SB 9200 (Inarigivir), an oral selective immunomodulator is safe and efficacious in treatment-naïve, non-cirrhotic HBV patients: Results from cohort 1 of the ACHIEVE Trial

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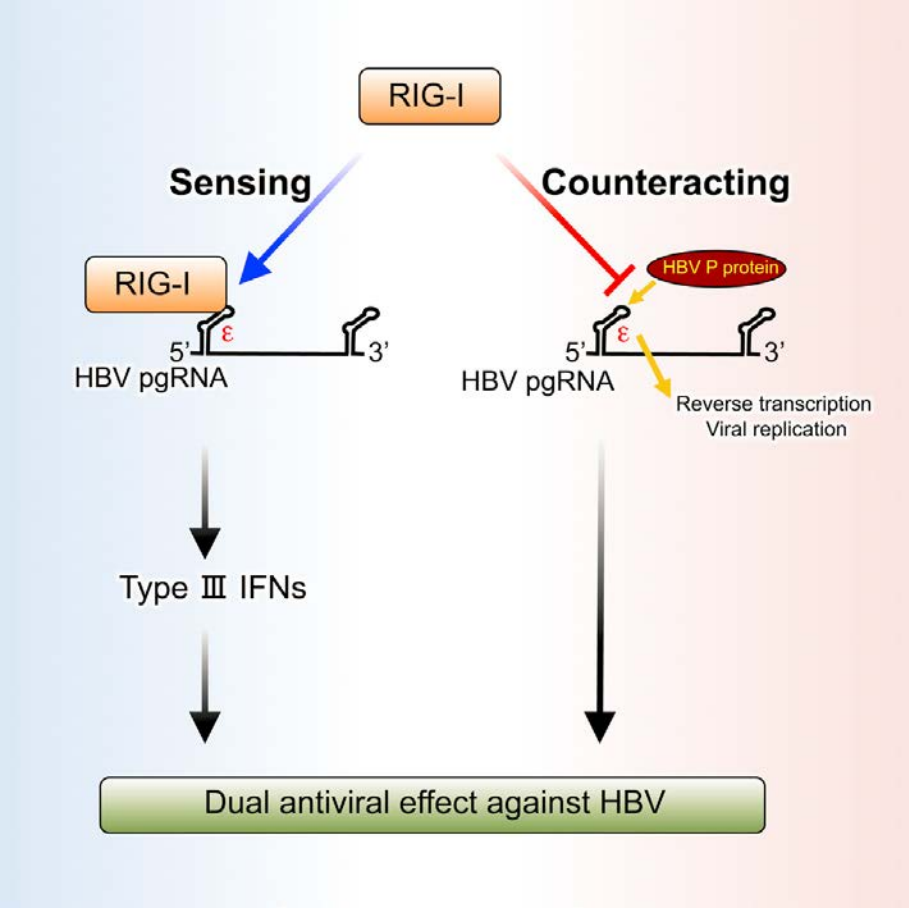
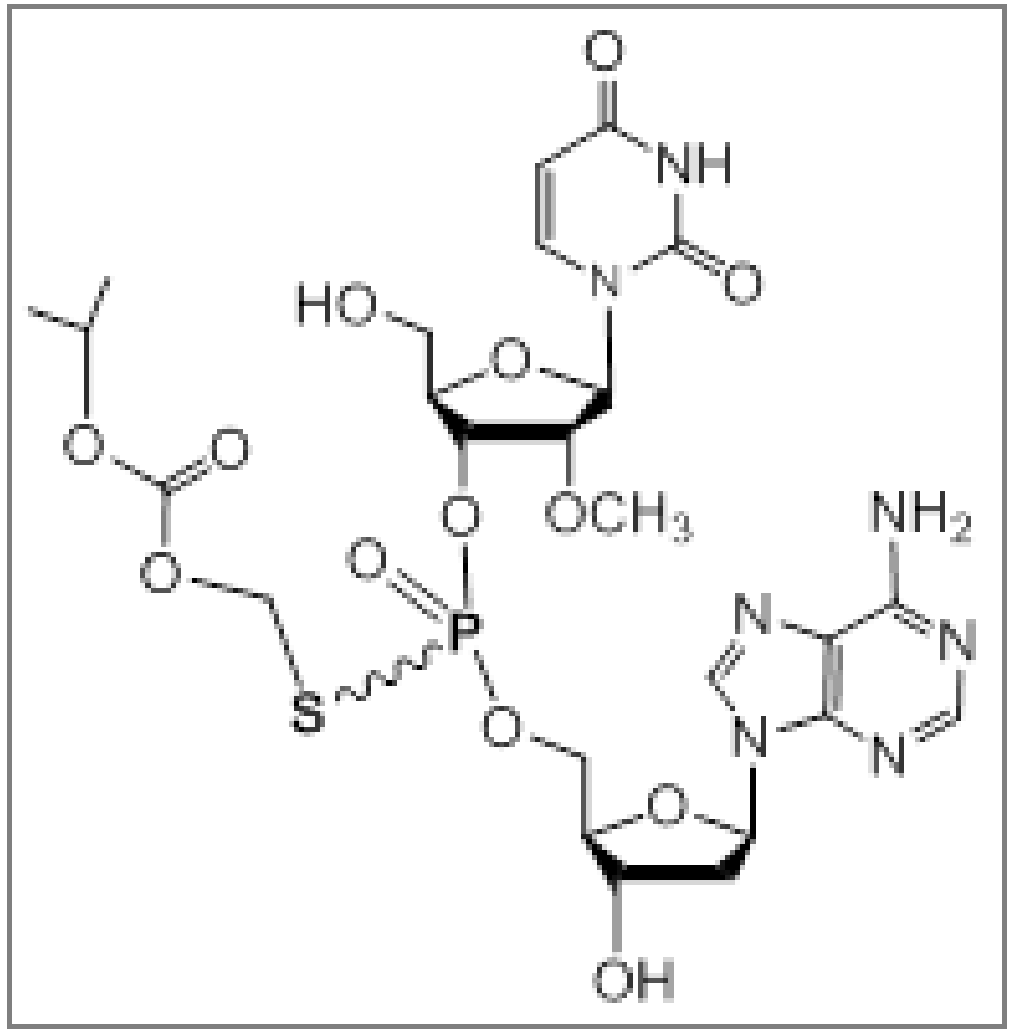
The RNA Sensor RIG-I Dually Functions as an Innate Sensor and Direct Antiviral Factor for Hepatitis B Virus



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

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

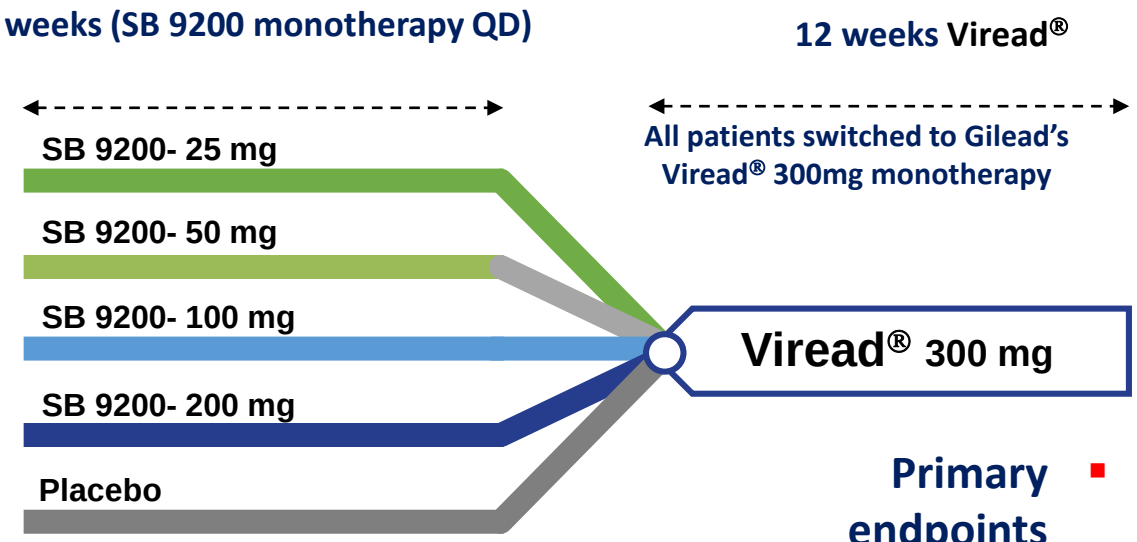
Inarigivir (SB 9200)



- 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, Cohort 1, SB 9200 25mg

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

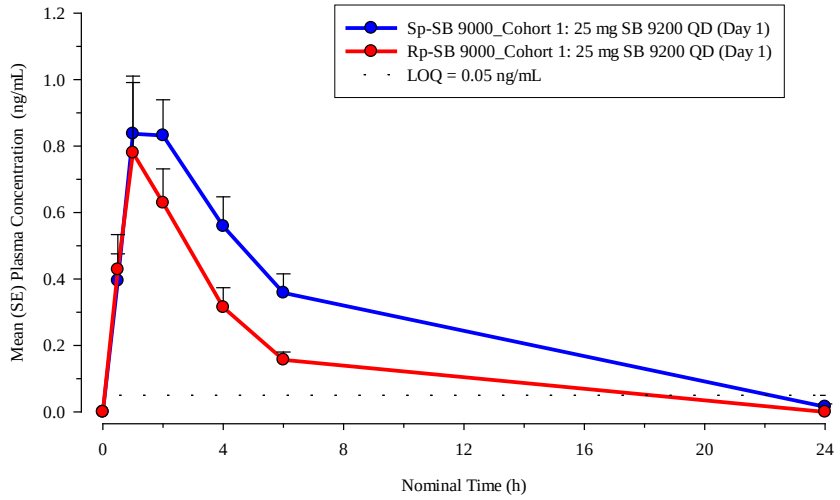
- F3 or F4 fibrosis
- Evidence of HCC by imaging
- Co-infection with HCV, HIV or HDV
- Creatinine > 1.2mg/dL

Patients

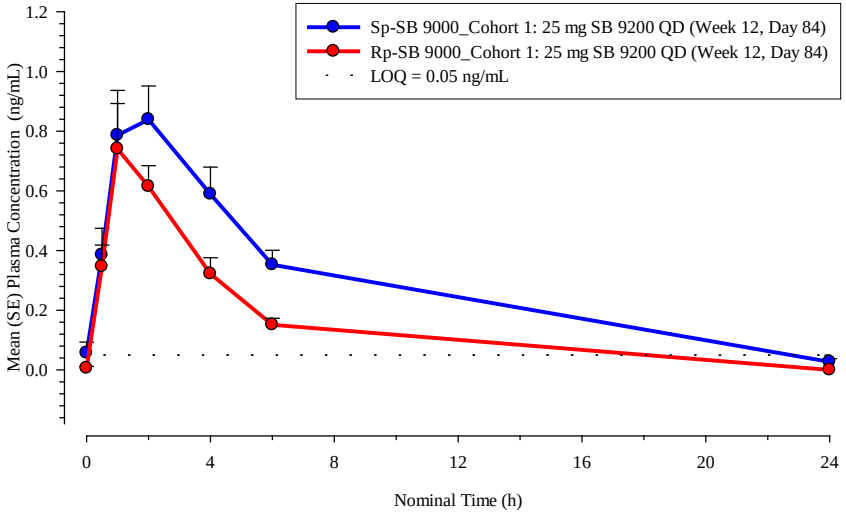
		HBeAg- (N=7)	HBeAg+(N=9)	Placebo (N=4)
HgB (g/L)		134	146	156
ALT		75	82	82
AST		45	45	46
Bilirubin (umol)		8.6	10	8
Genotype (n)		A:1; B:3; C:1; D:2	B:4 C:5	A:1 B:2 C:1
HBVDNA IU/ml		5.69	7.86	6.00
HBsAg IU/ml		3.17	4.46	3.70

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

Day 1



Day 42

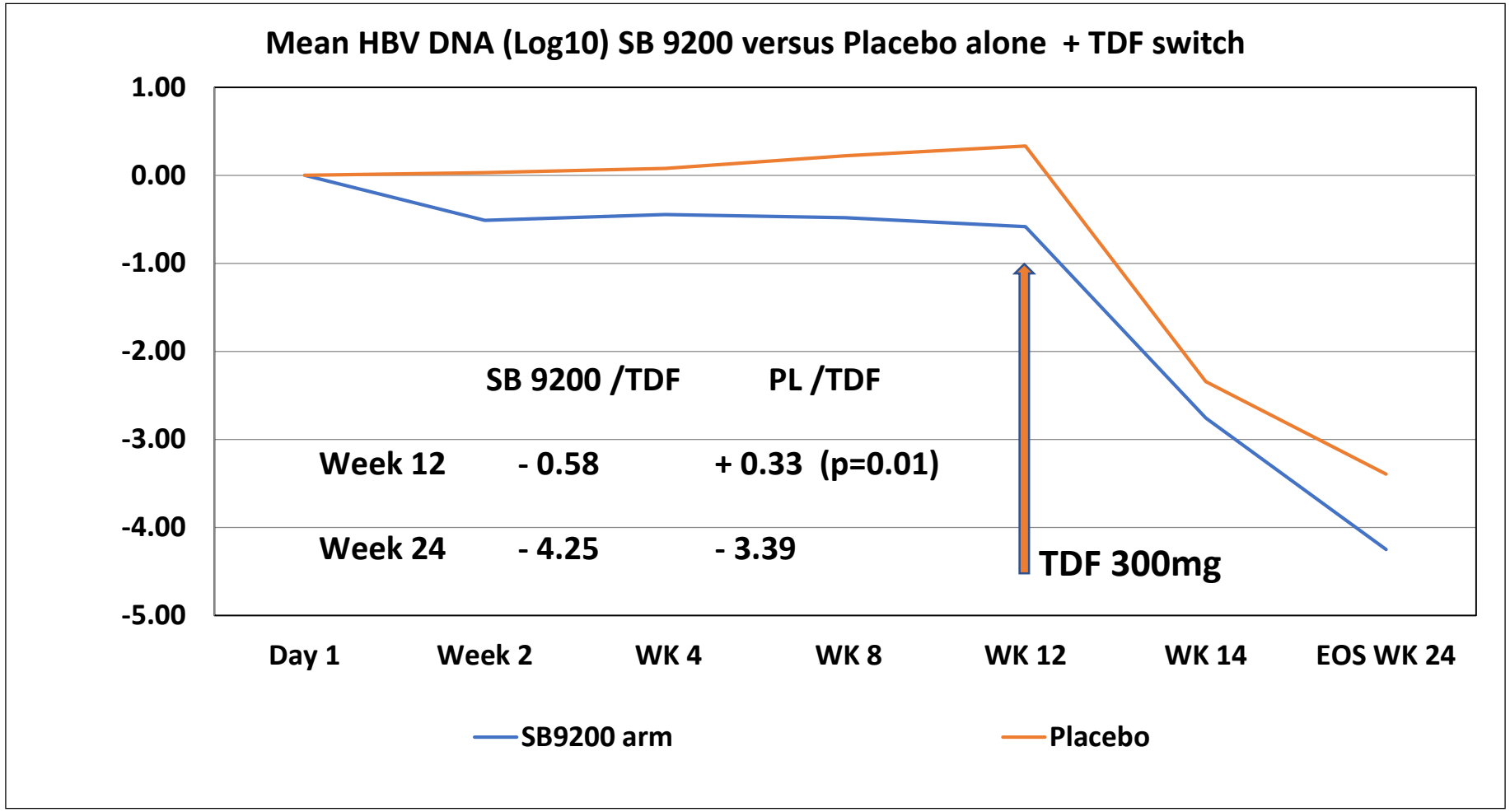


- No accumulation was observed following multiple once daily dosing of 25 mg SB 9200.
- Half life of metabolite 4 hours

SAFETY

- No SAE's
- No AE's clinical or laboratory grade 3 or greater
- All clinical AE's mild to moderate
  - > 10%: URTIs, fatigue, headache, GI symptoms
- 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

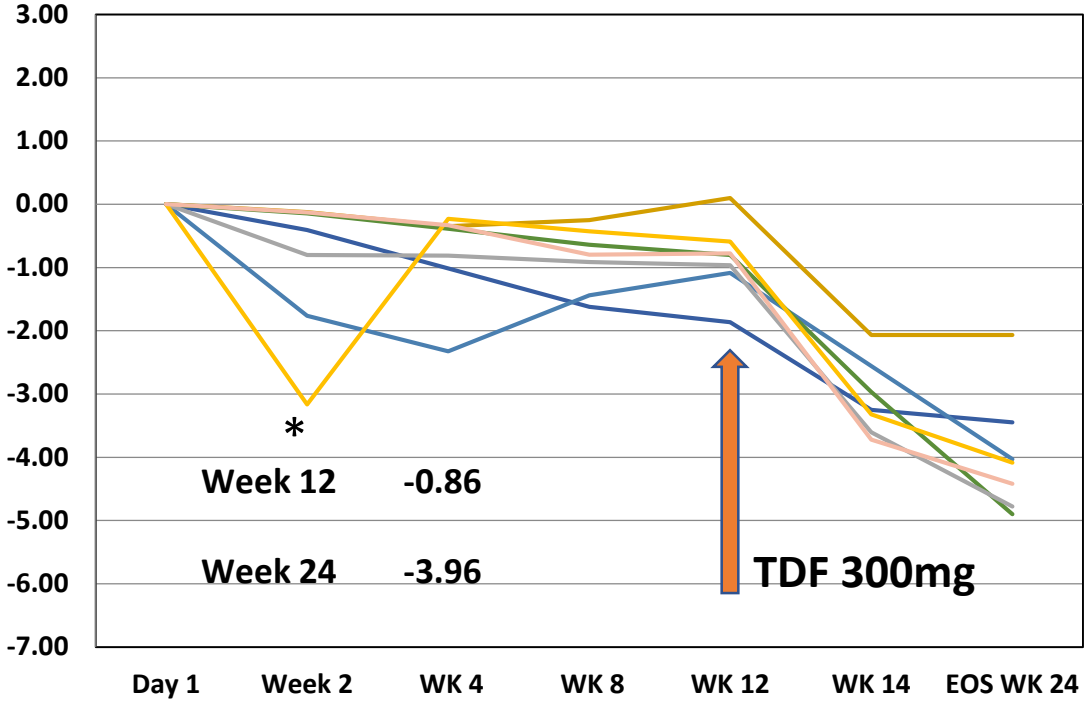
Week 12 HBV DNA reduction on SB 9200 or placebo and on switch to TDF from week 12 to 24



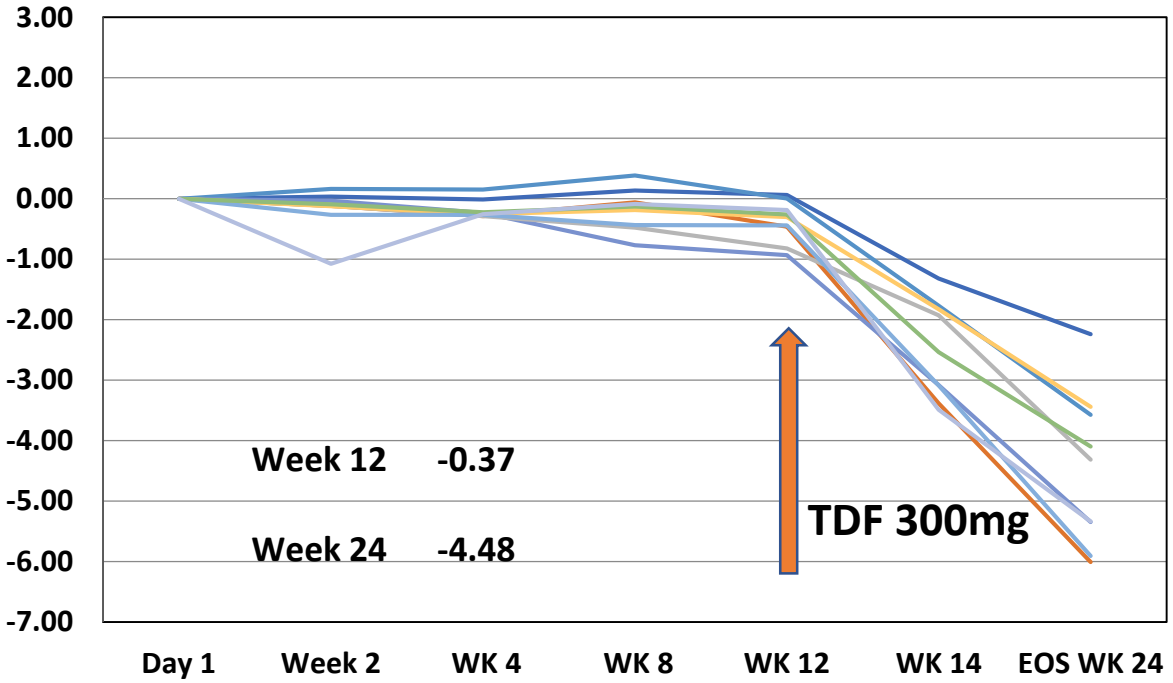
Week 12 HBV DNA reduction on SB 9200 and on switch to TDF from week 12 to 24

Individual patient data

Mean HBV DNA HBeAg - SB9200 with TDF switch



Mean HBV DNA HBeAg + SB 9200 with TDF switch



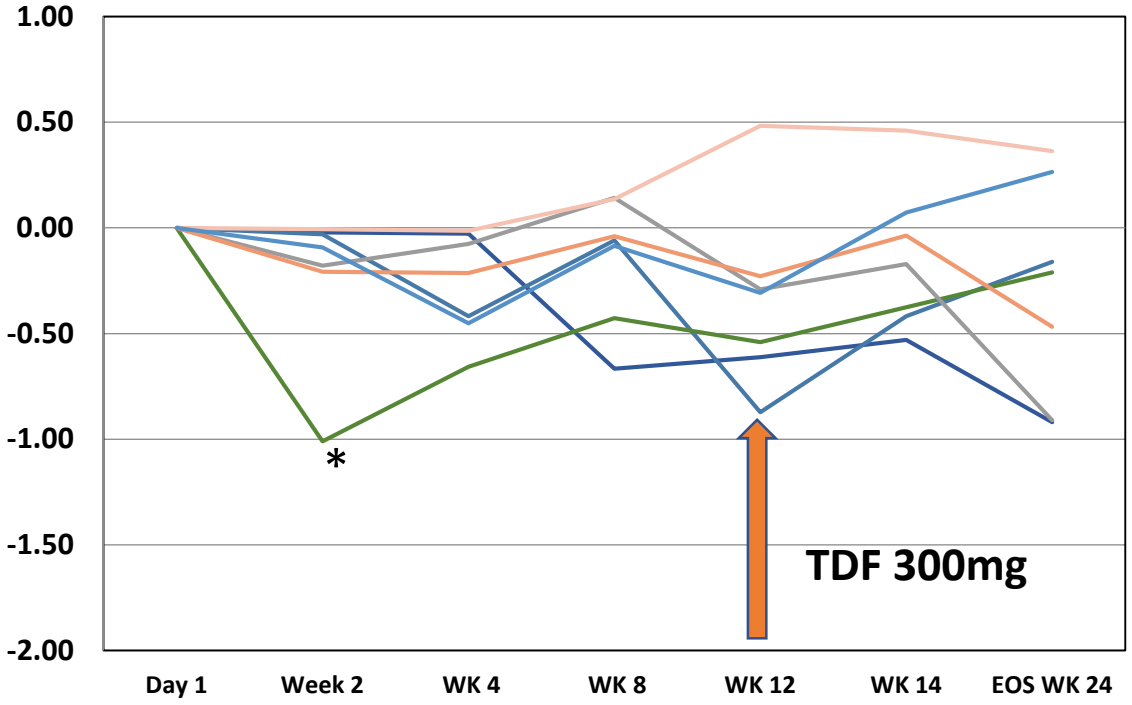
* Patient dose reduced ALT flare

- HBV DNA reduction significantly greater in HBeAg –ve patients on SB 9200 monotherapy
- ($p<0.01$ versus placebo)

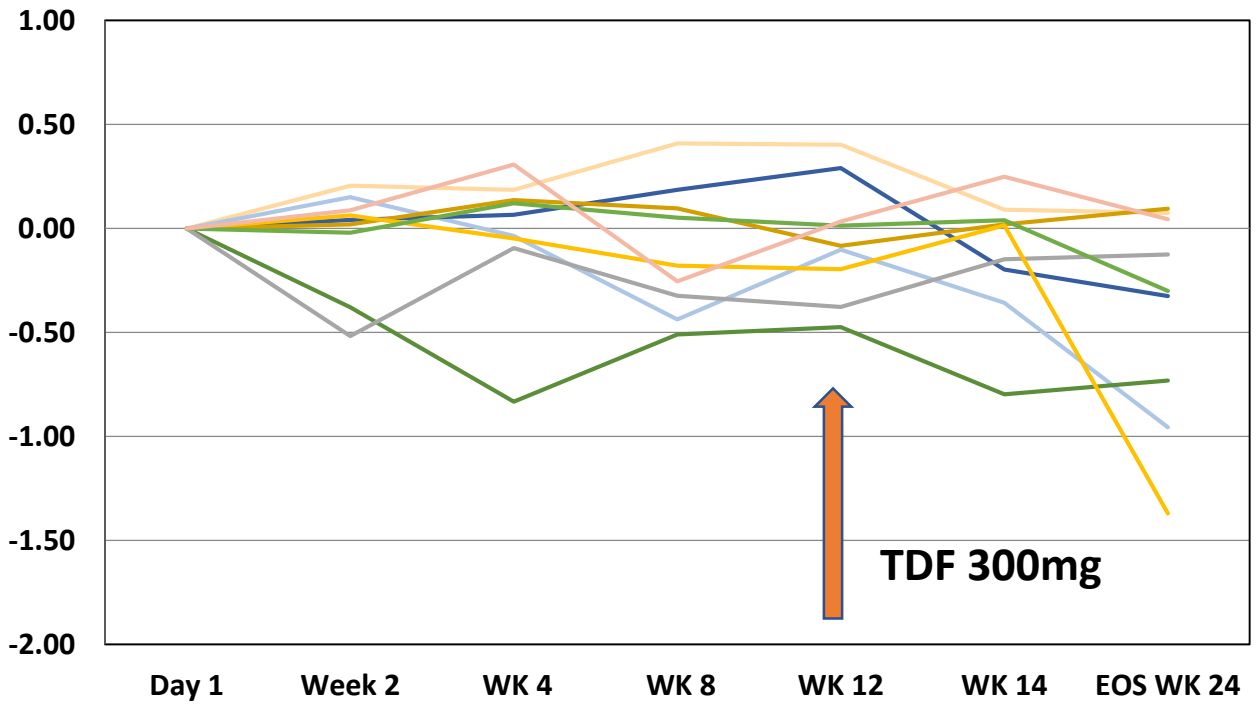
Week 12 HBsAg reduction on SB 9200 and on switch to TDF from week 12 to 24

Individual patient data

Mean HBsAg in HBeAg -ve SB9200 with TDF switch



Mean HBsAg in HBeAg +ve SB 9200 with TDF switch

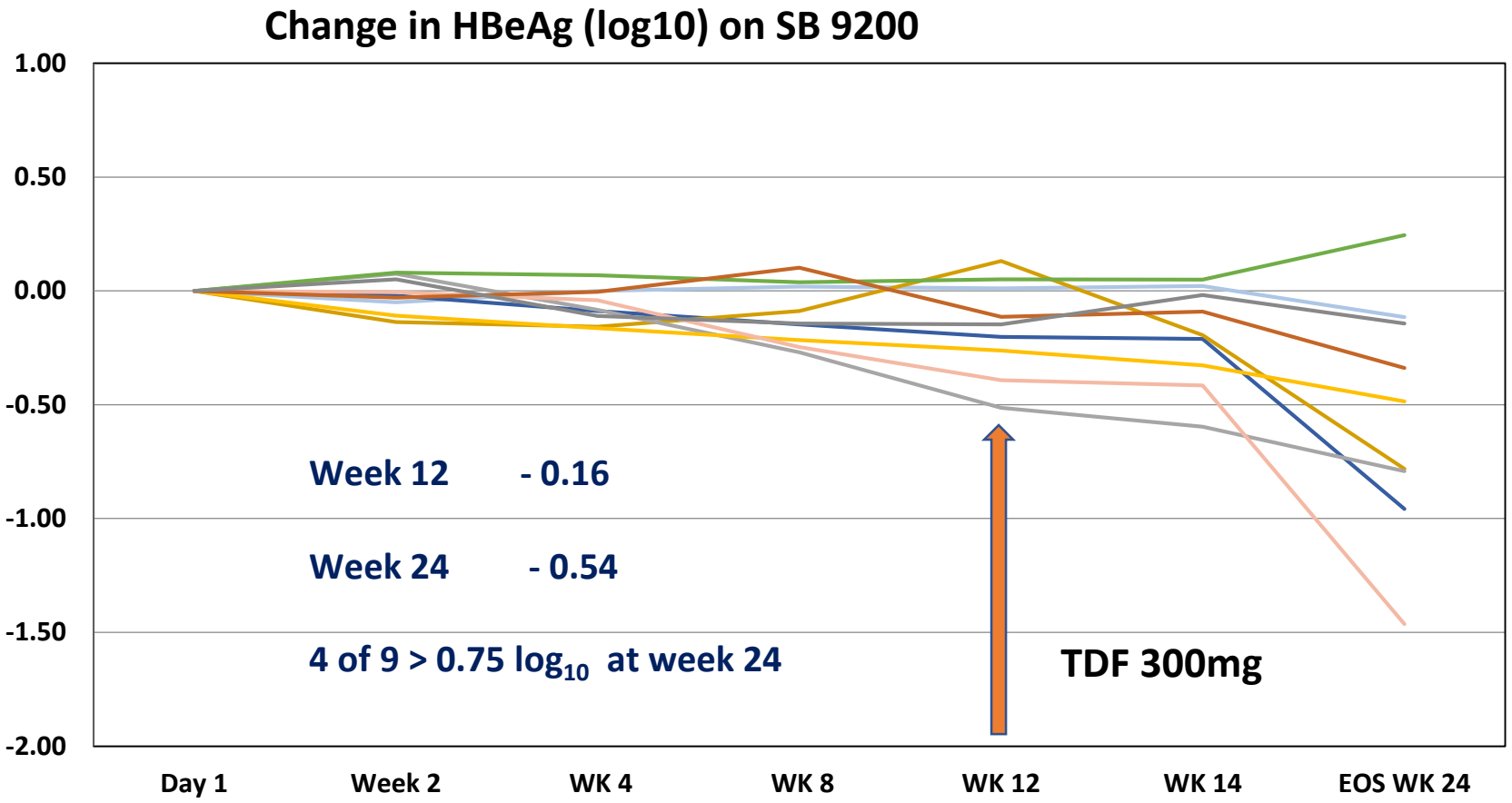


* Patient dose reduced ALT flare

- **3 of 16 patients > 0.5 $\log_{10}$ sustained reduction in HBsAg at week 12 on monotherapy – all HBeAg –ve**
- **6 of 16 patients > 0.5 $\log_{10}$ sustained reduction in HBsAg at week 24 after TDF – 3 HBeAg +ve and 3 HBeAg -ve**

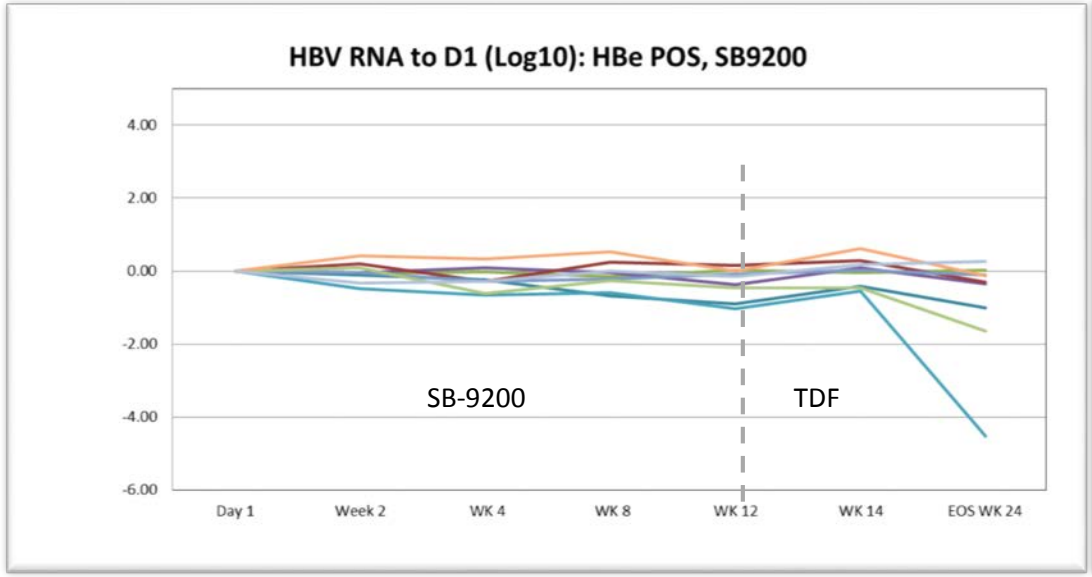
Change in HBeAg from baseline

Individual patient data

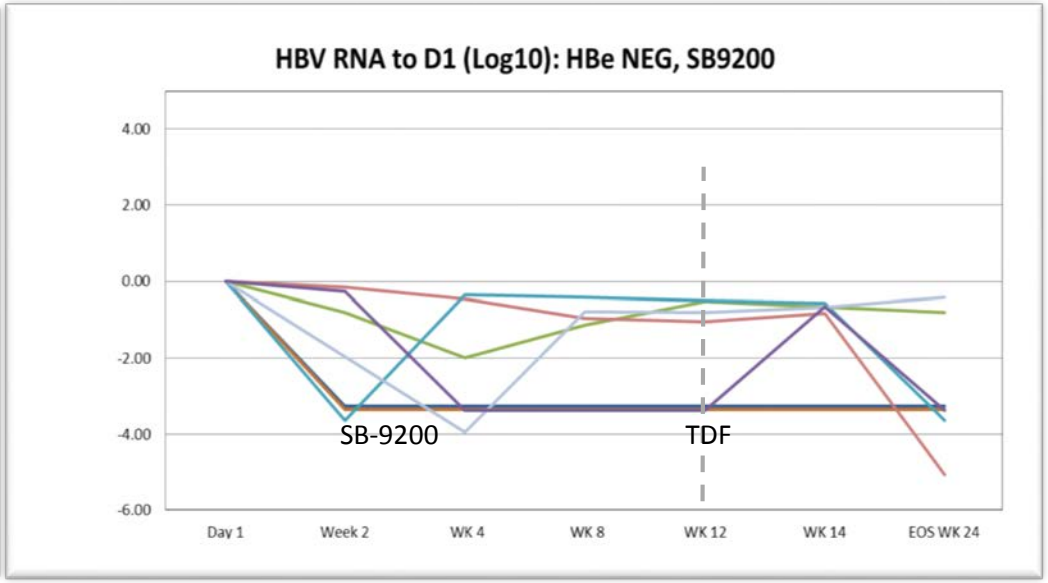


Change in HBV RNA on Inarigivir and TDF switch

HBeAg POS patients



HBeAg NEG patients

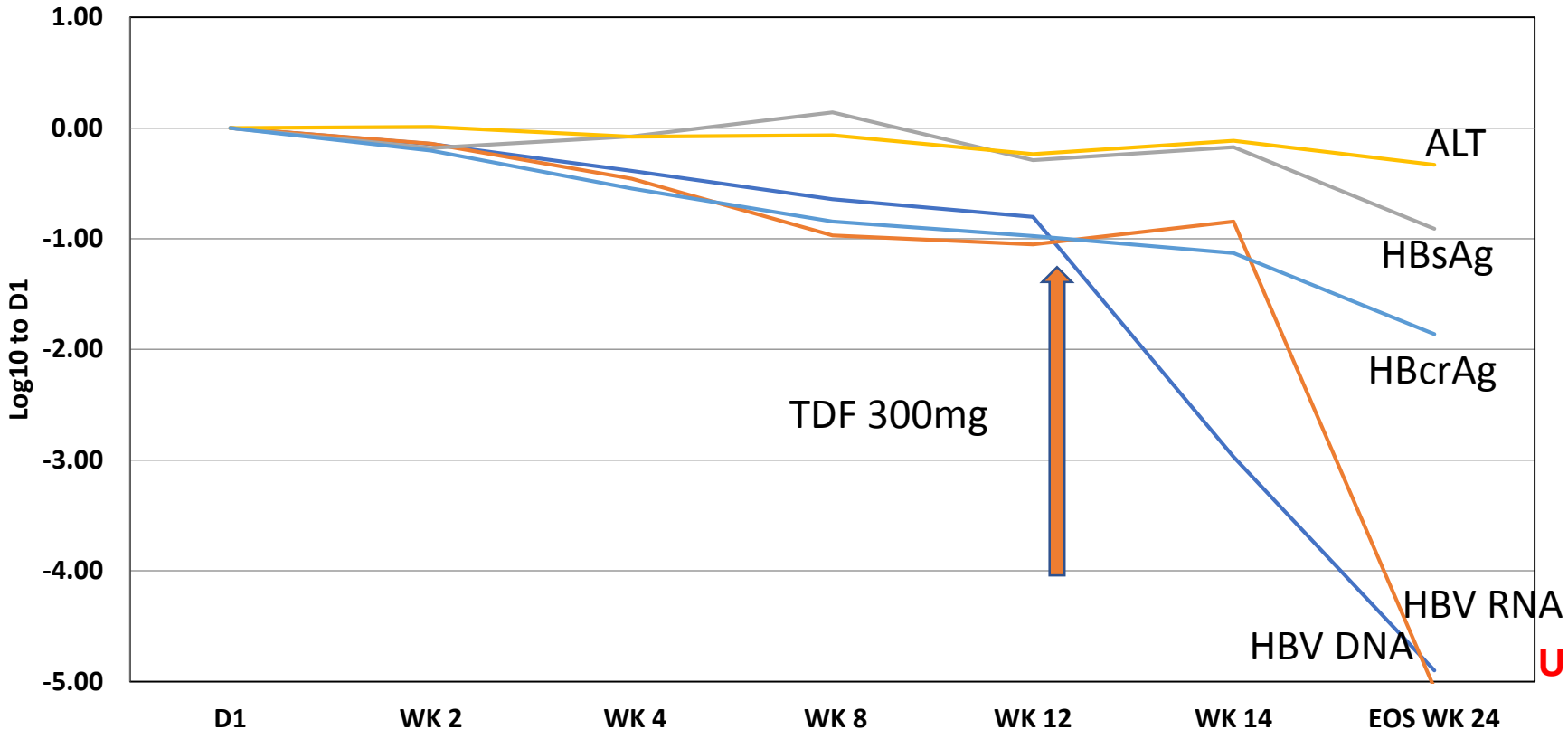


HBV RNA response in 7 HBeAg negative patients:

WEEK 12: Mean Decline: 1.8 $\log_{10}$
3 of 7 HBV RNA undetectable

WEEK 24: Mean Decline: 2.9 $\log_{10}$
5 of 7 HBV RNA undetectable

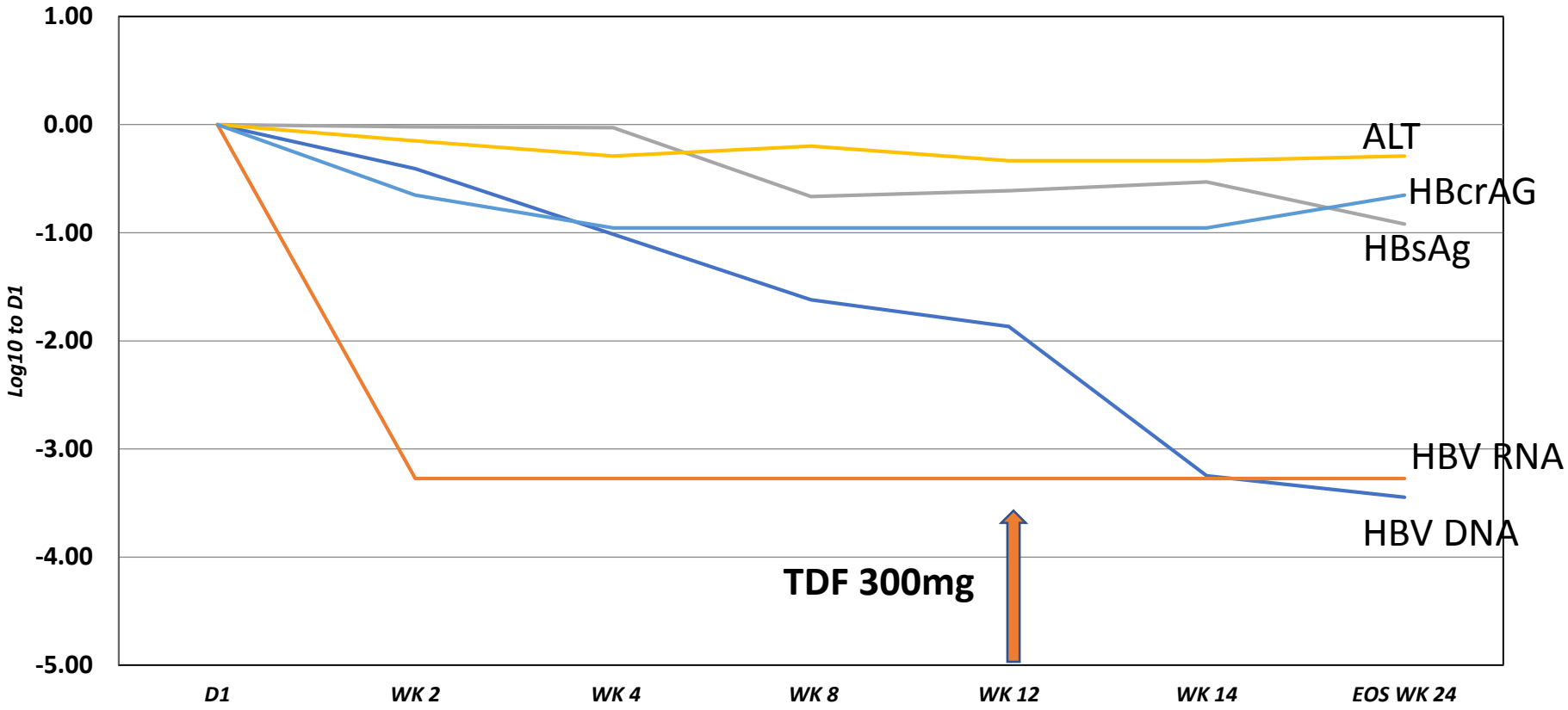
SB 9200 Partial Responder; TDF responder post SB 9200



Genotype B
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

SB 9200 Responder and additive effect of TDF



Genotype D
HBeAg - ve

Undetectable

	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

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 effects including reduction in HBV DNA, HBsAg, HBeAg and HBV RNA

Locarnini et al AASLD 2017, Late breaker poster October 23, 2017