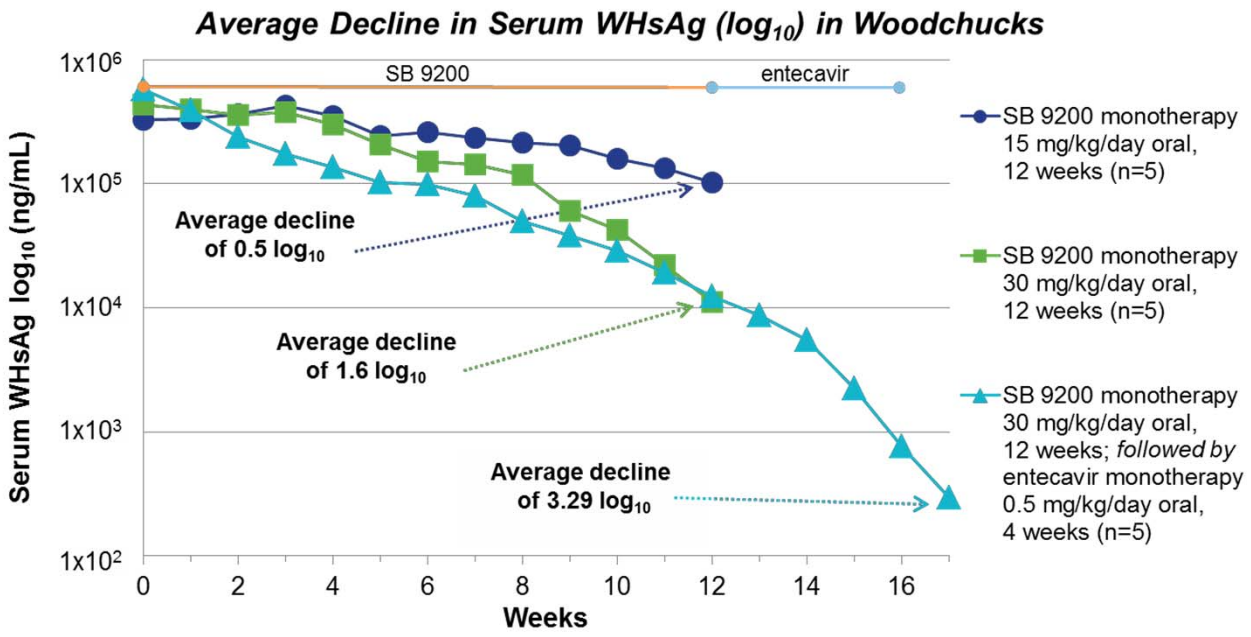
Restores interferon signaling pathway commonly shut down in virally infected cells

Key Characteristics

- Binds, activates and increases sensitivity of sensory proteins RIG-I and NOD2 to viral infection
- Potential to induce both innate and adaptive immune response
- Unique selectivity – designed to be active in virally infected cells
- Can be used in combination with other antiviral agents



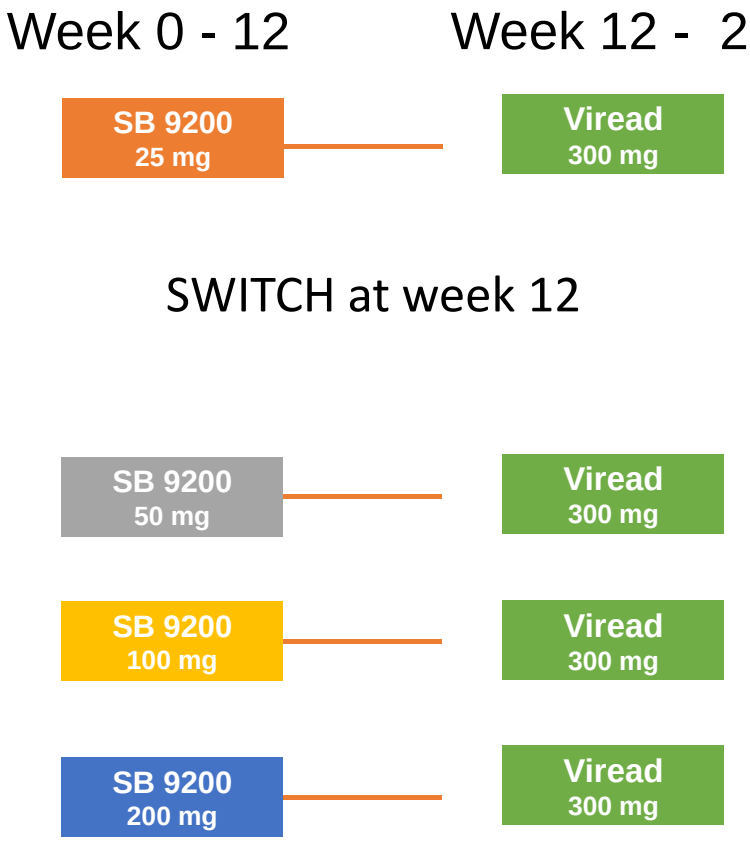
Additive / Synergistic effect of entecavir post SB 9200 Leads to Significant Decline in Serum WHsAg Levels in Chronically WHV-Infected Woodchucks



- **Four of five** woodchucks in the sequential dosing study of SB 9200 and entecavir demonstrated serum WHsAg levels near the[(2)] lower limit of quantification
- Entecavir alone for 4 weeks – mean 0.5log10 reduction in WHSAg

Menne PLOS1; 2016

ACHIEVE STUDY DESIGN – Part A Cohort 1, SB 9200 25mg



- Randomized, placebo-controlled, 4 active: 1 placebo
- SB 9200 administered once daily for 12 weeks, switch to tenofovir 300mg daily at week 12
- Endpoints:
  - Primary
    - safety
    - antiviral efficacy (change in HBV DNA at week 12)

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

Patients

M 12: F 8
Asian 18: Cauc 2
Mean age 40.5 years

1 placebo patient HBeAg positive;
3 HBeAg negative

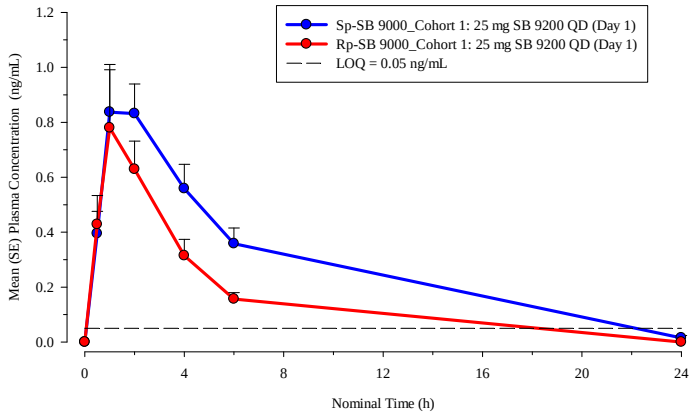
		HBeAg- (N=7)	HBeAg+(N=9)	Placebo (N=4)
ALT		75	82	82
AST		45	45	46
Bilirubin (umol)		8.6	10	8
Genotype (n)		A:1; B:3; C:1 ; D:2	 B:4 C:5	A:1 B:2 C:1
HBVDNA IU/ml		5.69	7.86	6.00
HBsAg IU/ml		3.17	4.46	3.70

SAFETY

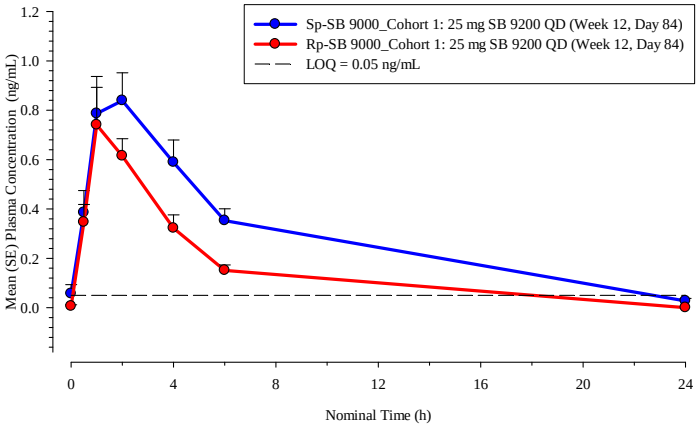
- No SAE's
- No AE's clinical or laboratory grade 3 or greater
- All clinical AE's mild to moderate
- 3 ALT flares > 200 IU/ml
  - 2 on placebo; 1 on active drug, none > 400 IU/ml
- 3 dose reductions for ALT flare as per protocol

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

Day 1



Day 42

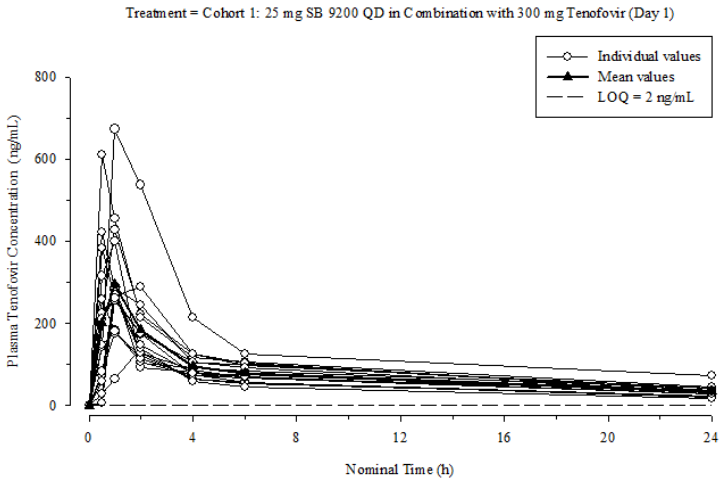


No accumulation was observed following multiple once daily dosing of 25 mg SB 9200.

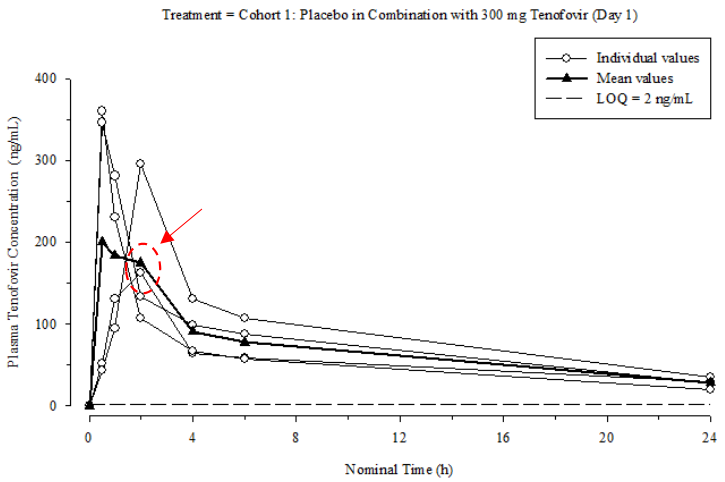
Half life of metabolite 4 hours

Mean (+SE) Plasma Concentrations of Tenofovir vs. Time Following a Single Oral Administration of 300 mg Tenofovir Alone or with SB 9200 mg at week 12 – Linear Scale

SB 9200 + TDF

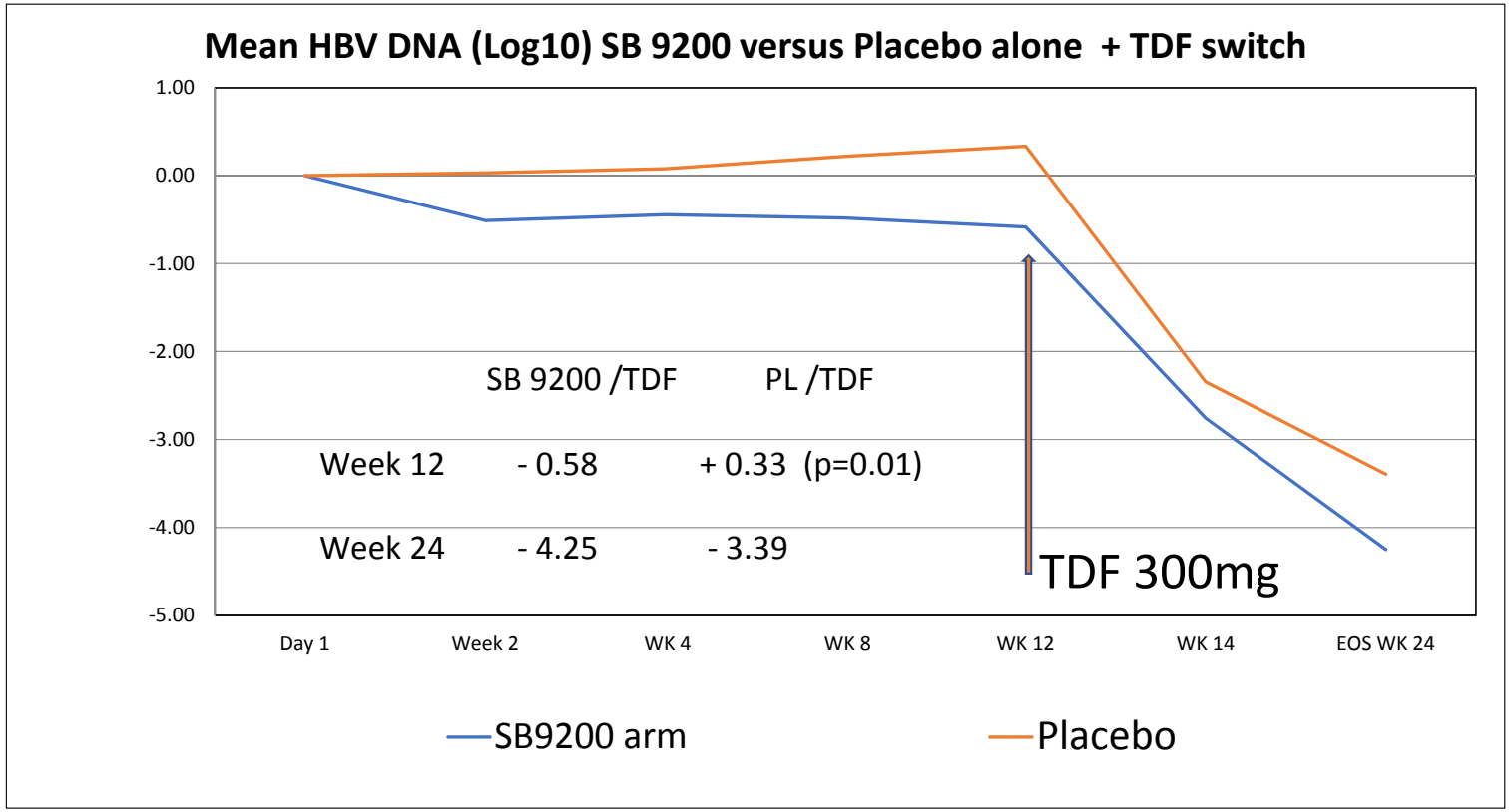


TDF alone

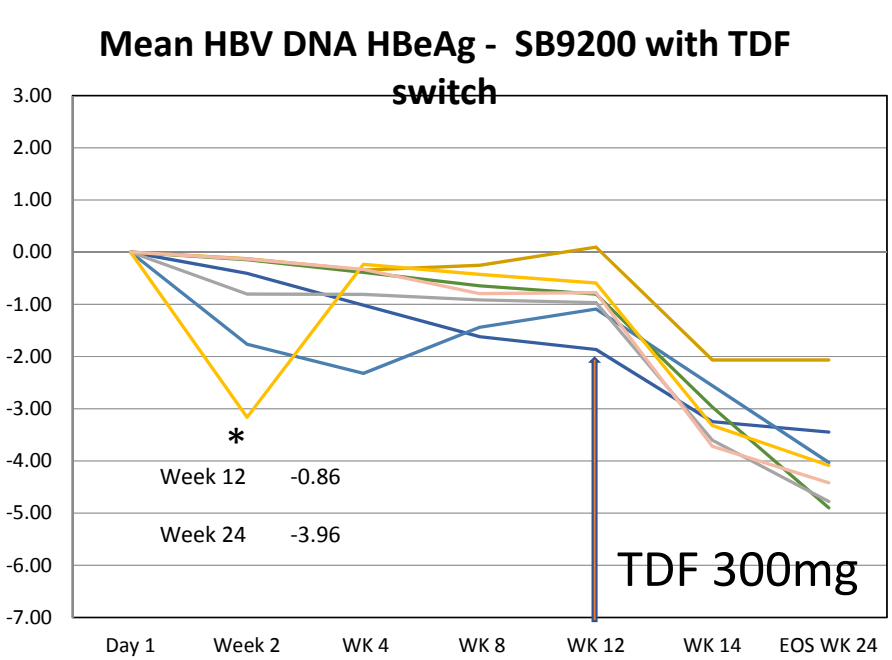


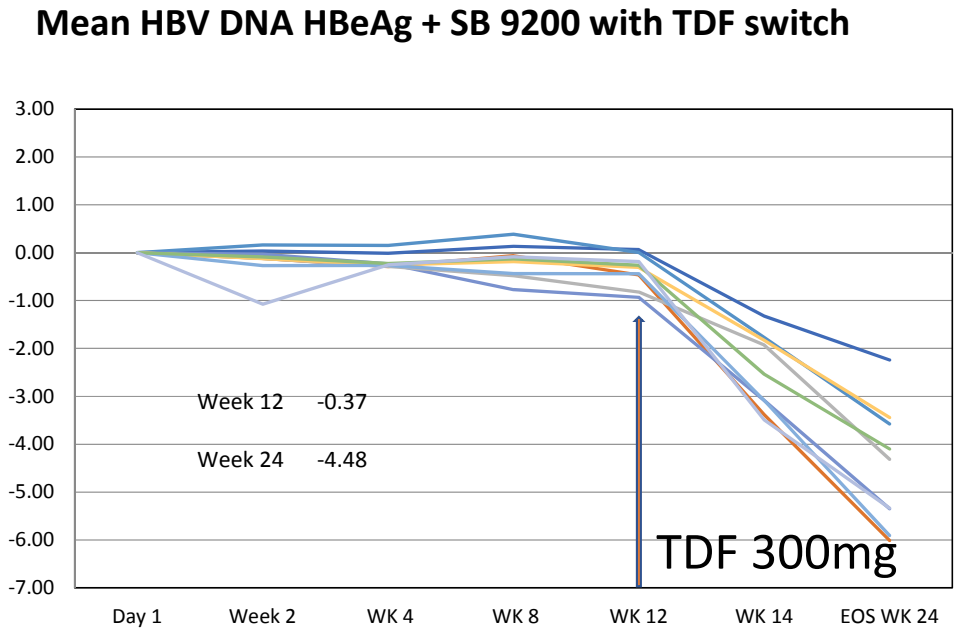
- Right panel: Mean plasma tenofovir peak plasma levels was delayed and reduced for only 1 subject when tenofovir was given alone. The different timing peak tenofovir levels for the 4 subjects resulted in a mean PK profile of tenofovir that appeared lower relative to subjects who had been taking SB 9200 for 12 weeks.

Week 12 HBV DNA reduction on SB 9200 or placebo and on switch to TDF from week 12 to 24



Week 12 HBV DNA reduction on SB 9200 and on switch to TDF from week 12 to 24



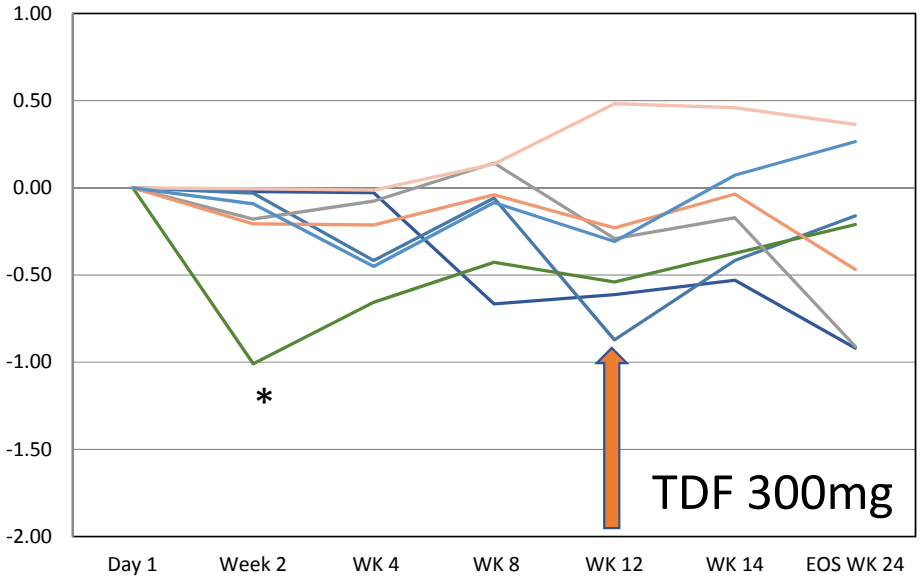


* Patient dose reduced ALT flare

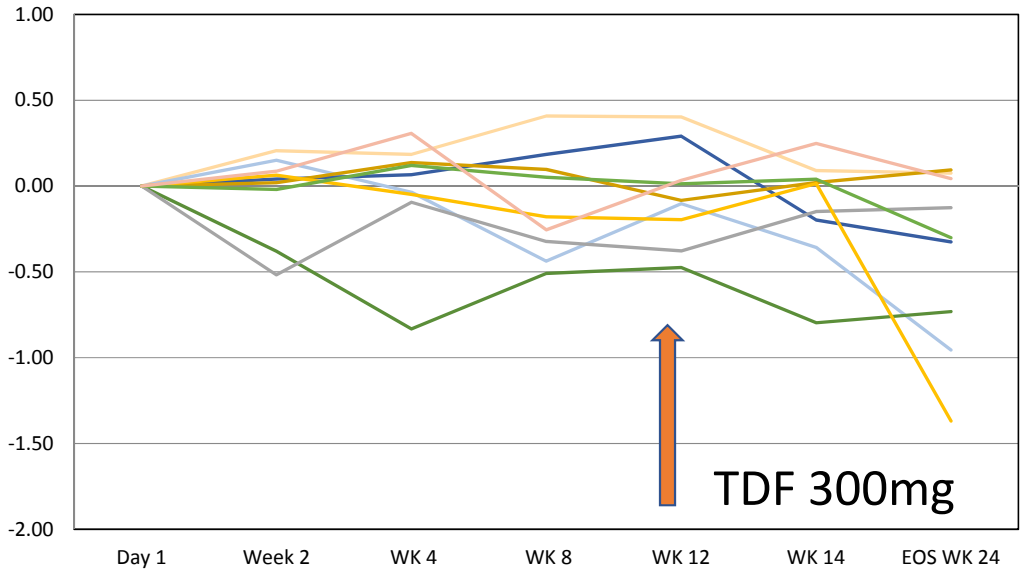
HBV DNA reduction significantly greater in HBeAg –ve patients on SB 9200 monotherapy

Week 12 HBsAg reduction on SB 9200 and on switch to TDF from week 12 to 24

Mean HBsAg in HBeAg -ve SB9200 with TDF switch



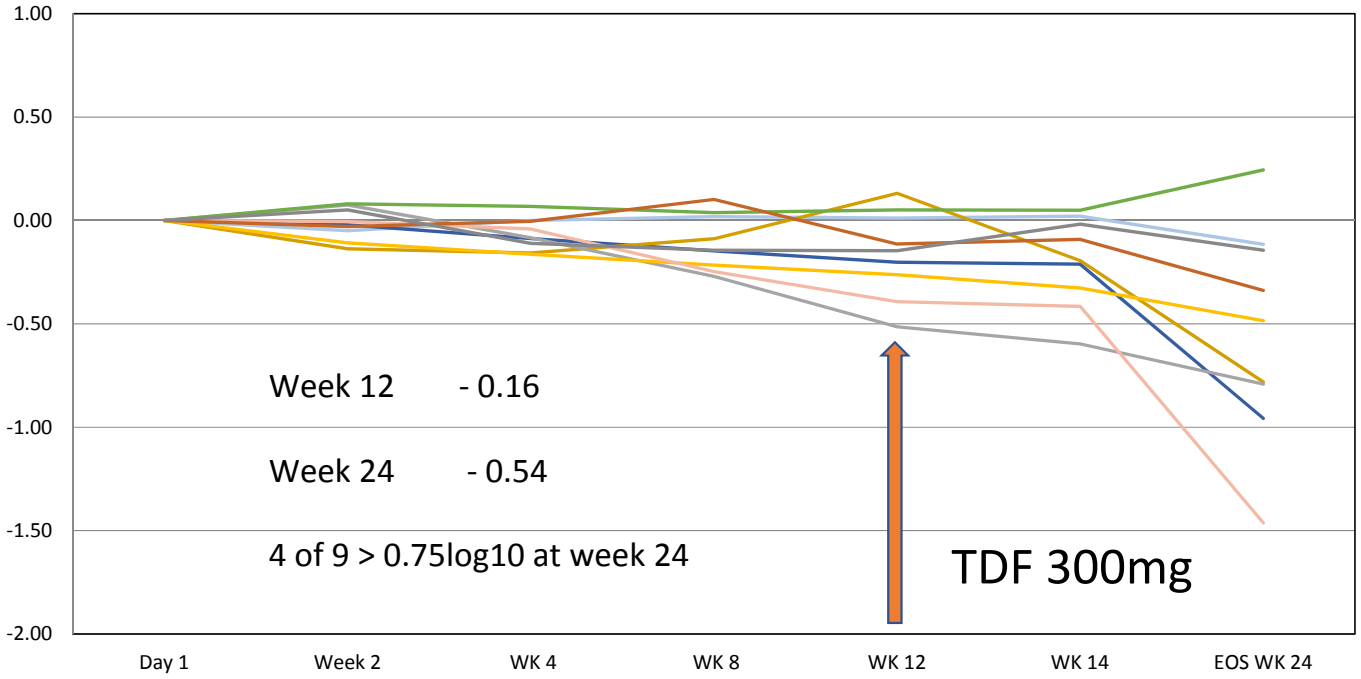
Mean HBsAg in HBeAg +ve SB 9200 with TDF switch

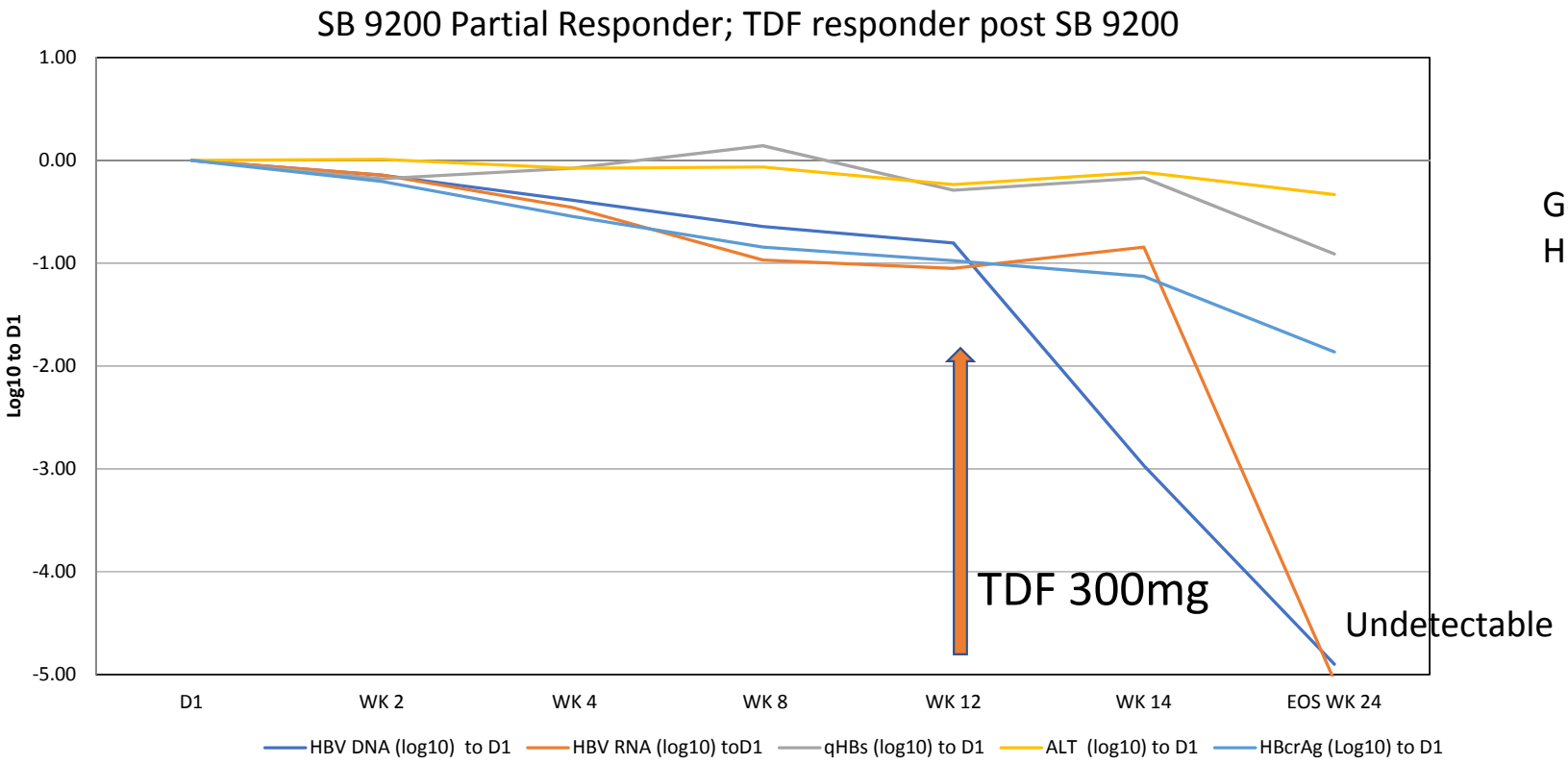


* Patient dose reduced ALT flare

3 of 16 patients > 0.5 log10 sustained reduction in HBsAg at week 12 on monotherapy – all HBeAg –ve
6 of 16 patients > 0.5 log10 sustained reduction in HBsAg at week 24 after TDF including HBeAg +ve

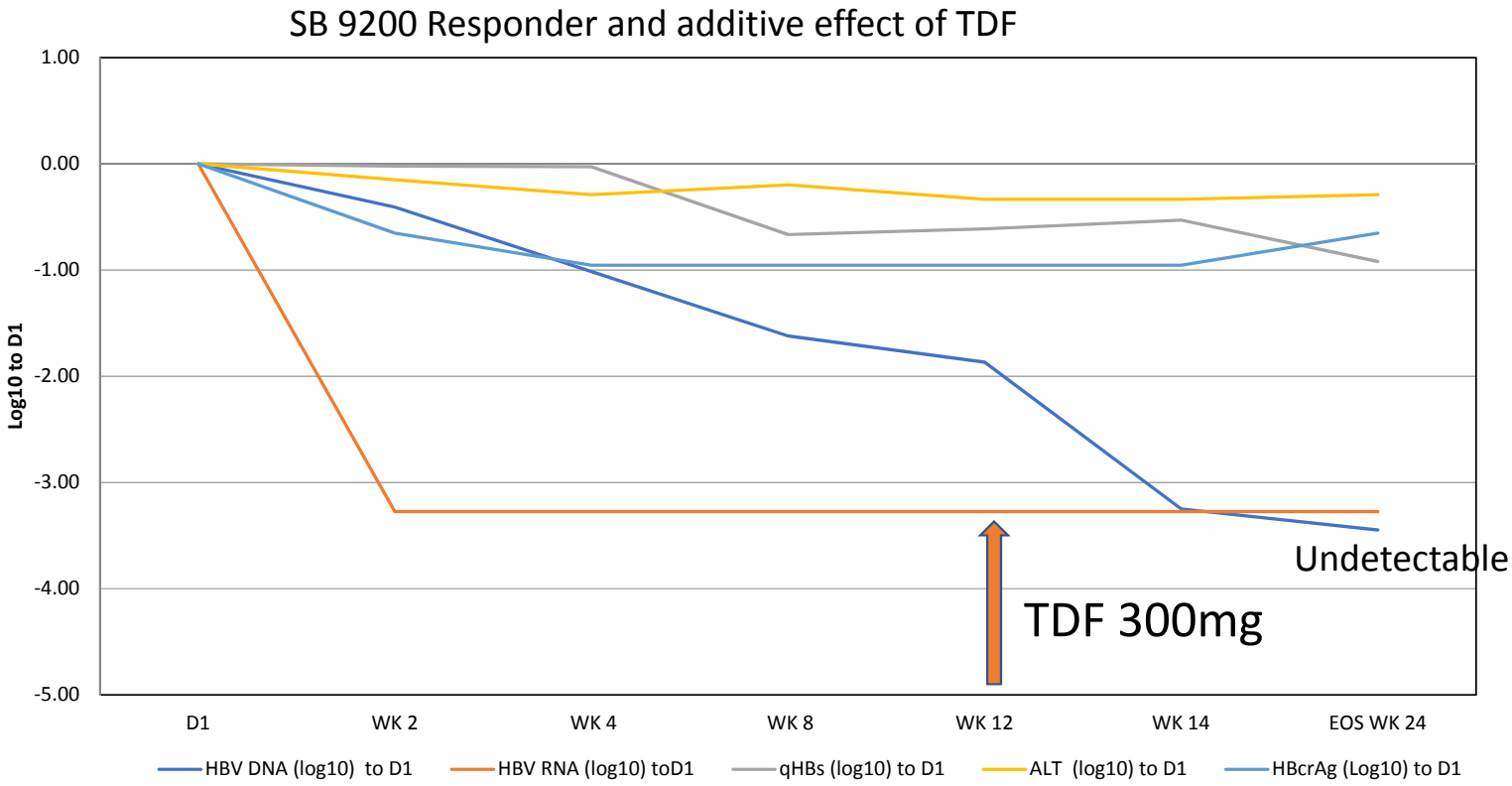
Change in HBeAg (log10) on SB 9200





Genotype B4
HBeAg - ve

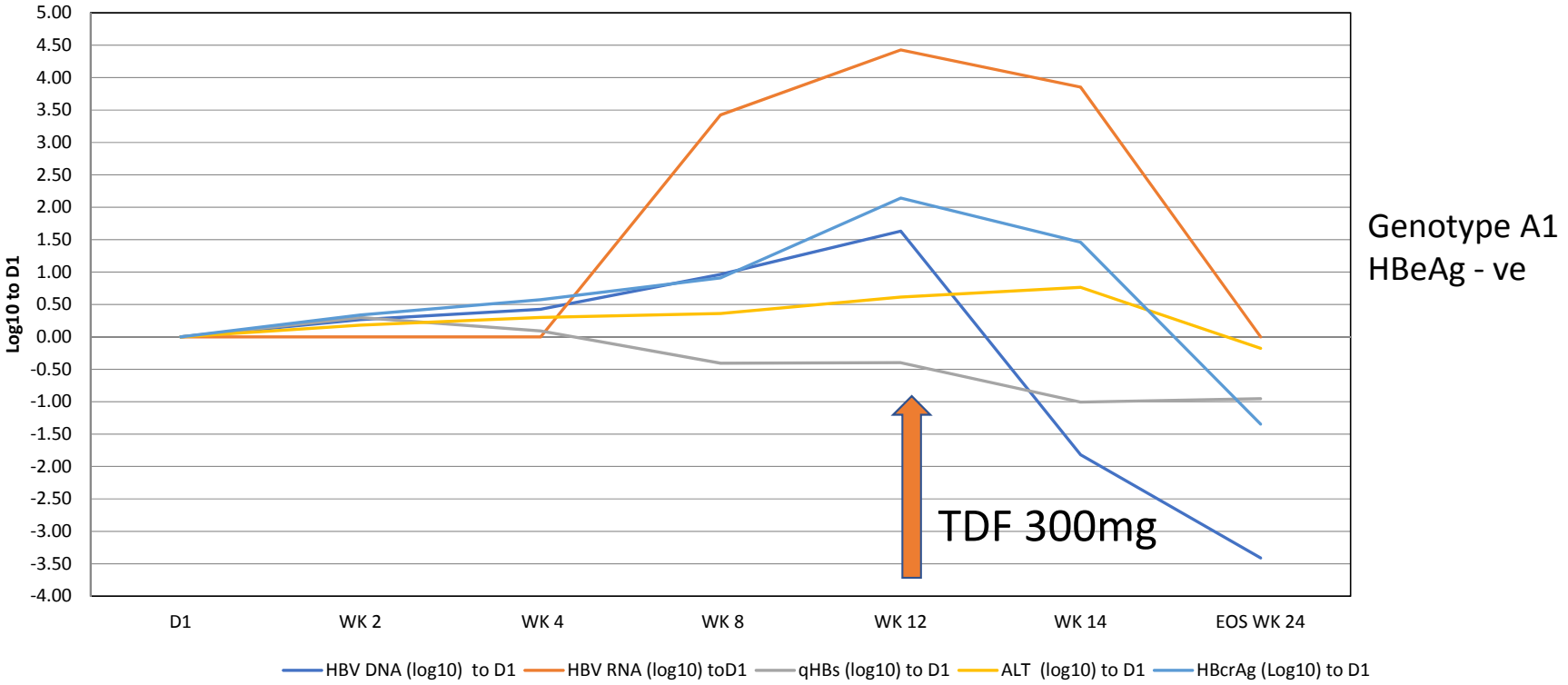
	HBV DNA (log10) to D1	HBV RNA (log10) toD1	qHBs (log10) to D1	ALT (log10) to D1	HBcrAg (Log10) to D1
D1	0.00	0.00	0.00	0.00	0.00
WK 2	-0.14	-0.14	-0.18	0.01	-0.20
WK 4	-0.39	-0.46	-0.08	-0.08	-0.55
WK 8	-0.64	-0.97	0.14	-0.07	-0.84
WK 12	-0.80	-1.05	-0.29	-0.24	-0.98
WK 14	-2.97	-0.84	-0.17	-0.11	-1.13
EOS WK 24	-4.90	-5.06	-0.91	-0.33	-1.86



Genotype D1
HBeAg - ve

	HBV DNA (log10) to D1	HBV RNA (log10) toD1	qHBs (log10) to D1	ALT (log10) to D1	HBcrAg (Log10) to D1
D1	0.00	0.00	0.00	0.00	0.00
WK 2	-0.41	-3.27	-0.02	-0.15	-0.65
WK 4	-1.01	-3.27	-0.03	-0.29	-0.95
WK 8	-1.62	-3.27	-0.67	-0.20	-0.95
WK 12	-1.87	-3.27	-0.61	-0.33	-0.95
WK 14	-3.25	-3.27	-0.53	-0.33	-0.95
EOS WK 24	-3.45	-3.27	-0.92	-0.29	-0.65

Placebo Patient with ALT and HBV DNA flare: HBeAg – to HBeAg + Reversion week 4



Genotype A1
HBeAg - ve

	HBV DNA (log10) to D1	HBV RNA (log10) toD1	qHBs (log10) to D1	ALT (log10) to D1	HBcrAg (Log10) to D1
D1	0.00	0.00	0.00	0.00	0.00
WK 2	0.27	0.00	0.30	0.18	0.34
WK 4	0.43	0.00	0.09	0.30	0.57
WK 8	0.96	3.42	-0.41	0.36	0.91
WK 12	1.63	4.43	-0.40	0.61	2.14
WK 14	-1.82	3.85	-1.01	0.76	1.46
EOS WK 24	-3.41	0.00	-0.95	-0.18	-1.35

Baseline HBeAg –ve
Week 4, HBV RNA increase 3 log; HBV DNA 1 log
ALT flare, HBeAg +ve
Week 12 TDF
Week 24 HBeAg –ve

Summary

- No safety issues seen at 25mg dose
- PK supports once daily administration and no DDI
- SB 9200 25mg low dose monotherapy demonstrates anti-viral efficacy on HBV DNA, HBsAg and HBV RNA at 12 weeks more prominent in HBeAg –ve patients
- Switch to TDF 300mg from week 12 to week 24 suggestive of enhancement of anti-viral effect in HBeAg +ve patients including reduction in HBV DNA, HBsAg, HBeAg and HBV RNA

MF Yuen et al, AASLD 2017, Sunday October 22nd
Locarnini et al AASLD 2017, Late breaker submitted

Conclusion

- 2nd cohort SB 9200 50mg will be completed October 2017
- Data support combination of SB 9200 plus oral nucleotide
  - SB 9200 50mg + TAF 25mg cohort in end 2017 (Gilead Sciences + Spring Bank)
  - SB 9200 100mg + TDF 300mg in mid 2018 (Spring Bank + Gilead Sciences)