FINAL RESULTS OF A PHASE 1B 28-DAY STUDY OF ABI-H0731, A NOVEL CORE INHIBITOR, IN NON-CIRRHOTIC VIREMIC SUBJECTS WITH CHRONIC HBV

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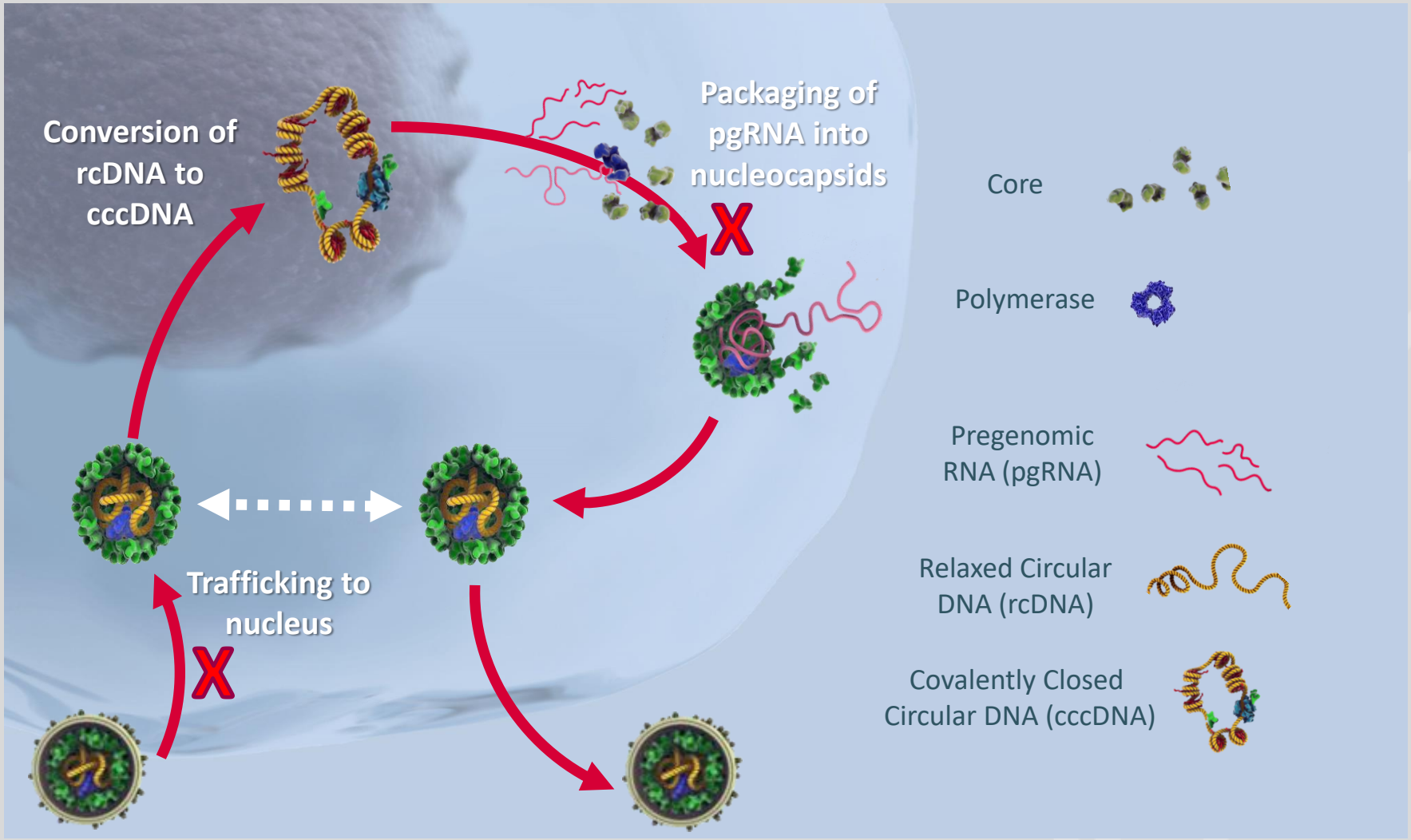
AASLD
AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES
San Francisco, CA
November 11, 2018

DISCLOSURES

Advisor: AbbVie, Arbutus, Arrowhead, Biocartis, Gilead Sciences, GSK, Ionis, Roche, Vir Biotechnology;

Received speaker and grant supports: AbbVie, Arrowhead, Bristol Myers Squibb, Fujirebio, Gilead Sciences, Merck Sharp & Dohme, Novartis Pharmaceuticals, Sysmex.

CORE INHIBITORS BLOCK VIRAL REPLICATION AND cccDNA ESTABLISHMENT



Core inhibition

- Unlike Nucs, Core Inhibitors block both production of new virus and trafficking of incoming nucleocapsid to nucleus, preventing establishment of new cccDNA
- Core Inhibitors have potential to be additive or synergistic with polymerase inhibitors

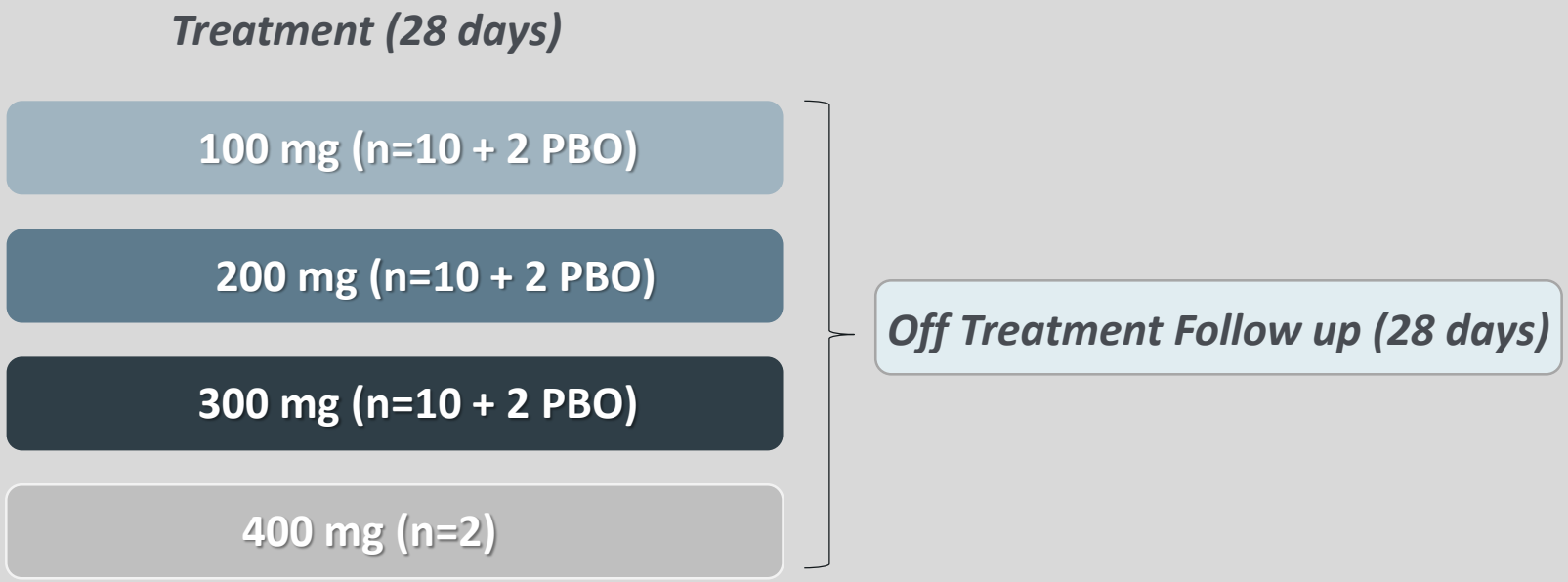
ABI-H0731: A POTENT CLINICAL STAGE CORE INHIBITOR

ABI-H0731 Preclinical Profile

- Potent and selective antiviral activity against all major HBV genotypes (A-E)
- Clean safety profile in animal studies (safety pharmacology, genotoxicity, reproductive and chronic toxicity studies)
- Excellent hepatocyte stability, minimal metabolism allowing QD dosing
- 20-30x liver/plasma ratio in primates

- >150 subjects dosed to date across all studies

PHASE 1b STUDY (101B) DESIGN: 28-DAY DOSING



- **Once-daily oral dosing**
- **HBeAg Pos and Neg patients (stratified 7:5)**

Objectives

Primary

- Dose-related safety and tolerability

Secondary

- Steady state human PK
- Dose-related antiviral effects
  - HBV DNA/RNA
  - HBsAg and HBeAg
  - Pre-existing and emergent resistance

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Parameter	ABI-H0731 QD Dosing				
	100 mg (N=10)	200 mg (N=10)	300 mg (N=10)	400 mg (N=2)	Placebo (N=6)
Male, n	9	9	9	2	6
Age, median yr	42	36	44	40	36
White, n	0	2	1	0	0
Asian, n	8	5	8*	2	6
BMI, median kg/m^2	24	28	25	27	22
Median Baseline ALT (IU/mL)	27	38	34	45	34

*One subject of mixed background

BASELINE VIROLOGY CHARACTERISTICS

Parameter		100 mg		200 mg		300 mg		400 mg	Placebo	
HBeAg (n)		Pos (6)	Neg (4)	Pos (5)	Neg (5)[d]	Pos (6)	Neg (4)	Neg (2)	Pos (3)	Neg (3)
Mean HBV DNA (Log_{10} IU/mL)		8.5	4.6	8.1	4.5	7.7	4.2	4.5	7.2	3.9
Mean HBsAg (Log_{10} IU/mL)		4.6	2.9	4.3	3.6	4.0	2.9	1.7	4.4	3.1
HBV RNA[a] (Log_{10} copies/mL)		7.3	2.8	7.1	4.9[b]	6.4	2.5	3.4	5.9	1.8[c]
Genotype, n	B	3	2	1	1	4	3	2	2	2
	C	2	1	3	0	2	0	0	1	1
	E	1	1	1	1	0	1	0	0	0
	A	0	0	0	3	0	0	0	0	0

[a]LOQ 4.04 Log_{10} copies/mL; [b]n=2/5 subjects detectable at Baseline; [c]n=2/4 detectable at Baseline; [d]1 subject was misstratified

OVERALL CLINICAL SAFETY SUMMARY

- ABI-H0731 was generally well tolerated, with no SAEs or dose limiting toxicities reported
- No dose related increases in number of AEs
- All but one TEAE was Grade 1 (mild)
- No treatment emergent clinical chemistry, hematology or coagulation abnormalities deemed treatment related/clinically significant

Summary of all Treatment-Emergent Adverse Events

Adverse Event Grade	Subjects with at least 1 TEAE, n (%)				
	100 mg (N=10)	200 mg (N=10)	300 mg (N=10)	400 mg (N=2)	Placebo (N=6)
Grade 1	9 (90%)	4 (40%)	6 (60%)	2 (100%)	4 (66.7%)
Grade 2	0	0	0	0	0
Grade 3	0	0	0	1 (50%)*	0

*Single Grade 3 AE was maculopapular in subject dosed at 400 mg; rash resolved following treatment discontinuation with no additional medical intervention required

ABI-H0731 PLASMA EXPOSURE LEVELS

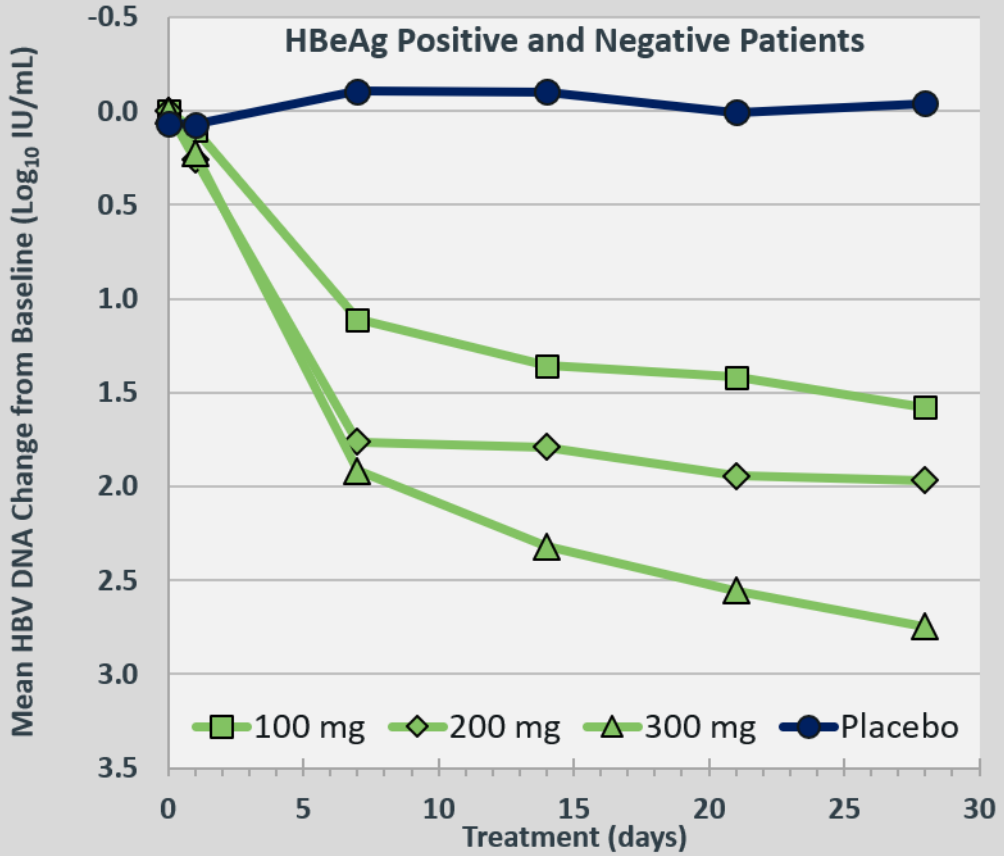
QD Dose	Steady State			Fold Accumulation*
	Mean C_{max} (ng/mL)	Mean C_{min} (ng/mL)	Mean AUC_{0-24} (ng*hr/mL)	
100 mg (n=10)	1,270	389	13,500	1.7
200 mg (n=10)	2,930	1,020	32,600	1.9
300 mg (n=10)	4,320	1,310	49,400	1.6
400 mg (n=2)	5,390	1,510	~50,000	1.8

*Steady state C_{max}/Day 1 C_{max}

- All patients exhibited good plasma exposure levels
- Minimal accumulation (<2-fold) observed
- Similar exposures between Caucasian and Asian patients *(data not shown)*

POTENT REDUCTIONS IN HBV DNA

- **Dose responsive declines; Reductions of up to 4.1 logs at 300 and 400 mg PO QD**
- **All subjects rebounded post therapy**

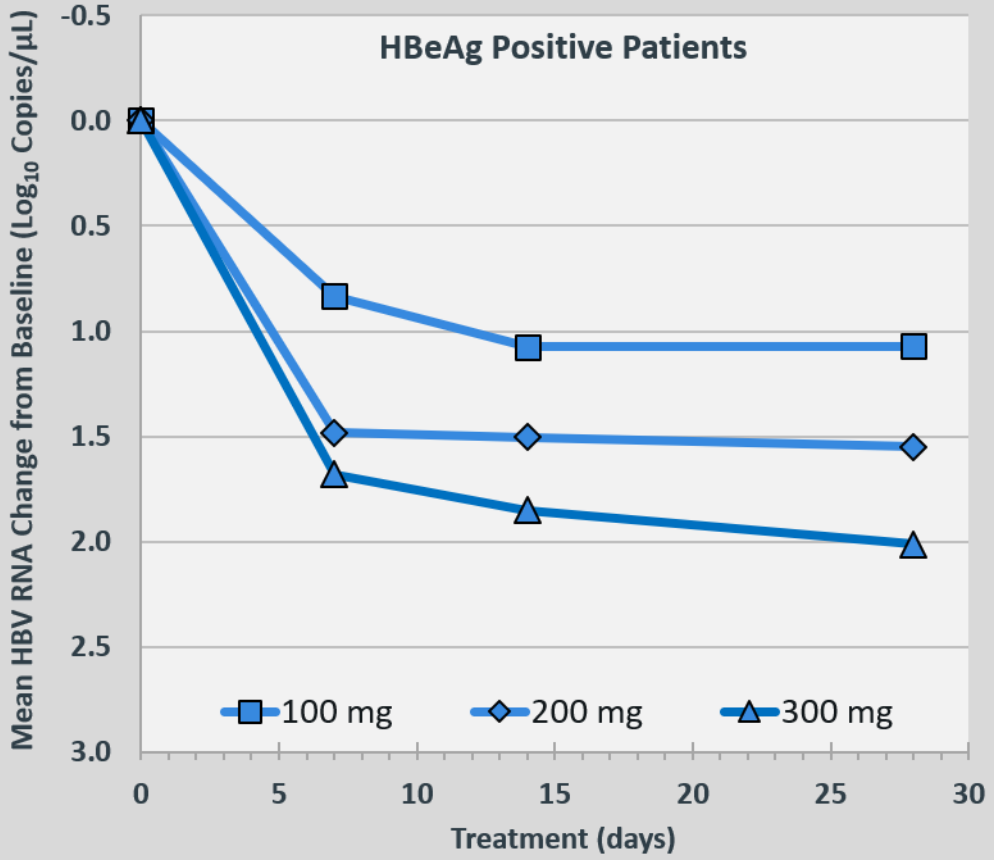


	Change from Baseline Log_{10} HBV DNA (IU/mL)			
Patients	**HBeAg Pos**		**HBeAg Neg**	
Dose (mg)	**N**	**Mean (Range)**	**N**	**Mean (Range)**
100 mg	6	1.3 (0.8 - 1.7)	4	2.2 (0.7 - 3.6)
200 mg	5	1.9 (1.0 - 2.6)	5	2.4 (1.5 - 3.8)
300 mg	6	2.9 (1.8 - 3.9)	3*	2.5* (0.8 – 4.1)
400 mg	0	NA	2	3.9 (3.9 –4.0)

*Excludes subject with known resistance at baseline

PARALLEL REDUCTIONS IN HBV RNA LEVELS

- HBV RNA reductions (1-2 logs) seen at all dose levels, and correlated with HBV DNA reductions ($p < 0.001$)
- Mechanism-based reduction in viral RNA levels is a differentiating feature of Core inhibitors



	Changes from Baseline	
Patients	HBeAg Pos	
Dose (mg)	N	Mean Copies/ uL (Range)*
100 mg	6	1.2 (0.7 - 1.6)
200 mg	5	1.7 (1.1 - 2.2)
300 mg	6	2.3 (1.7 – 2.6)
400 mg	0	NA

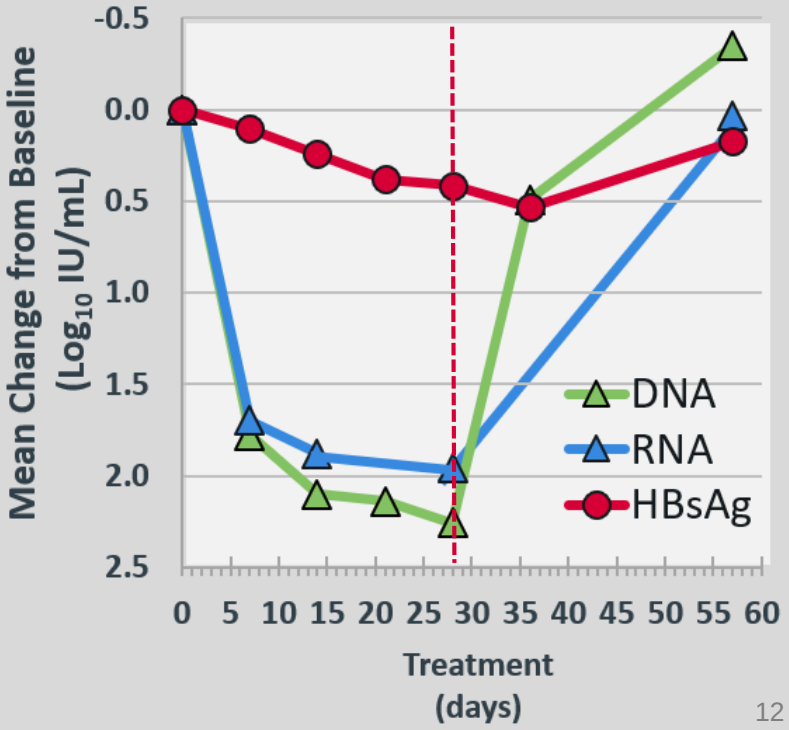
*Internal HBV RNA RT-qPCR assay, for HBeAg positive: LOQ = 10 copies/µL

HBeAg Neg patients

- RNA levels were lower at baseline and more difficult to quantitate
- All subjects with detectable RNA at baseline had RNA declines on treatment

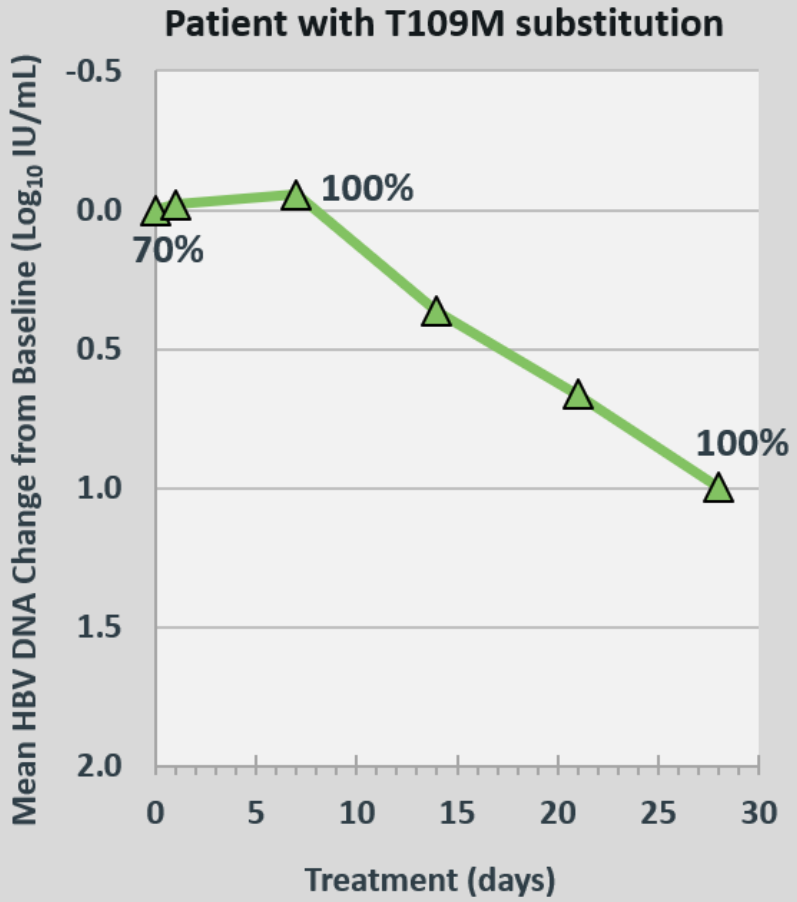
VIRAL ANTIGENS AND FLARES

- **No new flares developed on or post study**
- Among patients with abnormal liver function tests, most remained stable or showed improvement on therapy
- No significant changes seen in HBeAg or HBsAg levels, except in a single patient who was found to have a flare at baseline (ALT 399 U/L; pre-Dose)
- HBeAg positive patient (200 mg cohort) with Grade 3 ALTs at Baseline
  - Subject closely monitored
  - LFTs declined on treatment
  - Multi-log decline in HBV DNA and RNA levels
  - HBsAg declined ~0.5 log on treatment and then rebounded along with HBV DNA and RNA after therapy stopped



NO EMERGENCE OF NEW RESISTANCE VARIANTS

- All Baseline and end of treatment samples genotyped for pre-existing and emerging resistance mutations
- **No new resistant mutants found to emerge over 28-day monotherapy**
- Pre-existing resistant variants were identified
  - Single HBeAg neg patient (300 mg cohort) harbored a T109M substitution at Baseline, representing 70% of the viral population
  - T109M **enriched to 100**% by Day 8 in both the DNA **and RNA** populations
    - ***The enrichment in RNA suggests evolution of cccDNA pools in < 1 wk***
    - HBV DNA levels declined 1-log despite ~150-fold reduction in susceptibility
  - Three patients with Y38F substitution that enriched on treatment
    - No significant phenotypic resistance or correlation with clinical outcomes



SUMMARY AND CONCLUSIONS

- ABI-H0731 is a novel Core inhibitor with selective and potent activity against all major HBV genotypes
- Four dose levels (100, 200, 300 and 400 mg) of ABI-H0731 were tested in CHB patients
- ABI-H0731 was generally safe and well tolerated, with no SAEs or dose-limiting toxicities identified
  - All TEAEs were observed to be minor (Grade 1), with exception of isolated Grade 3 Rash that resolved rapidly without intervention other than treatment discontinuation
- All dose levels yielded potent antiviral activity, with overall Mean Maximal HBV DNA reductions of 2.8 Log_{10} IU/mL at 300 mg, and maximal declines of up to 4.0 log_{10} IU/mL
- Where measurable, reductions in HBV RNA correlated with HBV DNA decreases
- To date > 150 Healthy volunteers and patients with CHB have been dose with ABI-H0731

ABI-H0731 is currently undergoing Phase 2a clinical POC studies exploring 300 mg QD in combination with Nuc therapy

ACKNOWLEDGMENTS

The Patients!

The Clinical Study teams

- Queen Mary Hospital, HK
- Kings College Hospital, UK
- Auckland Clinical Studies, NZ
- Severance Hospital, Korea
- Hallyam University, Korea
- Asan Medical Center, Korea
- Linear Clinical Research, Australia
- Monash Health Australia
- St. Vincent's Hospital, Australia

Assembly Biosciences

- Sandy Liaw
- Eric Ruby
- Christine Schmidt
- Tina Hong
- Qi Huang
- Ran Yan
- Dawei Cai
- Richard Colonno
- Uri Lopatin