Immunomodulation

Nezam H. Afdhal MD, DSc

CMO, Spring Bank Pharmaceuticals

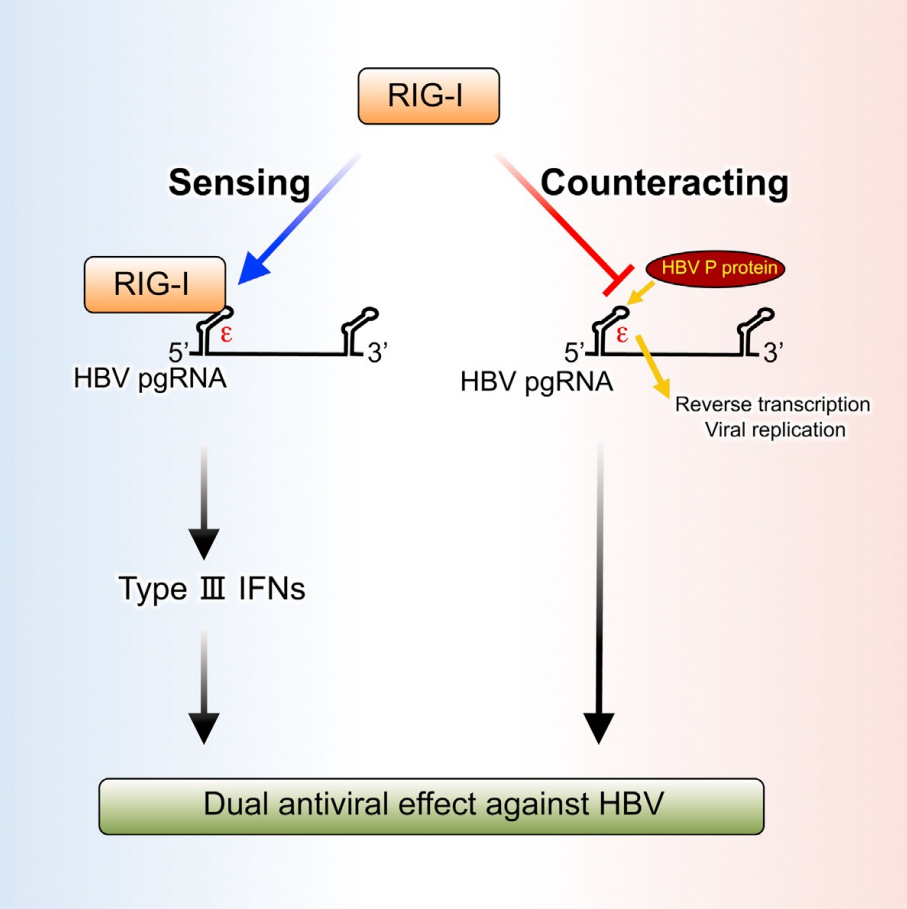
Role of Immune Modulators

- Promote HBsAg clearance for functional cure via activation of innate and adaptive immune responses
- Inactivate cccDNA transciption
- Clear viral infected cells
- Maintain immune response to prevent viral relapse / reactivation
- Accelerate time to clearance
- Backbone component of multi-drug regimens

Immuno-modulators in development for HBV

- TLR 7 – multiple
- TLR 8
- IDO inhibitors
- PD-1 / PDL-1
- siRNA’s ??
- STING agonists
- RIG-I agonist

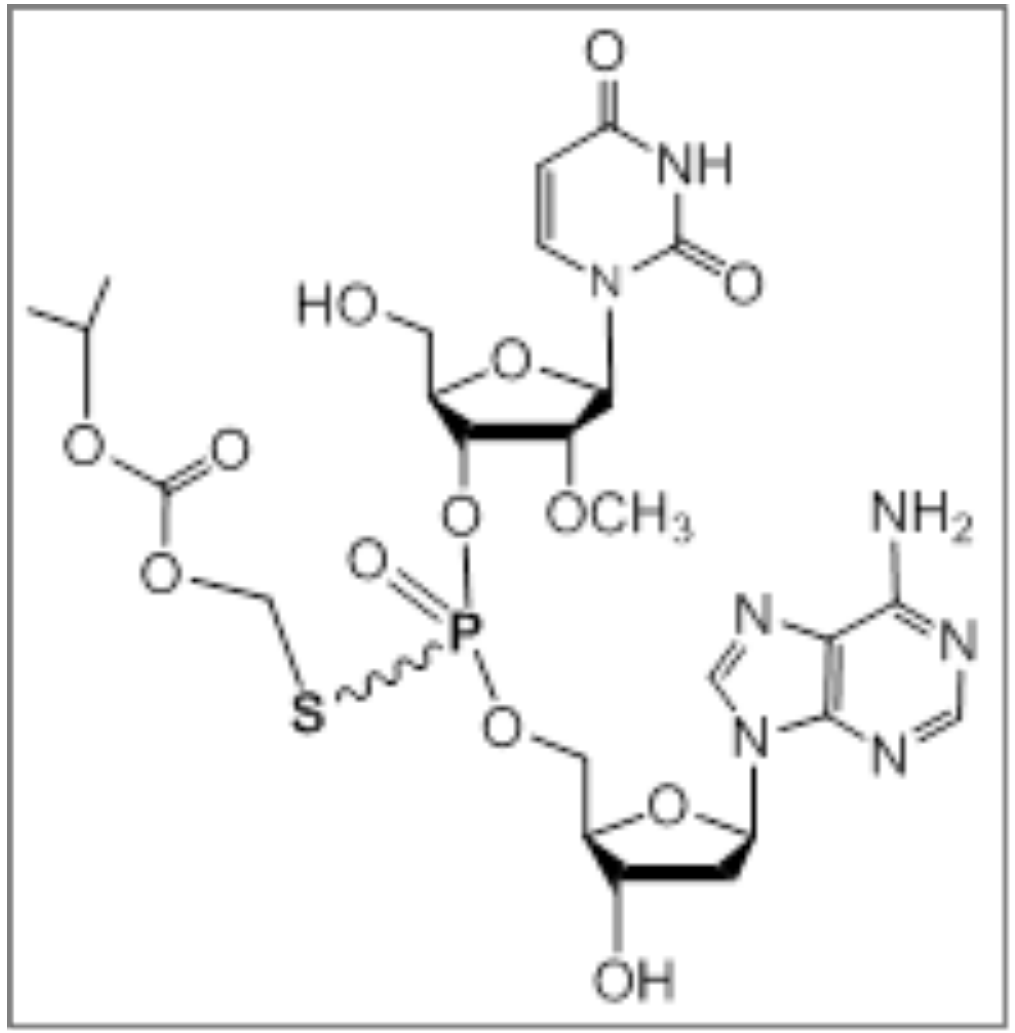
The RNA Sensor RIG-I Dually Functions as an Innate Sensor and Direct Antiviral Factor for Hepatitis B Virus



- 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)



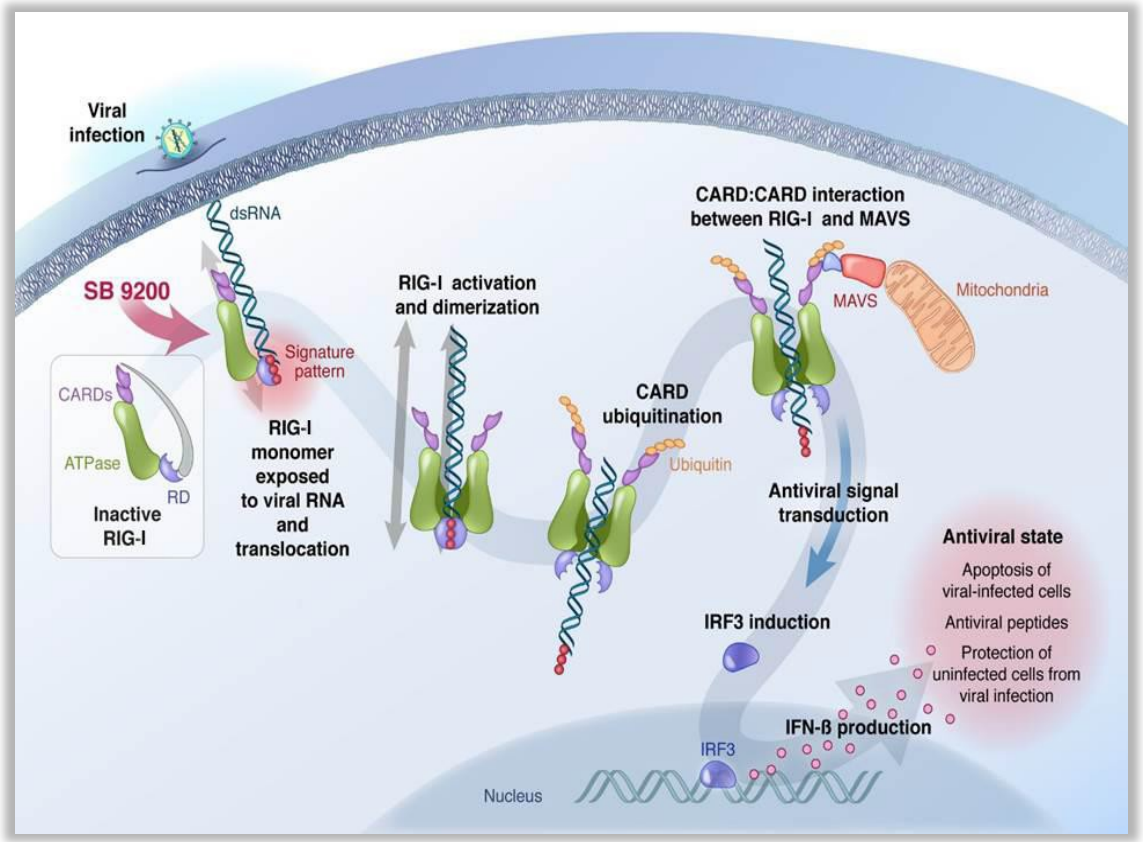
- Small molecule nucleic acid hybrid (SMNH)
- RIG-I activator
- Orally bioavailable prodrug
- Active metabolite SB 9000
- Actively transported into hepatocytes via OATP1
- 30:1 liver to plasma ratio
- Not metabolized, not phosphorylated.
- No direct activity against DNA polymerase

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

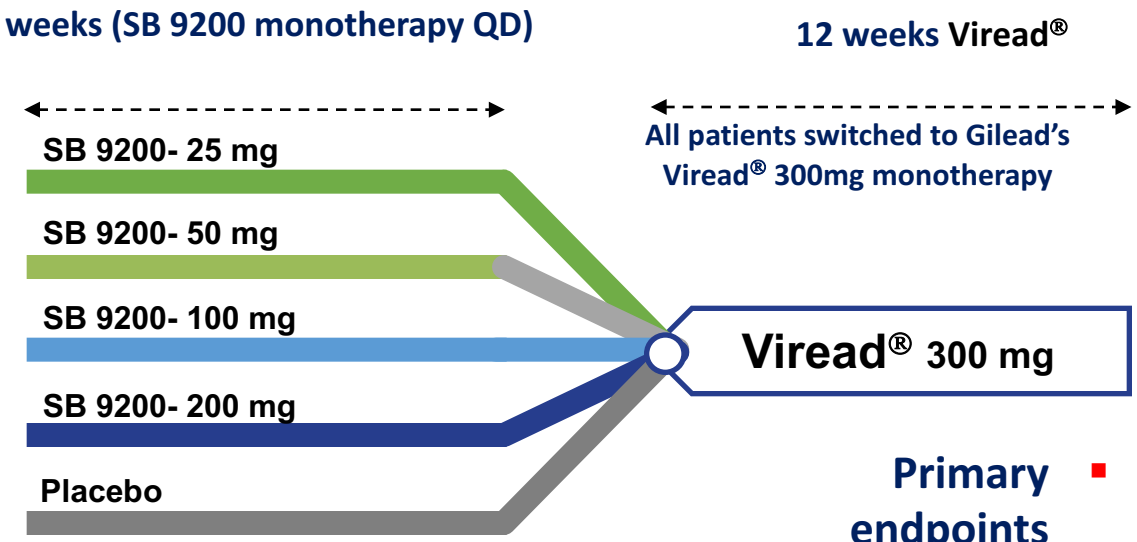
- Binds, activates and increases sensitivity of sensory proteins RIG-I and NOD2 to viral infection
- Potential to induce both innate and adaptive immune response
- Unique selectivity – designed to be active in virally infected cells
- Can also blocks viral replication via polymerase inhibition
- Can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



HYPOTHESIS: Host immune response is necessary for viral clearance and functional cure

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

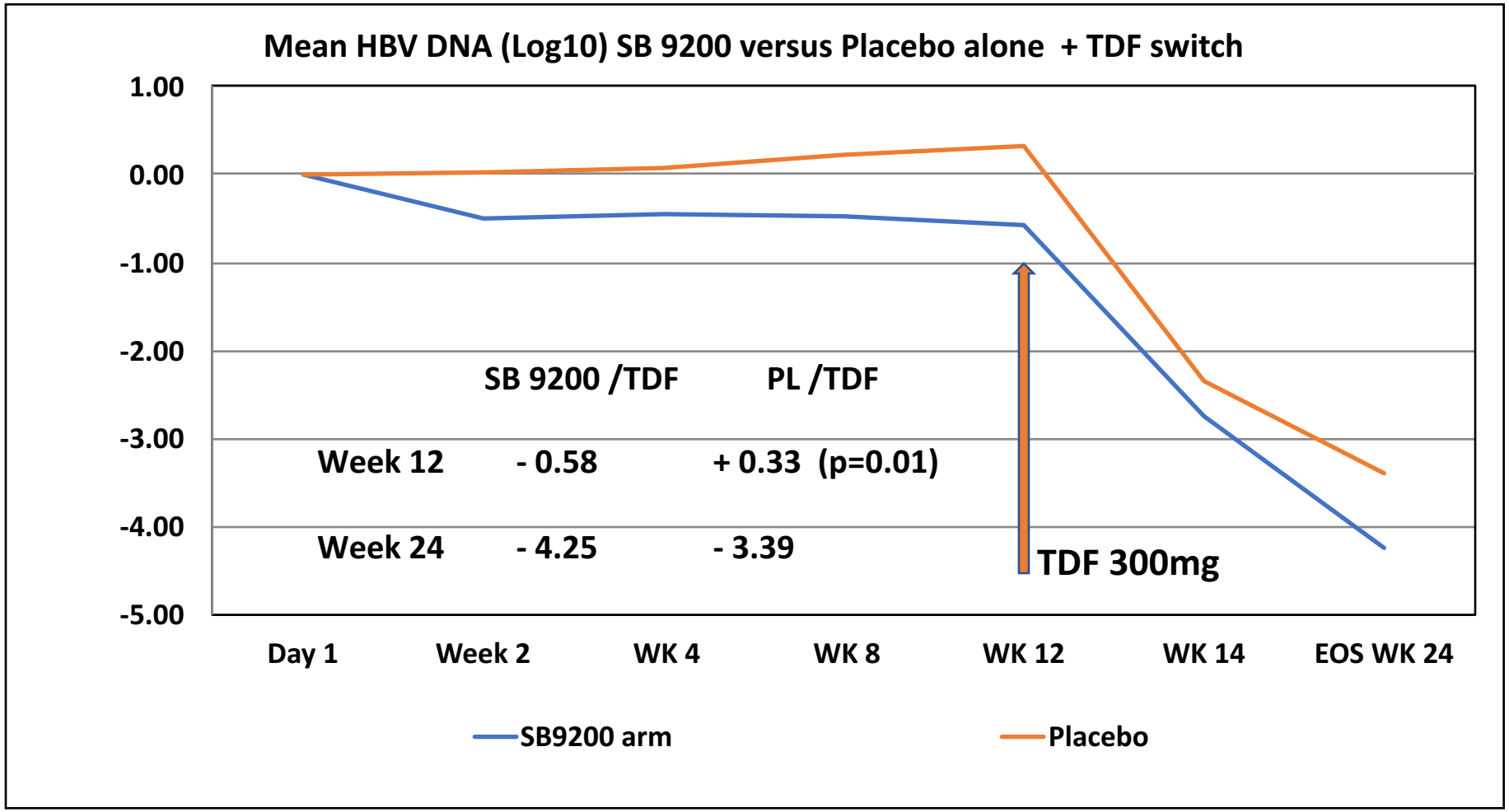
Patients

		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

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

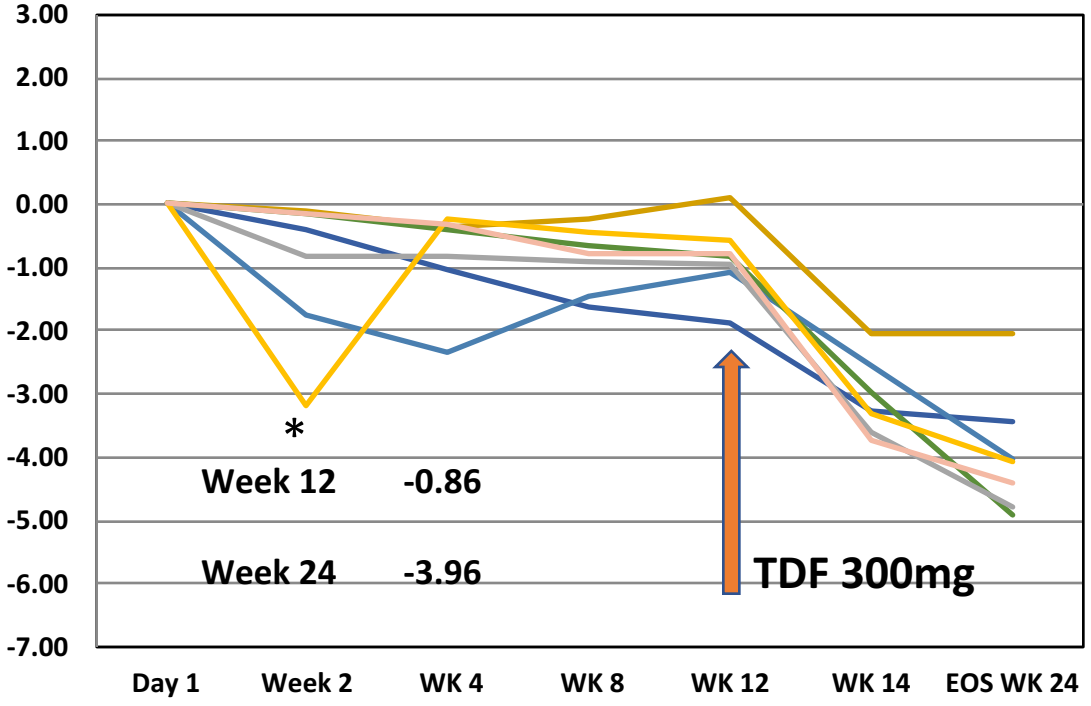
Week 12 HBV DNA reduction on SB 9200 or placebo and on switch to TDF from week 12 to 24



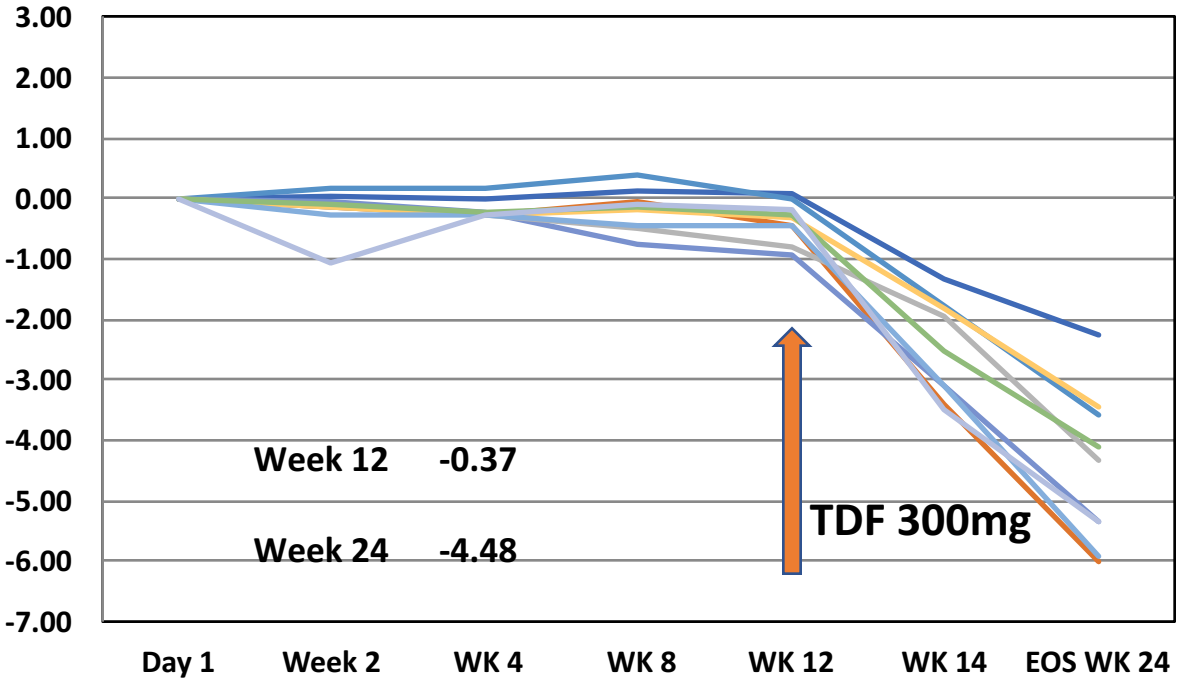
Week 12 HBV DNA reduction on SB 9200 and on switch to TDF from week 12 to 24

Individual patient data

Mean HBV DNA HBeAg - SB9200 with TDF switch



Mean HBV DNA HBeAg + SB 9200 with TDF switch



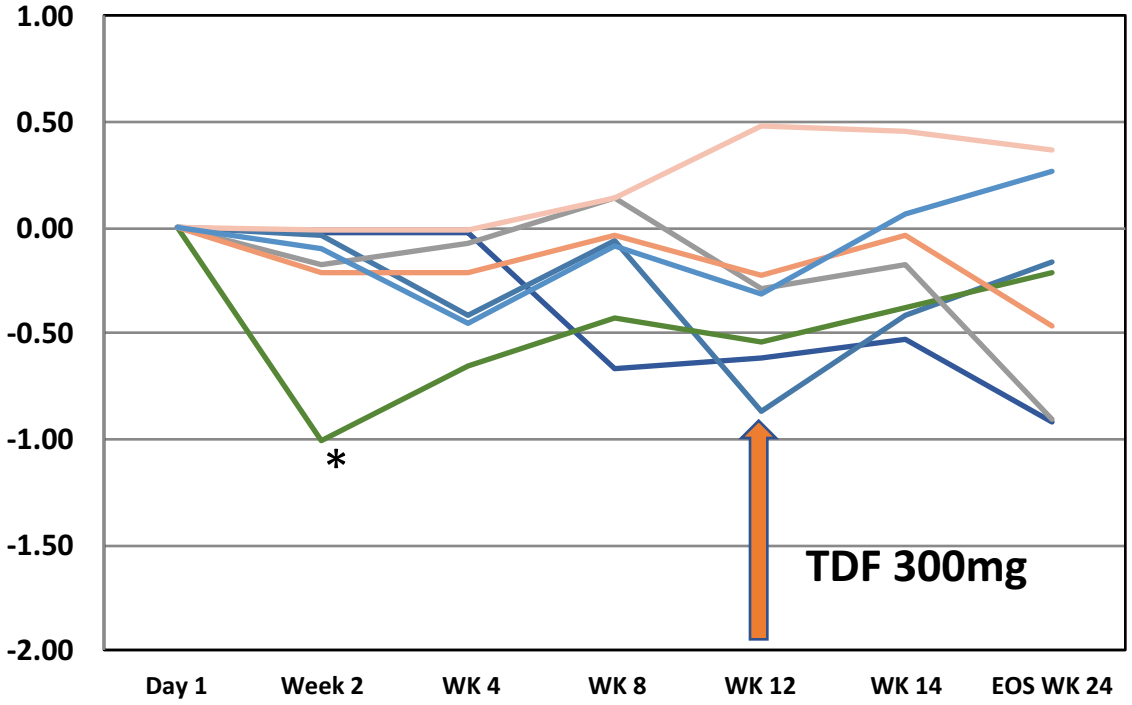
* Patient dose reduced ALT flare

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

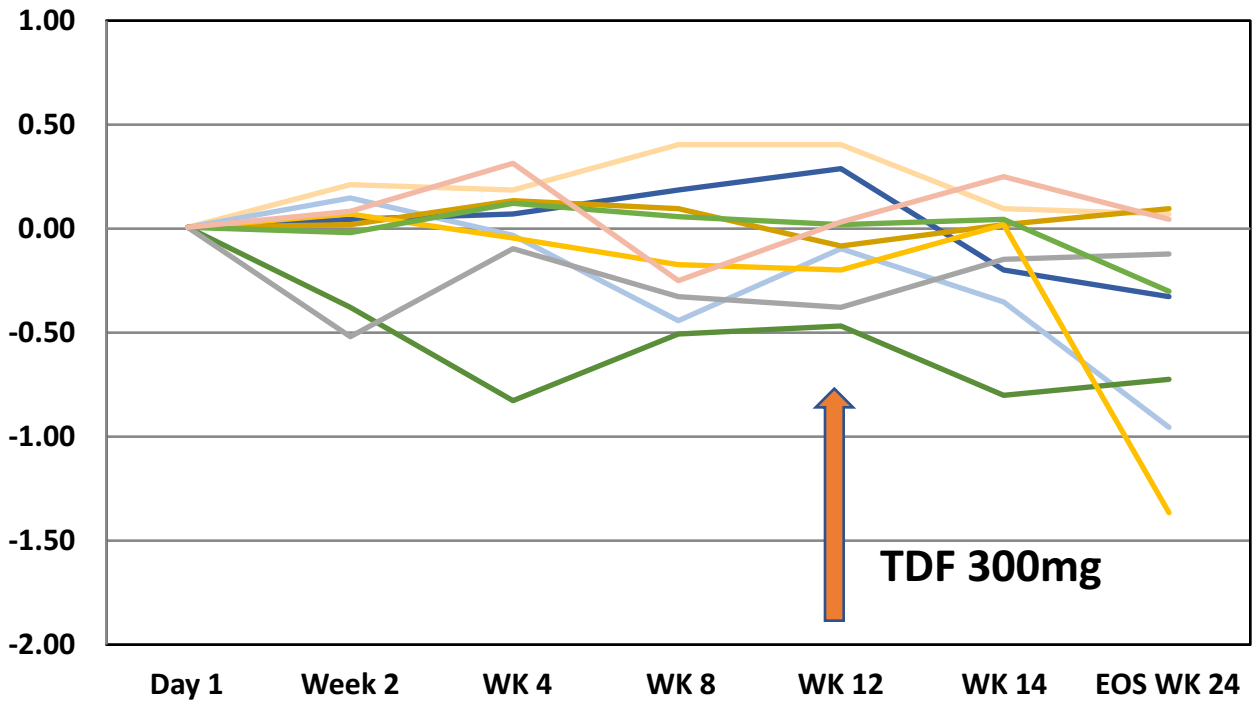
Week 12 HBsAg reduction on SB 9200 and on switch to TDF from week 12 to 24

Individual patient data

Mean HBsAg in HBeAg -ve SB9200 with TDF switch



Mean HBsAg in HBeAg +ve SB 9200 with TDF switch

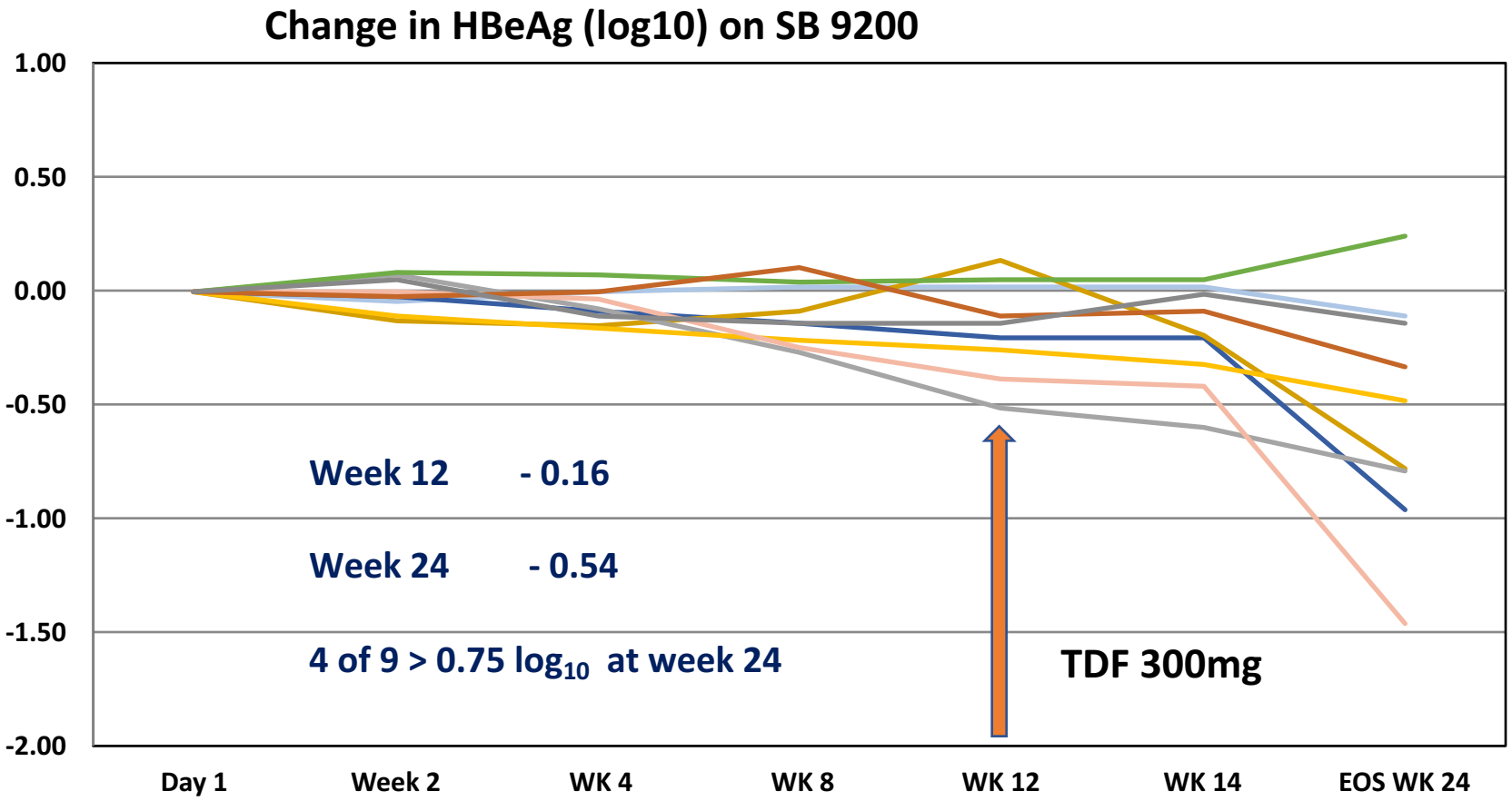


* Patient dose reduced ALT flare

- **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**

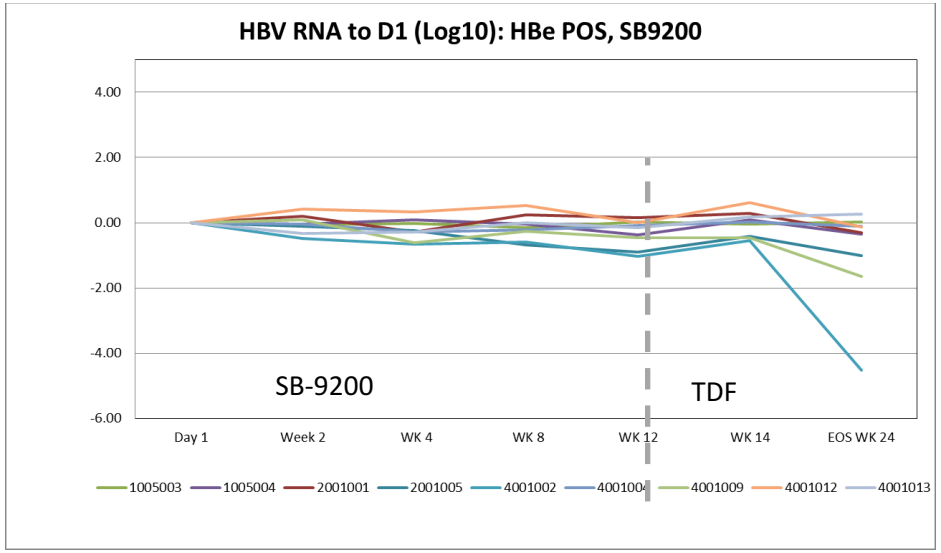
Change in HBeAg from baseline

Individual patient data

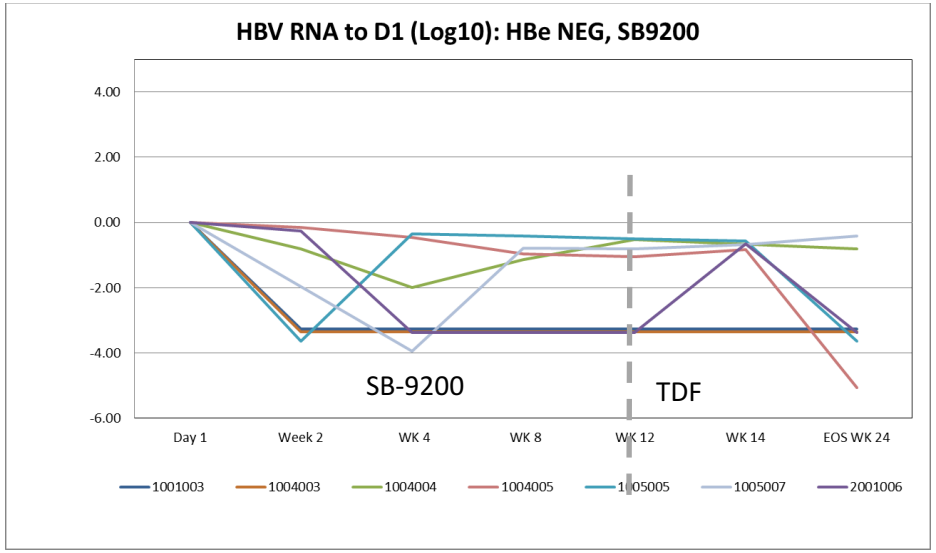


Change in HBV RNA on Inarigivir and TDF switch

HBeAg POS patients



HBeAg NEG patients

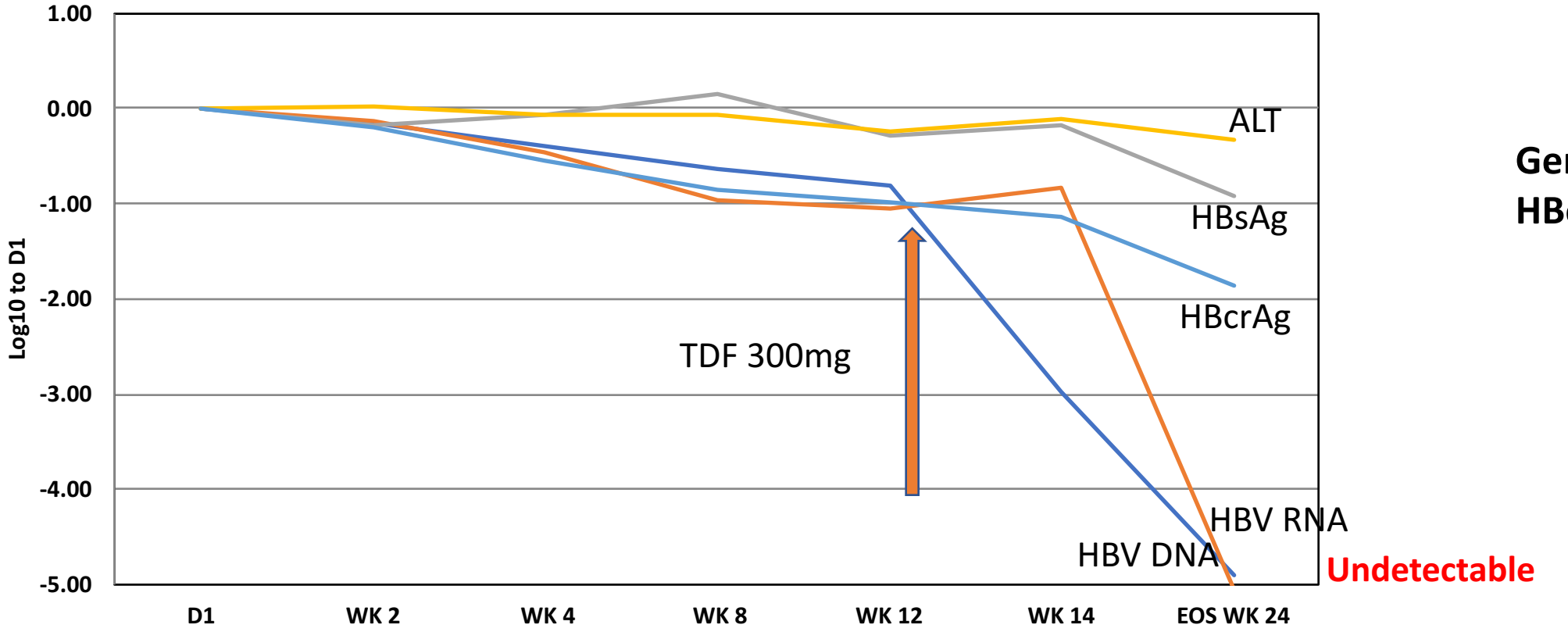


HBV RNA response in 7 HBeAg negative patients:

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,

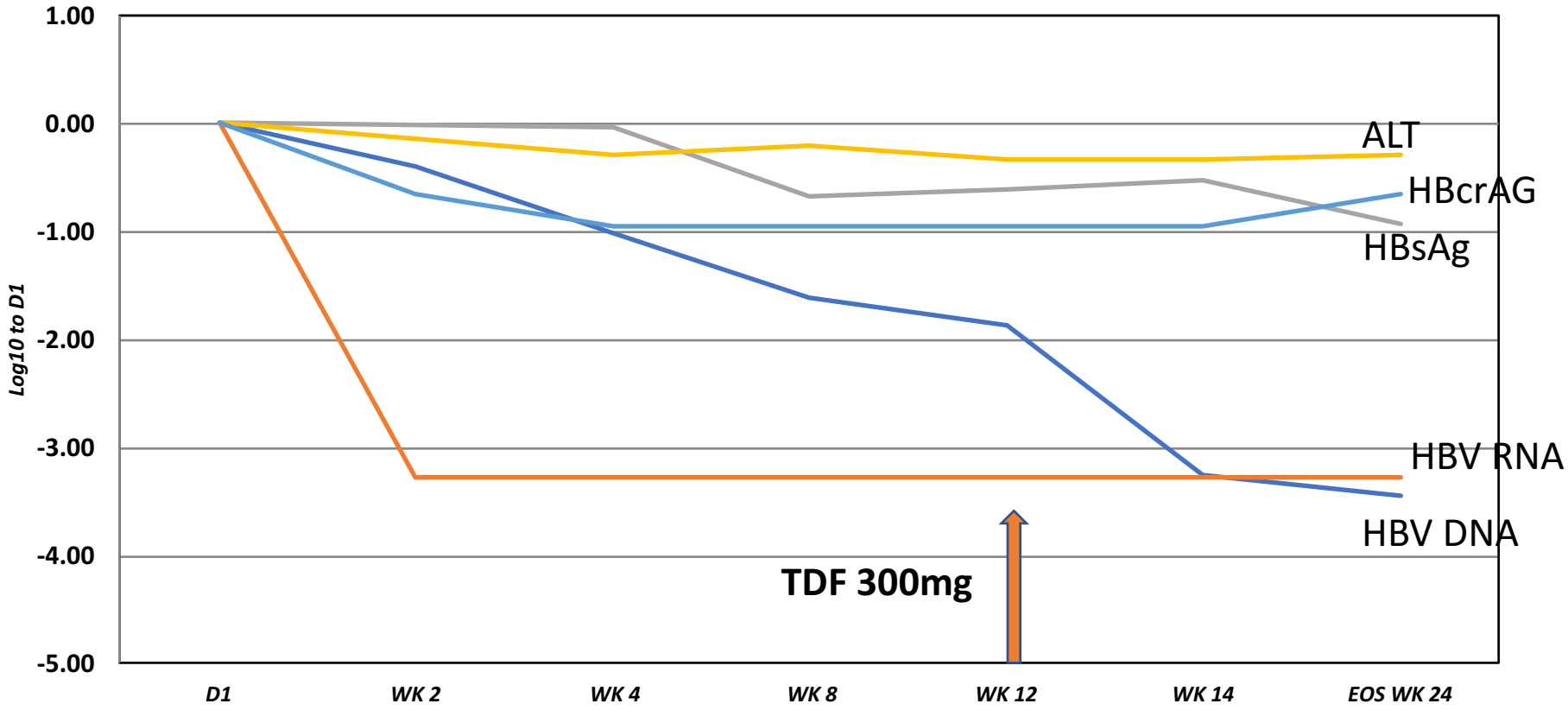
SB 9200 Partial Responder; TDF responder post SB 9200



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

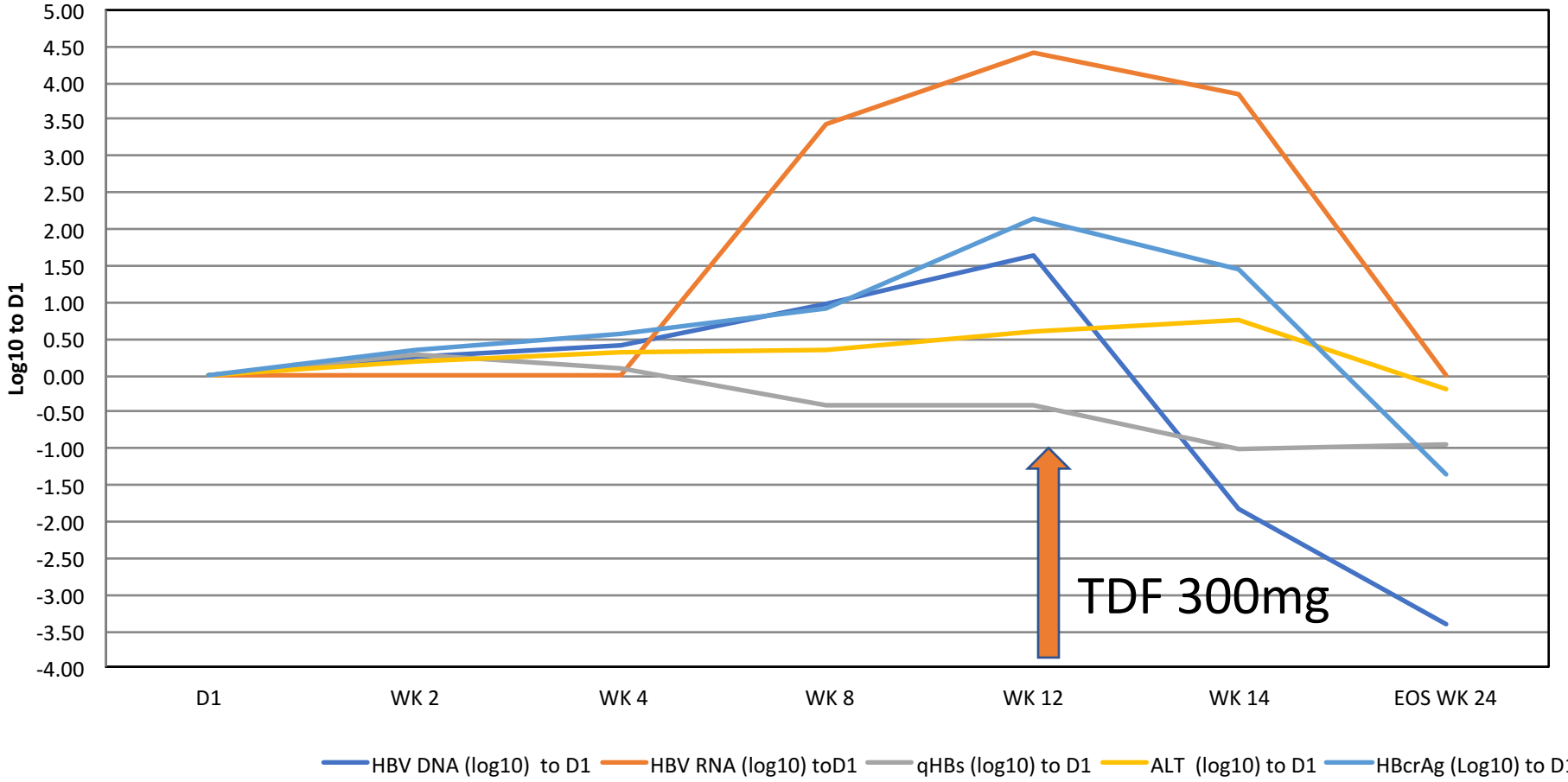


Genotype D
HBeAg - ve

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

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

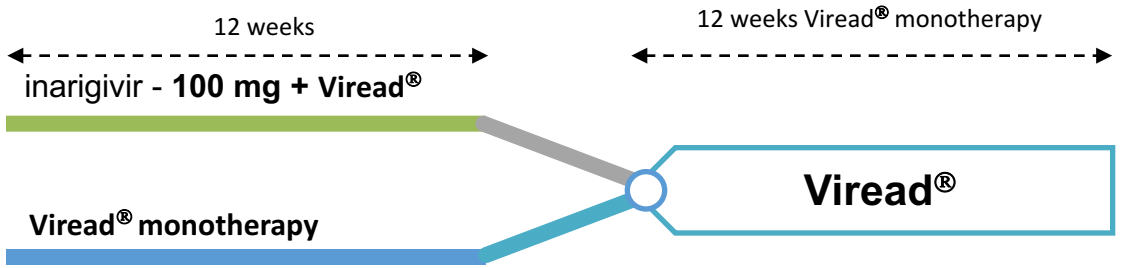
Summary

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

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

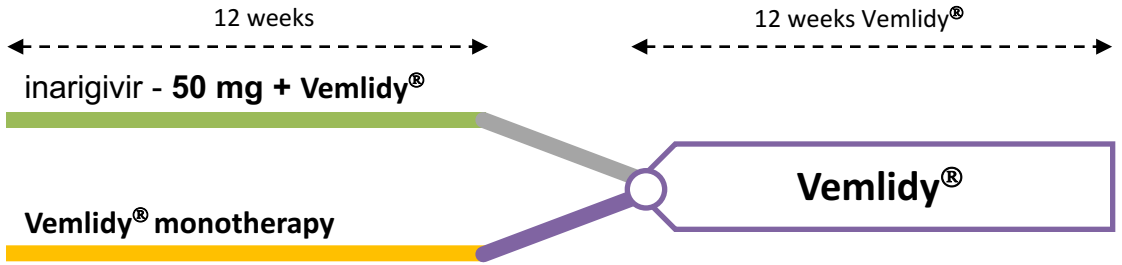
Inarigivir HBV Phase II Program

ACHIEVE Phase II (Part B) Study
inarigivir Co-administered with Viread® (tenofovir disoproxil fumarate) 300mg



Anticipated initiation in 2H 2018

Gilead Phase II HBV Trial
inarigivir Co-administered with Vemlidy® (tenofovir alafenamide) 25mg



Anticipated initiation in 1H 2018

Potential additional Phase II studies in 2018: inarigivir + novel MOAs (siRNAs and capsids)

Spring Bank Collaborations with Other Investigational MOAs for HBV

Examine the concept of the oral selective immunomodulator as the backbone of a potential multi-drug combination treatment of chronic HBV to increase functional cure rates

GILEAD

- Evaluating inarigivir, co-administered with Gilead's Vemlidy® (tenofovir alafenamide) 25mg in chronic HBV patients

arrowhead pharmaceuticals

- The collaboration will evaluate inarigivir's oral immunomodulatory characteristics with Arrowhead's siRNA
- Preclinical studies on hold until determination of new Arrowhead compound delivery

Potential to demonstrate increased HBV functional cure rates with more favorable tolerability profile and shorter duration of treatment relative to current IFN-based regimens

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