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Interim Safety and Efficacy Results of the ABI-H0731 Phase 2a Program Exploring the Combination of ABI-H0731 with Nuc Therapy in Treatment-Naive and Treatment-Suppressed Chronic Hepatitis B Patients

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Disclosures

- Consultant for Assembly Biosciences
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New Therapies Needed to Increase Cure Rates in CHB

Nucleos(t)ide polymerase inhibitors (Nuc)

- Are the standard of care (SOC)
- Inhibit conversion of pgRNA to dsDNA
- Exhibit potent reduction of viremia (DNA)
- Are safe and well tolerated
- Have a high barrier to resistance

BUT FAIL TO

- Eliminate **low-level** viremia
- Inhibit formation of cccDNA
- Achieve cure in vast majority of patients

Cure is not possible while residual virus persists

Core protein Inhibitors (CIs)

- Inhibit multiple steps in viral replication cycle
  - Packaging of pgRNA
  - DNA delivery to nucleus
  - **Generation of cccDNA**
- *In vitro,* can achieve deeper levels of viral inhibition than Nucs alone

HBV Core Inhibitor ABI-H0731

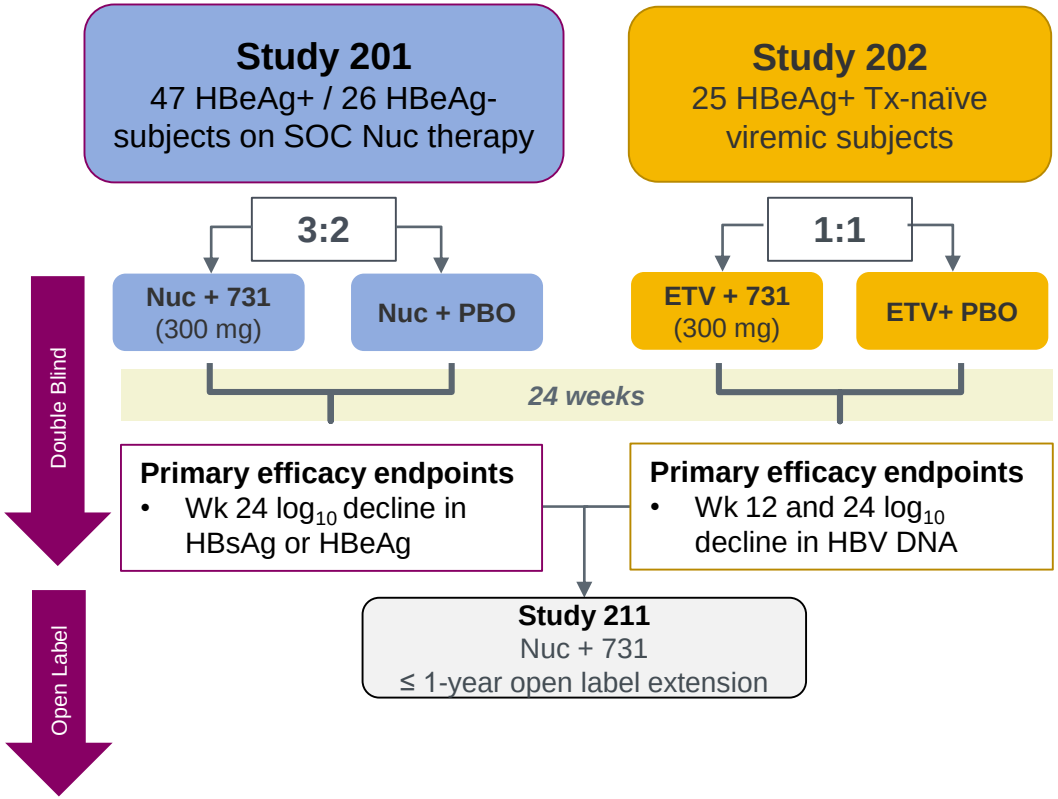
- Discovered and developed at ASMB
- Novel proprietary chemical class - DBAA (dibenzothiazepinecarboxamides)
- Well tolerated in Phase 1 studies
- Efficacious in a Phase 1b 28-day monotherapy study[1]
  - HBeAg pos patients (300 mg QD) exhibited
    - Mean DNA reduction = 2.9 $\log_{10}$ IU/mL
    - Mean RNA reduction = 2.0 $\log_{10}$ copies/mL

Phase 2 program explores critical steps needed to achieve higher cure rates

1. Elimination of viremia
2. Prevention of new cccDNA generation
3. Demonstrate viral suppression sustained off therapy

[1]Yuen et al, AASLD 2018

Interim Review of ABI-H0731 Phase 2a Studies



Key enrollment criteria

- Good general health
- Metavir F0-F2 or equivalent (no history of hepatic decompensation)
- **Study 201:** HBsAg > 400 IU/mL (HBeAg pos) or > 100 (HBeAg neg)
- **Study 202:** HBV DNA > 10^5 IU/mL

Additional Endpoints

- Safety and tolerability
- Change in $\log_{10}$ HBV RNA
- HBV DNA (PCR target not detected)
- Resistance monitoring

	D1	Wk 12	Wk 24
Study 201	73	65	11
Study 202	25	24	12

Demographics and Baseline Characteristics

	Study 201 (N = 73)		Study 202 (N = 25)
Demographics	**HBeAg Pos (n = 47)**	**HBeAg Neg (n = 26)**	**HBeAg Positive**
Age, mean (range) years	44 (19-66)	48 (34-64)	35 (19-66)
Female, n (%)	16 (34%)	10 (38%)	17 (68%)
Asian, n (%)	41 (87%)	21 (81%)	23 (96%)
Genotype B,C (%)	11,28 (83%)	4,8 (46%)	11,11 (88%)
Mean Baseline Values			
ALT (SD) U/L	27 (17)	25 (12)	57 (66)
HBV DNA (SD) $\log_{10}$ IU/mL	BLQ	BLQ	7.8 (0.8)
HBV RNA (range) $\log_{10}$ copy/mL	5.9 (2.4 -7.1) [a]	≤ 2.3 (2.4-3.2)[b]	8.0 (5.6-9.3)
HBsAg (range) IU/mL	5,569 (722-30,946)	2,970 (142-14,165)	57,179 (2,200-168,461)
HBeAg (range) PEU/mL	29 (0.14 - 400)	N/A	791 (0.18 to >1400 (ULQ))

[a] 37/47 patients with baseline RNA > 200; [b] 4/26 patients with RNA > 200 copies)

Interim Safety

Blinded, Pooled Safety – Summary: Well Tolerated with Favorable Safety Profile

Blinded Summary of TEAEs (Studies 201 and 202)

- No SAEs or treatment related discontinuations or interruptions
- Adverse events were mostly mild, infrequent, and considered unrelated to study drug
- No Flares on treatment
- No clinical AE > grade 2
- 3 patients with rash considered “possibly related” (2x grade 1, 1x grade 2); none associated with systemic findings
- Only 1 patient in each study has had a grade 2 AE considered possibly related to study drug
  - Macular/maculopapular rash–resolved on antihistamine, (Study 201)
  - ALT increase–resolved with continued treatment, (Study 202)

Blinded Pooled TEAE[1] Lab Abnormality ≥ 2 Patients (N = 98)

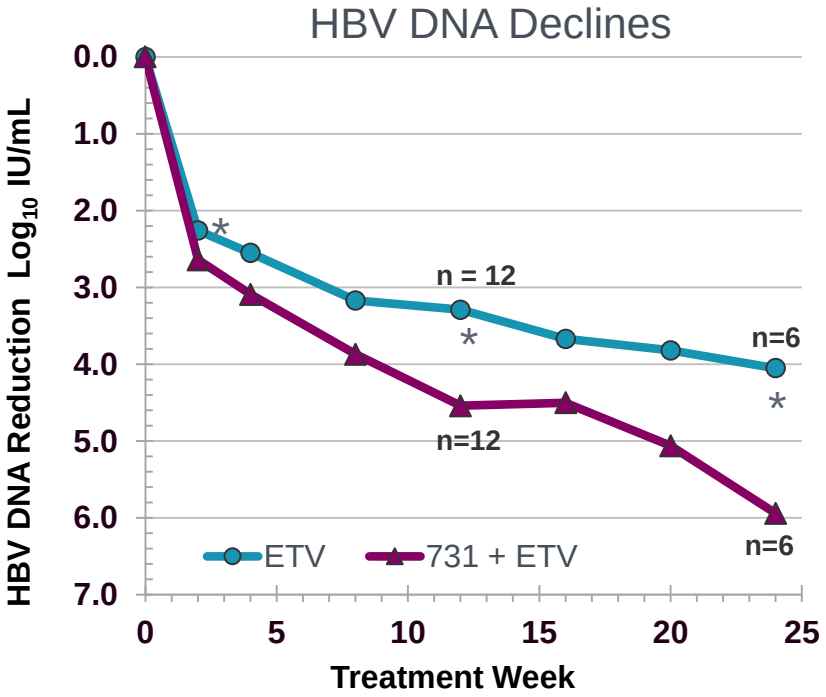
	Study 201 (N = 73)		Study 202 (N= 25)	
Lab Analyte	Grade 2 Patients, n(%)	Grade 3 Patients, n(%)	Grade 2 Patients, n(%)	Grade 3 Patients, n(%)
ALT (SGPT)	3 (4%)	--	4 (5%)	1[2](1%)
AST (SGOT)	3 (4%)	--	4 (5%)	--
Lipase	2 (3%)	--	1 (1%)	--
Lymphocytes	1 (1%)	1[3](1%)	--	--
Serum amylase	2 (3%)	--	3 (4%)	--
Serum glucose	3 (4%)	--	1 (1%)	--
Urine blood[4]	4 (5%)	--	--	--

[1] Treatment Emergent AE
[2] G3 ALT at entry to study,
[3] Transient, in context of and attributed to flu-like illness
[4] Attributed to menses
[5] ~60% of lab abnormalities overall on ABI-H0731, proportional to randomization

Study 202
Interim Antiviral Efficacy

Highly Viremic Subjects

Study 202: Superior DNA Reductions with 731 Combination



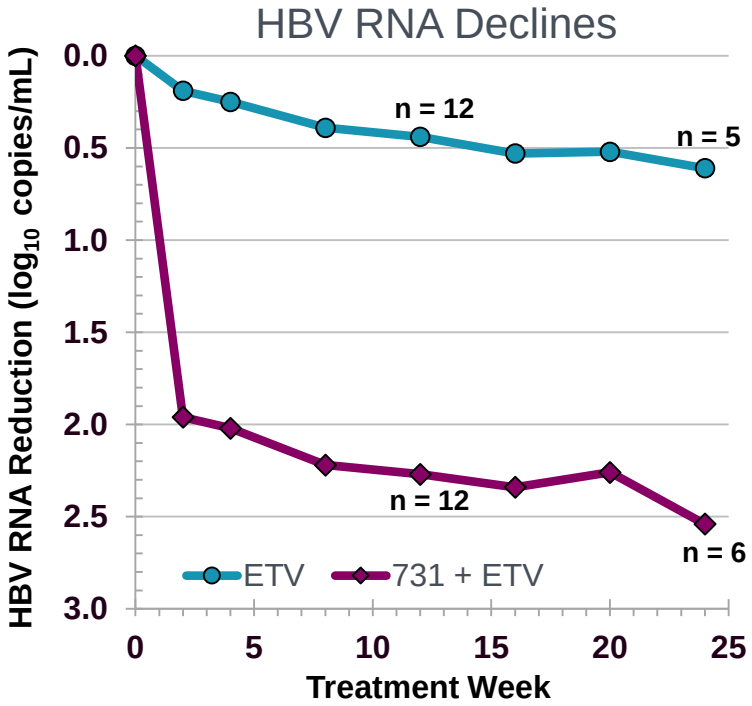
Mean Log_{10} HBV DNA Decline			
Week	**ETV**	**ETV + 731**	**P Value**
12	**3.29**	**4.54**	**<.011**
24	**3.99**	**5.94**	**<.005**

HBV DNA assessed by Roche Cobas qPCR; LOQ = 20 IU

- Significantly **faster** and **deeper** reductions in HBV DNA levels, as early as Week 2 (P=.03)
- Among subjects with abnormal ALT at entry, more rapid ALT normalization seen in combination arm
  - 5/7 vs. 0/5 by Week 4 (P <.05)
  - 7/7 vs. 2/5 by Week 12 (P <.05)

*Statistically significant at (P < .05 or better)

Study 202: Superior RNA Reductions with 731 Combination



Mean Log_{10} HBV RNA Decline			
Week	**ETV**	**731 + ETV**	**P Value**
12	**0.44**	**2.27**	**<.005**
24	**0.61**	**2.54**	**<.005**

HBV RNA assessed by RT qPCR; LOQ = 200 copies/mL

- **All patients on combination achieved a rapid decline in RNA levels**

Study 201
Interim Antiviral Efficacy

HBV DNA “Nuc Suppressed” Subjects

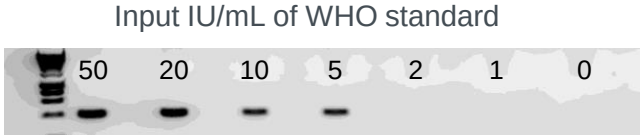
Elimination of Residual Viremia is an Important Unmet Medical Need

- **Nucs do not eliminate HBV viremia even after years on treatment**[1]

- **Detected DNA represents "infectious virus"**
  - ILC2019, PS-150: "Evidence for the presence of infectious virus in the serum from chronic hepatitis B patients suppressed on nucleos(t)ide therapy with detectable but not quantifiable HBV DNA"

- **A highly sensitive semi-quantitative PCR assay was developed at ASMB to detect viral DNA levels to 2-5 IU/mL to monitor loss of residual virus**

Assay Standardization and Validation

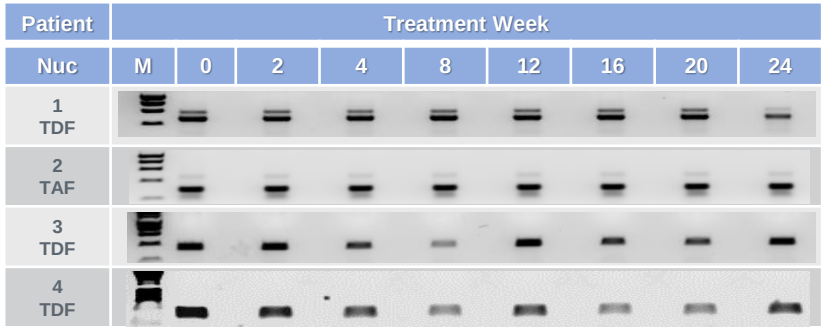


[1] Marcellin, et al, AASLD 2014, P1861

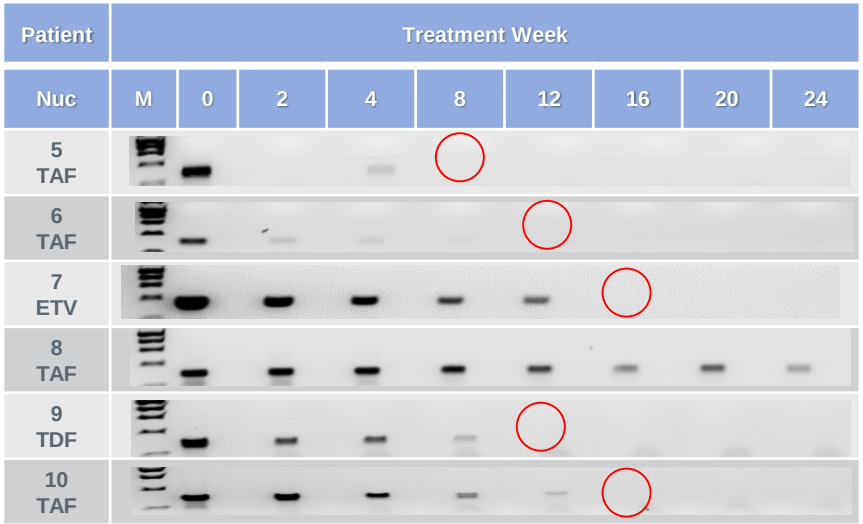
Study 201: Elimination of Detectable Virus Only on Combination

At Week 24, longitudinal serum samples were assayed for detectable virus

Nuc Monotherapy



731 Combo Therapy



HBV DNA PCR Assay To Quantitate Low Level Viremia

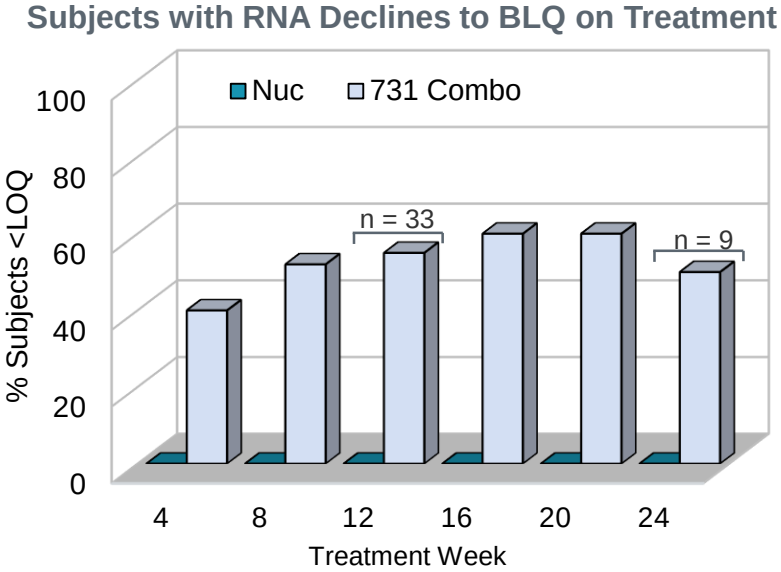
- DNA purified from longitudinal serum samples (0 – 24 Wk)
- PCR amplification (40-45 cycles) using individually optimized primers

Residual viremia not eliminated by Nuc

Residual viremia decline below detection (2-5 IU/mL)

Study 201: RNA Reductions to BLQ Only on Combination

HBeAg Positive Patients with RNA >LOQ at Baseline (N = 37)



Mean Log_{10} HBV RNA Decline			
Week	**Nuc**	**731 + Nuc**	**P Value**
12	**0.05**	**2.34**	**<.001**
24	**0.15**	**2.20**	**.012**

- All subjects on combination arm achieved rapid RNA declines
- **Of subjects with detectable baseline RNA, 60% of 731 combo subjects achieved RNA <LOQ (200 copies/mL) by Week 16 vs. 0% on Nuc arm**

Study 201: Antigen Declines at Interim Analysis

Patients Treated 24 Weeks*		
Treatment	**Nuc**	**731 + Nuc**
DNA (TND[1])	**0/4 (0%)**	**5/6 (83%)**
RNA (<200 Copies/mL)	**0/3 (0%)[2]**	**3/6 (50%)**
HBeAg ≥ 0.5 Log_{10} Decline	**0/3 (0%)**	**1/6 (17%)**
HBsAg ≥ 0.5 Log_{10} Decline	**0/4 (0%)**	**0/6 (0%)**

*Subjects with available data

[1] Target not detected by ASMB semi-quantitative PCR
[2] a 4th subject on Nuc was BLQ at baseline

- Antigen declines anticipated to follow elimination of residual viremia
- Study subjects continue to be treated and followed in open label Study 211
- Safety, viremia and viral antigens continue to be monitored over time

Summary of Interim Data for Phase 2a Studies on ABI-H0731

Favorable safety and tolerability profile

- AEs and lab abnormalities were generally considered unrelated, grade 1 and transient

Combination of 731+Nuc demonstrated superior antiviral activity vs. Nuc alone

- In treatment naïve patients, faster and deeper declines in HBV DNA observed starting at Week 2
- In Nuc “suppressed” patients, HBV DNA reductions to below limits of high-sensitivity PCR assay
- In both studies, significant HBV RNA declines

To prevent new cccDNA formation and increase cure rates, elimination of residual viremia will likely be required

- HBeAg and HBsAg decline are anticipated to follow elimination of viremia

Ongoing studies to define timelines to see cccDNA loss, sustained suppression & potential cure

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