Anti-viral effect of the RIG-I agonist, Inarigivir

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on behalf of the ACHIEVE TRIAL Investigators

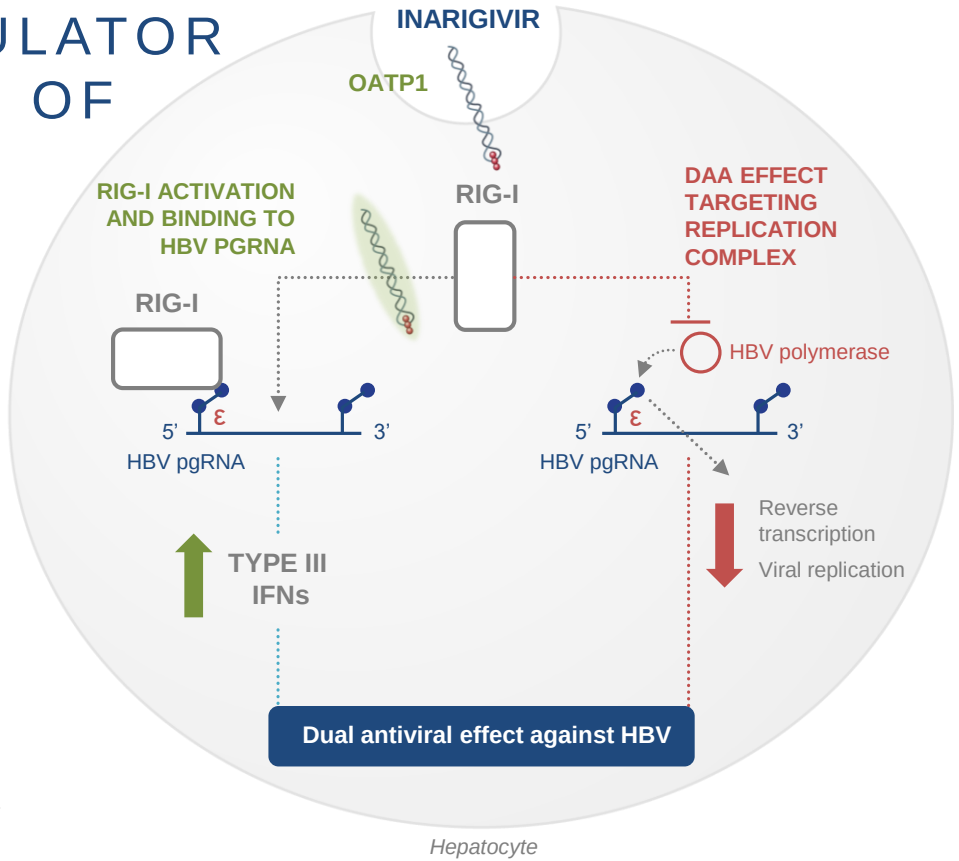
- DISCLOSURE:

  Dr. Afdhal is the Chief Medical Officer of Spring Bank Pharmaceuticals

INARIGIVIR: A NOVEL, ORAL SELECTIVE IMMUNOMODULATOR WITH A DUAL MECHANISM OF ACTION

INARIGIVIR is a RIG–I AGONIST which is designed to:

- **Restore hepatic selective innate and adaptive immune response** stimulating the production of type I and III IFNs
- Inhibit the HBV replication complex via a direct acting anti-viral effect
- Result in significant anti-HBV activity with reduction in HBV DNA, HBV RNA, HBsAg and cccDNA



HBV, hepatitis B virus; IFN, interferon; pgRNA, pregenomic RNA; RIG-I, retinoic acid-inducible gene-I.

Sato et al. *Immunity*. 2015;42:123-132.

INARIGIVIR – MOA STUDIES INDICATE KEY ROLE FOR SELECTIVE HEPATIC IMMUNO-MODULATION

PRE-CLINICAL DATA

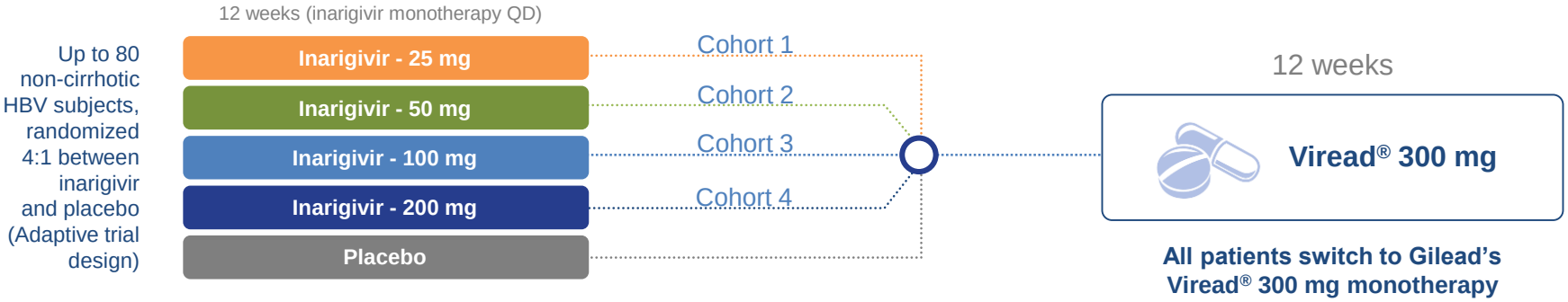
- Host mediated pan viral agent against RNA viruses
- Inarigivir binds to CARDs and regulatory domain of RIG-I with activation of IRF-3 and hepato-selective innate immune response
- Inarigivir up-regulates intra-hepatic RIG-I, activates intra-hepatic ISGs and suppresses HBsAg, HBV DNA, HBV RNA and cccDNA in the woodchuck model

CLINICAL

- Inarigivir potent antiviral against HCV with response proportional to ISG activation and IL-28b status
- Preliminary data shows inarigivir responses in HBV associated activation of ISGs in PBMCs
- Inarigivir activates a B-cell neutralizing HBsAb response in responder patients

ACHIEVE PHASE 2 (PART A) MONOTHERAPY DOSE ESCALATION STUDY

Clinical trial collaboration with Gilead to evaluate inarigivir followed by tenofovir 300 mg



PRIMARY ENDPOINT

Safety and antiviral activity at 12 weeks

SECONDARY ENDPOINT

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

DNA, deoxyribonucleic acid; HBeAg, hepatitis B e antigen; RNA, ribonucleic acid; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; QD, once daily.

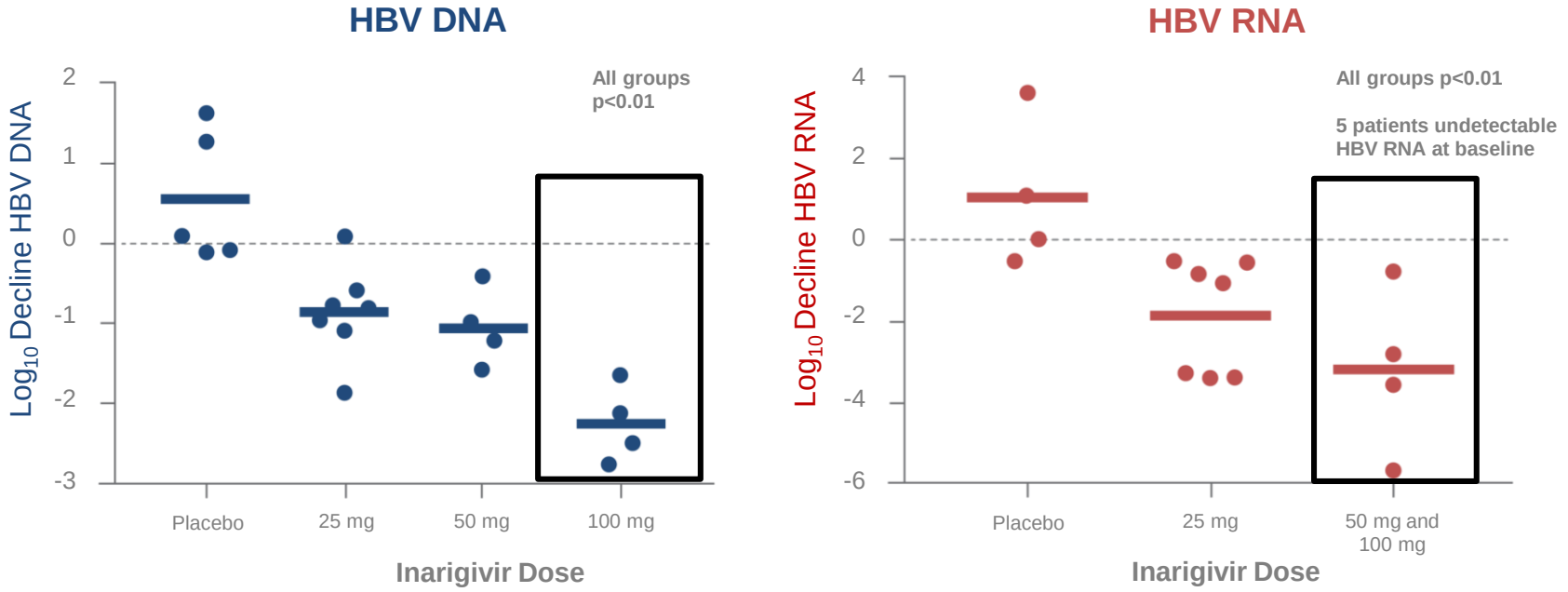
ACHIEVE STUDY BASELINE DEMOGRAPHICS

Representative demographics of the global "real world" HBV patient population

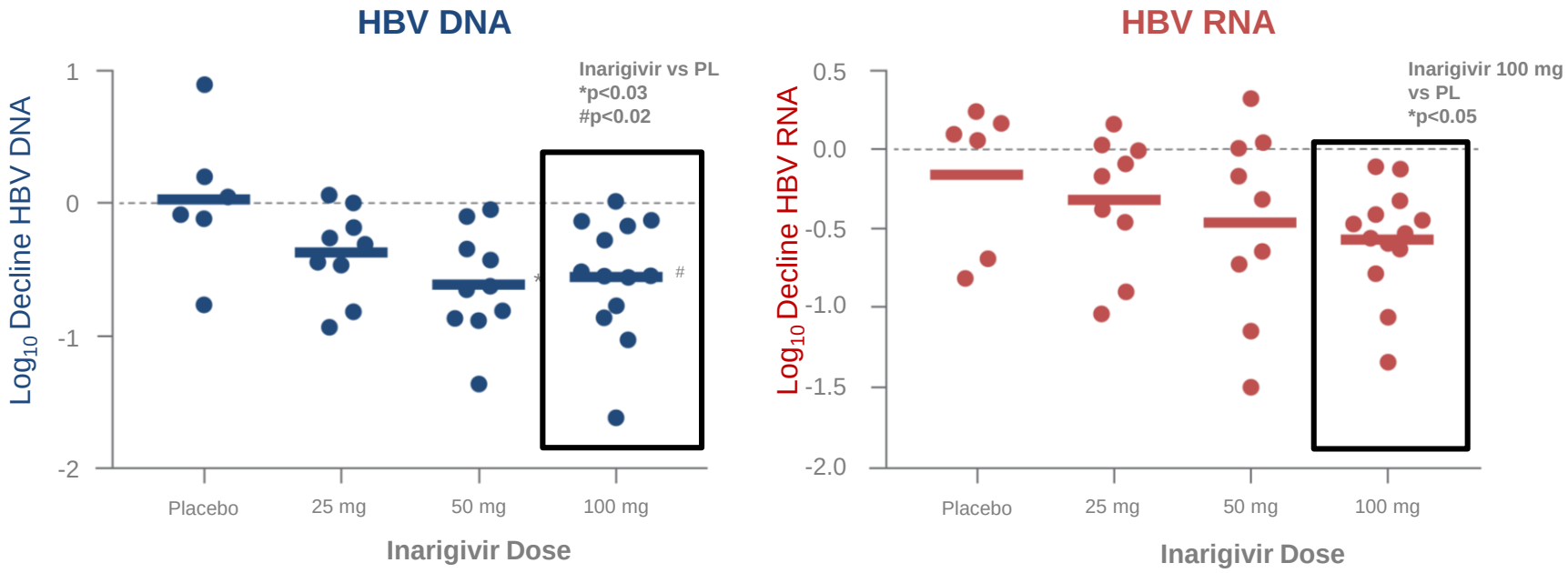
			Cohort 1		Cohort 2		Cohort 3	
		Placebo	25 mg HBeAg +ve	25 mg HBeAg -ve	50 mg HBeAg +ve	50 mg HBeAg -ve	100 mg HBeAg +ve	100 mg HBeAg -ve
Number		11	9	7	11	5	13	4
Mean Age		40	37	43	36	47	34	46
Gender M:F		7:4	5:5	3:3	9:2	5:0	7:6	3:1
Mean Baseline ALT		69	82	75	75	65	75	90
Mean Baseline HBV DNA log_{10}		6.20	7.86	5.69	7.79	4.55	8.20	5.95
Genotype	A	1		1				
	B	6	4	3	3	3	4	3
	C	4	5	1	7	1	8	1
	D			2	1		1	

In cohort 2 (50 mg), two patients (1 HbeAg +ve and 1 HBeAg –ve) withdrew at day 1 and day 14 from patient choice

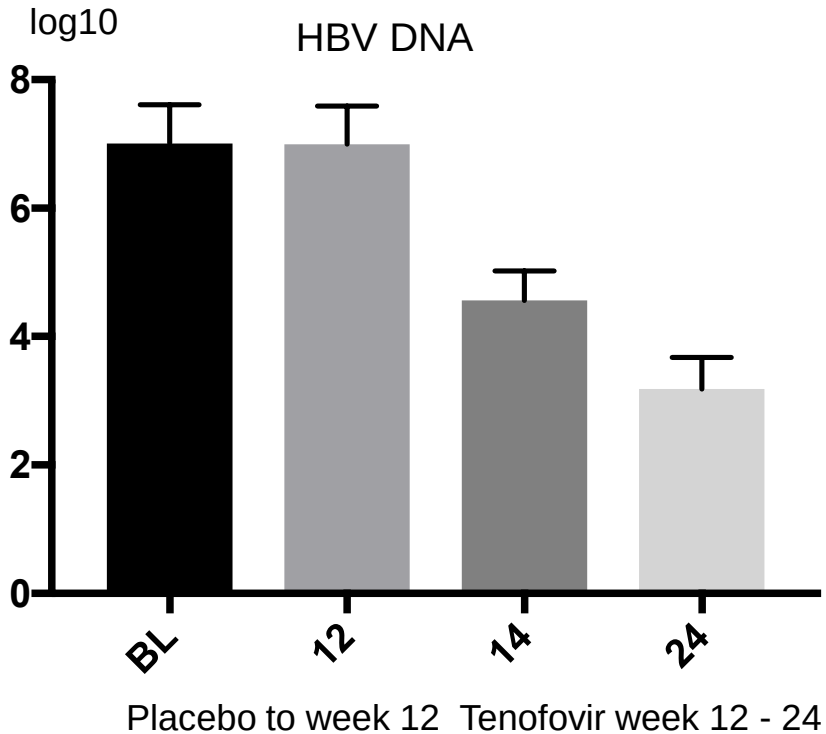
INARIGIVIR DEMONSTRATES A CONTINUING POSITIVE DOSE RESPONSE IN HBeAg -VE PATIENTS AT WEEK 12

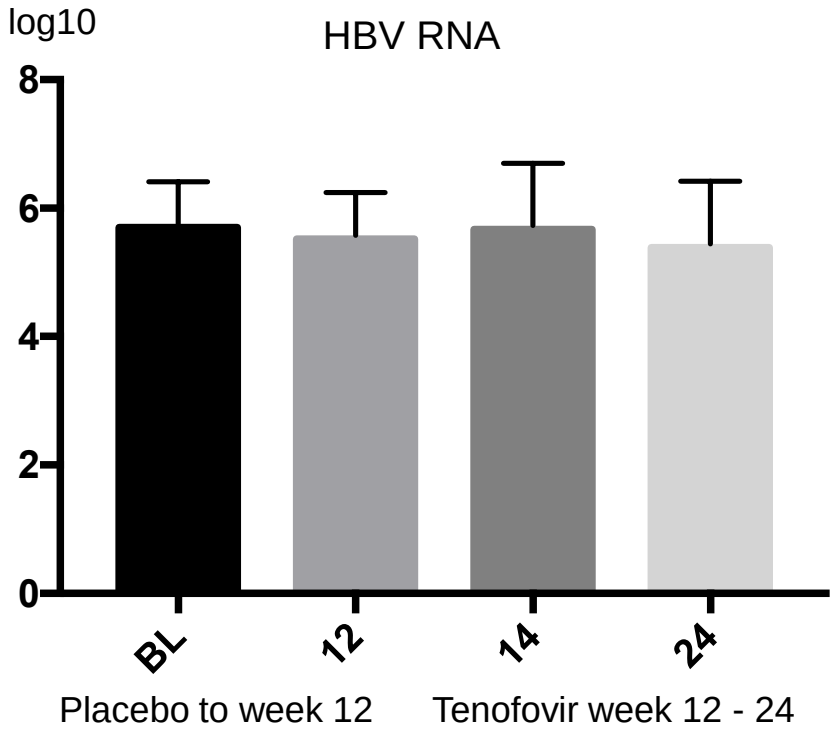


INARIGIVIR DEMONSTRATES A CONTINUING POSITIVE DOSE RESPONSE IN HBeAg +VE PATIENTS AT WEEK 12

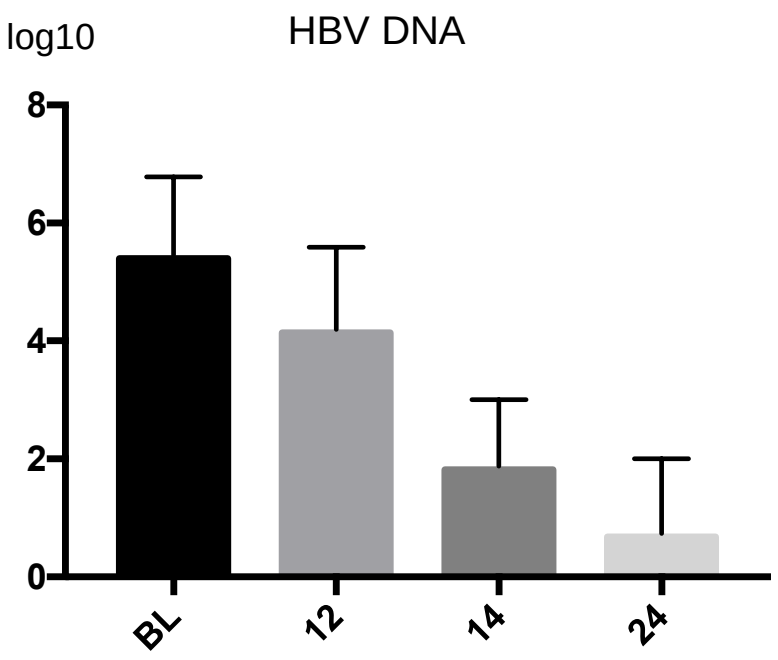


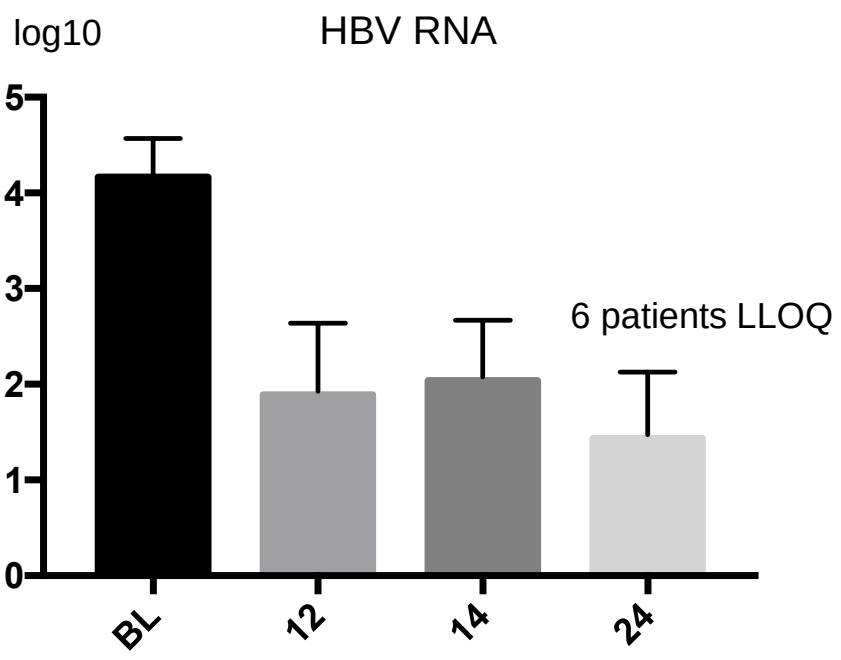
Placebo followed by tenofovir – no effect on HBV RNA (n=8 patients)



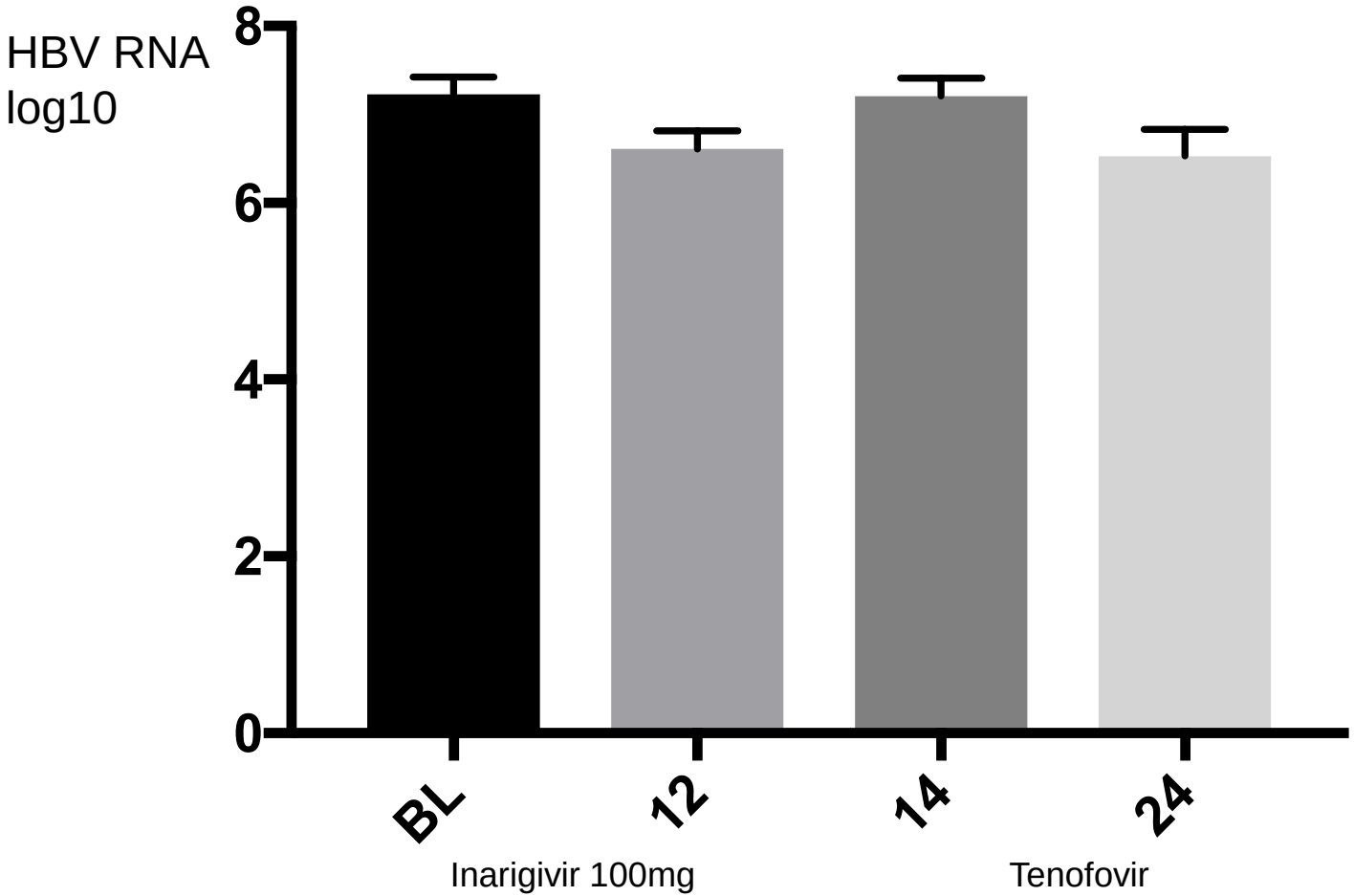


HbeAg negative patients (n=10) – Inarigivir effect on HBV RNA persists on TDF

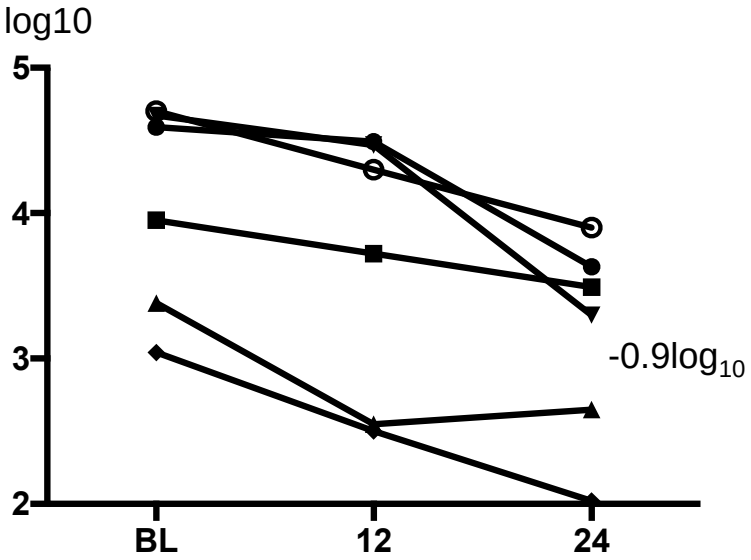




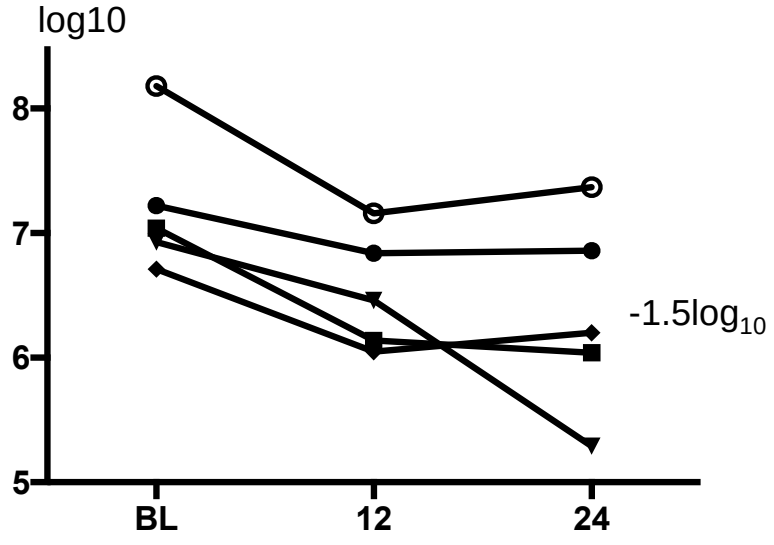
HBeAg positive patients on Inarigivir 100mg show new HBV RNA set point



HBsAg decline in HBeAg positive responders



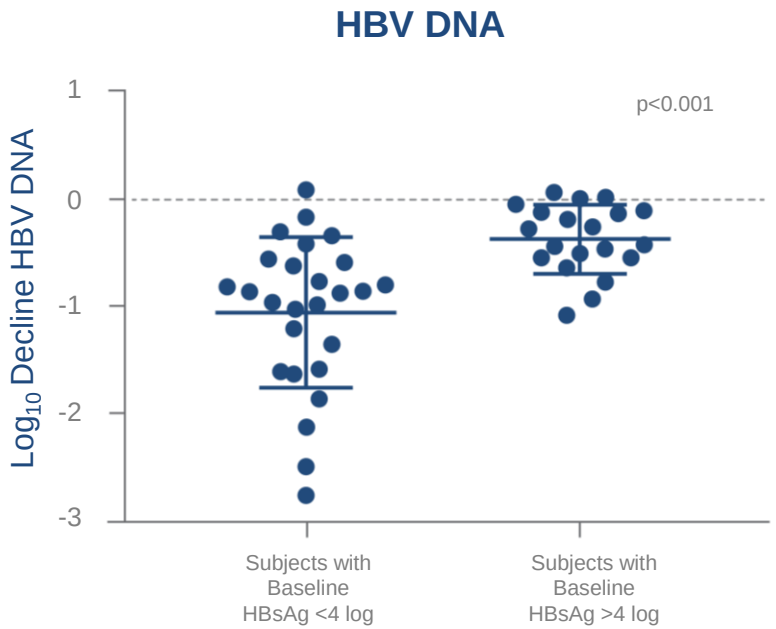
HBV RNA decline in HBeAg positive responders

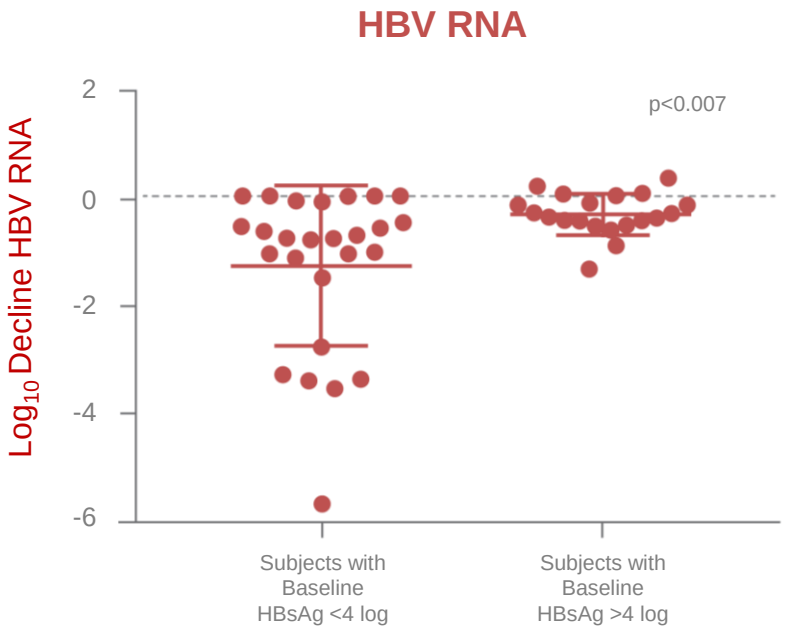


SUMMARY OF ACHIEVE PHASE 2 DATA FROM COHORTS 1,2 and 3 ON quantitative HBsAg

- Overall, 13 of 47 (28%) patients experienced a 0.5 $\log_{10}$ reduction on inarigivir alone or at 24 weeks after TDF switch
- Mean and median HBsAg reduction 0.8 $\log_{10}$ (range 0.5 – 1.4 $\log_{10}$) in 13 responder patients
- Effect on HBsAg seen at all doses in both monotherapy and after TDF switch
- HBsAg response seen in 7 HBeAg -ve and 6 HBeAg +ve patients across all genotypes
- HBsAg response associated with declines in HBV DNA and HBV RNA
- HBsAg reduction can be associated with “immune flares” in HBeAg negative patients on Inarigivir monotherapy

IN ALL COHORTS: BASELINE HBsAg PREDICTS RESPONSE OF BOTH DNA AND RNA TO INARIGIVIR



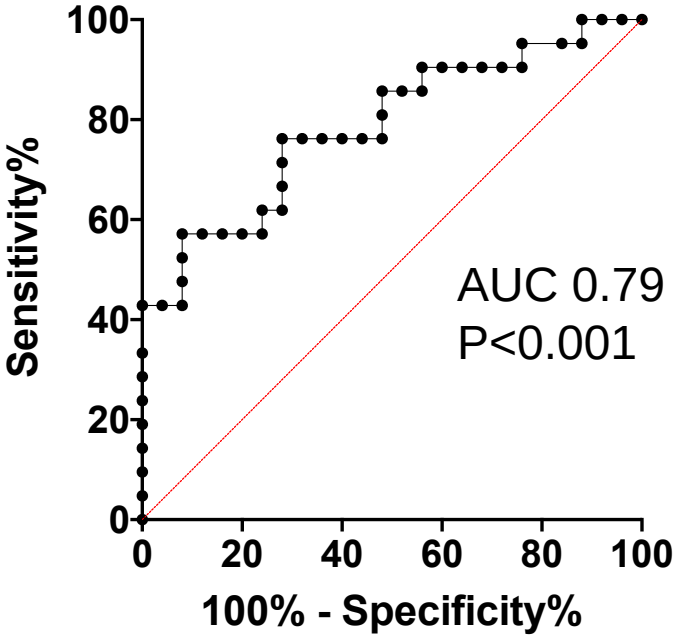


Patients: **HBsAg <4 log: 16 HBeAg –ve, 10 HBeAg +ve**

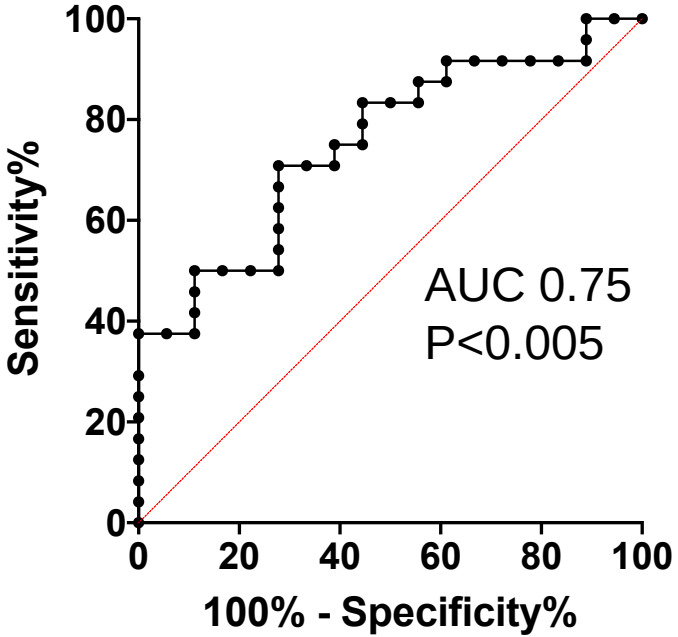
HBsAg >4 log: 1 HBeAg –ve, 19 HBeAg +ve

Baseline serum IP-10 predicts HBV DNA and HBV RNA reduction by inarigivir

DNA reduction > 0.75log$_{10}$ at week 12

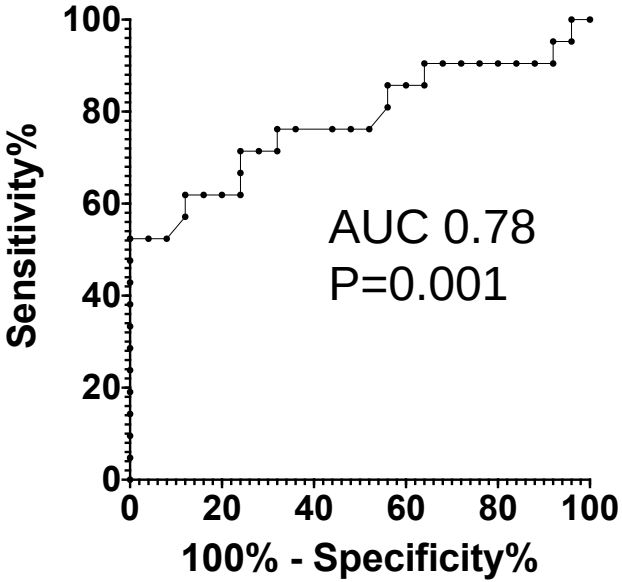


RNA reduction > 0.5log$_{10}$ at week 12

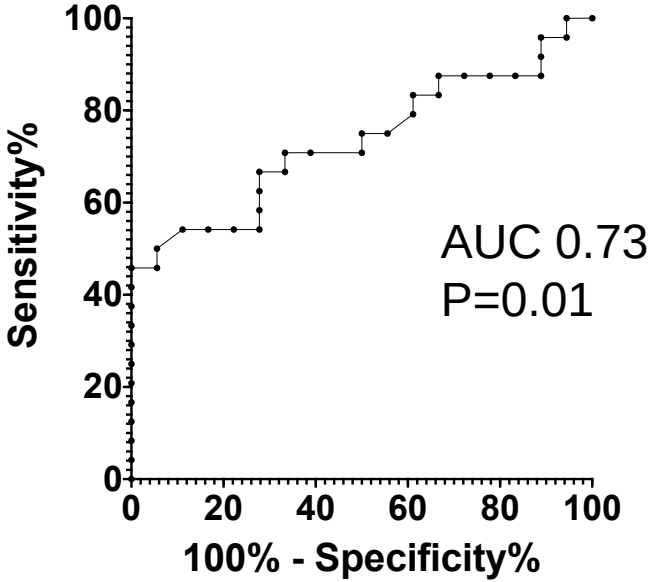


Reduction in serum IP-10 at week 12 predicts HBV DNA and HBV RNA response

DNA reduction > 0.75$\log_{10}$ at week 12



RNA reduction > 0.5$\log_{10}$ at week 12



INARIGIVIR ACHIEVE TRIAL SAFETY

- ALT flares > 200 IU/ml seen in 6 patients on Inarigivir and 3 patients on placebo
- Inarigivir flares associated with reduction in HBV DNA and HBsAg and occurred within 4 weeks of treatment
- No changes in bilirubin, INR or albumin seen with flares
- Per protocol dose reduction in 6 patients, 1 dose discontinuation for ALT > 400 IU/ml
- 1 grade 3 transient hypertriglyceridemia not sustained on retesting
- 1 hospitalization for unrelated knee pain
- No flu like symptoms, no IFN like side effects to date

SUMMARY

- Dose dependent response from 25mg to 10mmg Inarigivir monotherapy on HBV DNA and HBV RNA
- Response predicted by HBsAg baseline levels in both HBeAg positive and HBeAg negative patients
- HBV RNA response unique to Inarigivir, enhanced by TDF in HBeAg negative patients and results in a lower set point in HBeAg positive patients on 100mg inarigivir
- 28% of patients meet pre-defined responder criteria with a mean / median HBsAg decline 0.8$\log_{10}$
- Good safety and tolerability profile

CONCLUSIONS AND FUTURE DIRECTIONS

- Inarigivir is both a novel DAA and immuno-modulator
- 200mg and 400mg doses under study for full dose range
- 4 clinical trials for 2018/19
  - Inarigivir + TAF in treatment naïve (in Progress, Gilead Sciences)
  - Inarigivir in NUC suppressed patients (in Progress, Gilead Sciences)
  - “STOP and SHOCK” and “SUPPRESS and SHOCK” Global trials
  - Intra-hepatic virology and immunology Liver Biopsy study
  - Novel Combinations