LBP-012

Interim Safety, Tolerability, Pharmacokinetics, and Antiviral Activity of ABI-H0731, a Novel Core Protein Allosteric Modifier (CpAM), in Healthy Volunteers and Non-Cirrhotic Viremic Subjects with Chronic Hepatitis B

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Introduction

- Currently approved treatments for chronic HBV include nucleos(t)ide analogs (Nuc), such as entecavir (ETV) and tenofovir, and interferons (IFN and PEG-IFN)[1]. While Nuc therapy is highly effective at inhibiting HBV replication for prolonged periods, sustained clearance of viremia off treatment only occurs in <10% of treated patients. New classes of anti-HBV molecules are needed to significantly improve cure rates.
- HBV core protein (Cp) plays a critical role in multiple steps of the HBV life cycle, including formation and amplification of cccDNA. A novel class of direct-acting HBV antivirals, Core Protein Allosteric Modifiers (CpAMs), has been discovered and developed to target HBV Cp and inhibit cccDNA formation in cell-based assays[2].
- ABI-H0731 is a potent and selective orally available CpAM that exhibits potent antiviral activity in Primary Human Hepatocytes, is pangenotypic (A, B, C, and D) and retains activity against Nuc-resistant variants[2,3]. In addition, ABI-H0731 possesses favorable DMPK properties, such as excellent metabolic stability in hepatocytes and a $T_{1/2}$ of ~24 hr in humans[3].
- Here we report preliminary clinical data obtained on ABI-H0731 in two clinical studies
  - ABI-H0731-102: A 14-day repeat dose study in healthy adult volunteers evaluating the safety and pharmacokinetics of multiple dose levels of orally administered ABI-H0731
  - ABI-H0731-101(B): An ongoing 28-day repeat dose study in otherwise healthy, non-cirrhotic adults with chronic hepatitis B (CHB) evaluating the safety, pharmacokinetics, and antiviral efficacy of multiple dose levels of orally administered ABI-H0731

References

[1]*EASL 2017 Clinical Practice Guidelines on the management of HBV infection. Journal of Hepatology. (2017)*
[2]*Huang, Qi et al. Blockade of HBV Virus Replication and Inhibition of cccDNA Establishment by CpAMs. Poster 1897, AASLD. (2016)*
[3]*Huang, Qi et al. Preclinical Characterization of Potent CpAMs for the Treatment of Chronic Hepatitis B. Poster 104, EASL. (2016)*

Key Study Objectives

Primary Objectives

- Assess the dose-related safety and tolerability of ABI-H0731 after multiple oral doses in healthy human volunteers (Study ABI-H0731-102) and in CHB Patients (Study ABI-H0731-101(B))

Secondary Objectives

- Assess steady state human pharmacokinetics following multiple oral doses of ABI-H0731
- Assess the dose-related antiviral efficacy of ABI-H0731 during short-term (28 day) monotherapy as measured by absolute changes in HBV viral load (DNA and RNA)
- Evaluate effects on HBV surface antigen (HBsAg) and HBV E antigen (HBeAg, where applicable)
- Monitor for pre-existing and emergence of ABI-H0731 resistance, if any

Key Inclusion/Exclusion Criteria

Studies ABI-H0731-102 and ABI-H0731-101(B)

- Able and willing to give informed consent
- Male or female between 18 and 65 years of age, BMI 18-32/38 kg/m^2 *(102/101(B))*
- No history of chronic/recurrent medical conditions requiring frequent medical interventions
- No clinically significant abnormalities at time of screening
- No ongoing illness at time of screening or within 30 days prior to study start
- No medical condition that may interfere with the absorption, distribution, or elimination of study drug (ABI-H0731), or with the clinical and laboratory assessments in this study
- No participation in a study of another investigational agent in the last 60 days

Study ABI-H0731-101(B)

- Chronic Hepatitis B infection (HBsAg positive for at least 6 months)
- HBV viral loads at screening: HBeAg positive ≥2 x 10^4 IU/mL and HBeAg negative ≥2 x 10^3 IU/mL
- Clinical history compatible with compensated liver disease with no evidence of cirrhosis by biopsy or imaging study (Metavir F0-F2 or equivalent)

Study Design

Study ABI-H0731-102

Once daily dosing of ABI-H0731/placebo (10:2) in healthy volunteers, in a fed state

Treatment 14 days	Off Treatment 7 days
100 mg PO QD (n=12)	*Follow up*
200 mg PO QD (n=12)	*Follow up*
300 mg PO QD (n=12)	*Follow up*

Study ABI-H0731-101(B)

Once daily dosing of ABI-H0731/placebo (10:2) in CHB HBeAg positive and HBeAg negative patients stratified 7:5, respectively

Treatment 28 days	Off Treatment 28 days
100 mg (n=12)	*Follow up*
200 mg (n=12)	*Follow up*
300 mg* (n=12)	*Follow up*
400 mg* (n=2)	*Follow up*

*Ongoing or incomplete

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Demographics and Baseline Characteristics

QD Dose	ABI-H0731-102				ABI-H0731-101(B)				
	100 mg (n=10)	200 mg (n=10)	300 mg (n=10)	Placebo (n=6)	100 mg (n=10)	200 mg (n=10)	300 mg (n=10)	400 mg (n=2)	Placebo (n=6)
Male, n (%)	10 (100)	9 (90)	10 (100)	5 (83)	9 (90)	9 (90)	9 (90)	2 (100)	6 (100)
Age, median yr (range)	48 (32 - 61)	33 (24 - 55)	37 (22 - 63)	37 (30 - 54)	42 (26 - 55)	36 (26 - 55)	44 (32 - 65)	40 (31,48)	36 (27 - 48)
White, n (%)	6 (60)	3 (30)	4 (40)	2 (33)	0	2 (20)	1 (10)	0	0
Asian, n (%)	1 (10)	1 (10)	0	1 (17)	8 (80)	5 (50)	8* (80)	2 (100)	6 (100)
BMI, median kg/m^2 (range)	27 (23 - 31)	27 (22 - 31)	27 (22 - 31)	27 (23 - 30)	24 (20 - 31)	28 (22 - 36)	25 (20 - 28)	27 (22,32)	22 (21 - 25)
Median Baseline ALT, IU/mL (range)	23 (15 - 3)	19 (16 - 47)	23 (14 - 117)	22 (12 - 27)	27 (15 - 40)	38 (9 - 399)	34 (23 - 57)	45 (40,50)	34 (18 - 37)

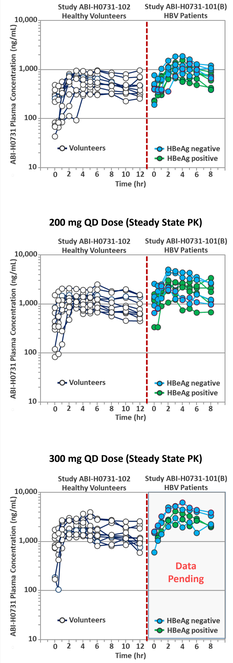
*One subject of mixed background

ABI-H0731-101(B) - Baseline Virology Characteristics

QD Dose		100 mg (n=10)		200 mg (n=10)		300 mg (n=10)		400 mg (n=2)	Placebo (n=6)	
HBeAg (n)		Pos (6)	Neg (4)	Pos (6)	Neg (4)	Pos (6)	Neg (4)	Neg (2)	Pos (3)	Neg (3)
Mean HBV DNA Log_{10} IU/mL (SD)		8.5 (±0.3)	4.4 (±1.0)	8.4 (±0.6)	4.0 (±1.6)	7.8 (±0.6)	4.3 (±0.2)	4.6 (±0.8)	7.9 (±2.0)	3.4 (±0.8)
Mean HBsAg IU/mL		4.7 x 10^4	1 x 10^3	3.4 x 10^4	2 x 10^5	1.6 x 10^4	2.2 x 10^3	2.8 x 10^2	1.9 x 10^4	4.7 x 10^3
HBV RNA[a] Log_{10} Copies/mL		7.2	2.8	6.8	4.2[b]	6.3[c]	2.5	3.4	5.9	1.8[d]
Genotype, n (%)[e]	B	3 (50)	2 (50)	1 (17)	1 (25)	4 (67)	3 (75)	2 (100)	2 (67)	2 (67)
	C	2 (33)	1 (25)	3 (50)	0	2 (33)	0	0	1 (33)	1 (33)
	E	1 (17)	1 (25)	1 (17)	1 (25)	0	1 (25)	0	0	0
	A	0	0	1 (17)	2 (50)	0	0	0	0	0

[a]LOQ 10^4 copies/mL; [b]n=1/4 subjects detectable at Baseline; [c]n=5/6 available at Baseline; [d]n=2/4 detectable at Baseline; [e]Genotyping performed by sequencing HBsAg region or by WGS when available

PK Parameters



QD Dose		Day 1 Mean C_{max} (ng/mL)[a] ±SD	Day 1 Mean $AUC_{0\text{-}24}$ (ng*hr/mL) ±SD	Steady State Mean C_{max} (ng/mL) ±SD	Steady State Mean C_{min} (ng/mL) ±SD	Steady State Mean $AUC_{0\text{-}24}$ [a] (ng*hr/mL) ±SD	Accumulation (Steady State/ Day 1)
ABI-H0731-102	100 mg (n=10)	501 ±161	6,080 ±1,310	717 ±187	263 ±142	11,500 ±4,040	1.9
	200 mg (n=10)	911 ±217	11,200 ±2,760	1,540 ±501	651 ±490	22,900 ±10,300	2.0
	300 mg (n=10)	1,620 ±621	19,000 ±5,640	2,380 ±948	943 ±464	36,100 ±14,200	1.9
ABI-H0731-101(B)	100 mg (n=10)	768 ±292	7,950 ±2,920	1,270 ±343	389 ±216	13,500 ±4,990	2.2
	200 mg (n=10)	1,560 ±344	16,100 ±3,680	2,930 ±1,110	1,020 ±632	32,600 ±14,100	2.0
	300 mg (n=10)[c]	2,640 ± 873	25,300 ± 6,370	4,320 ±1,470	1,310 ±436	49,400 ± 16,700	2.0
	400 mg (n=2)	2,980	32,400	5,390[b]	1,510[b]	~50,000[b]	1.8[b]

[a]Extrapolated for Study ABI-H0731-101(B); 300 mg cohort reflects partial data; [b]n = 1; [c]Includes 10 Baseline and 5 Steady State samples

Methods

- Plasma concentrations of ABI-H0731 were determined using a validated liquid chromatography mass spectrometry method
- PK parameters were determined by non-compartmental methods, using Phoenix WinNonLin

Study ABI-H0731-102

- Twelve healthy volunteers/cohort randomized 10:2 (ABI-H0731:Placebo) received indicated oral QD doses of CpAM under fed conditions
- Intensive PK samples obtained on Day 1 and Day 14

Study ABI-H0731-101(B)

- Twelve CHB patients/cohort randomized 10:2 (ABI-H0731:Placebo) received indicated oral QD doses of CpAM under fed conditions
- Intensive PK samples obtained on Day 1 and either on Day 15 or Day 22

Conclusions

- Plasma exposure levels similar between healthy volunteers and non-cirrhotic CHB patients, with a trend towards higher exposure seen in patients
- Minimal accumulation (approximately 2-fold) was seen at steady state over Baseline in both populations
- All patients exhibited good absorption and exposure levels

Clinical Safety and Tolerability

Topline Summary*

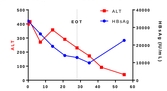
- Generally well tolerated, with no SAEs reported
- No clinically significant or persistent/worsening vital sign abnormalities reported
- Most Treatment-Emergent Adverse Events (TEAEs) occurred as single events
- All TEAEs (n=6 in Study ABI-H0731-102; n=65 in Study ABI-H0731-101(B)) were Grade 1 (mild), except for a single subject with a Grade 3 AE of Rash in the 400 mg Cohort of ABI-H0731-101(B), leading to treatment discontinuation

Treatment-Emergent Adverse Events (TEAE)*

- **ABI-H0731-102**: 6 Grade 1 AEs (Headache, Dizziness, Abdominal Pain, Lightheadedness, Nausea, Vasovagal Response) were noted among 30 volunteers treated with ABI-H0731, none were deemed related to study drug
- **ABI-H0731-101(B)**: 65 TEAEs were noted across all cohorts, (27 subjects with TEAEs across 38 total subjects)
  - There was no dose related increases in AEs
  - 10 unique TEAEs observed in 8 subjects were deemed to be possibly or probably related to ABI-H0731 (Increased Appetite, Diarrhea, Abdominal Pain, Insomnia, Postural Dizziness, Pruritus, Rash, Mouth Ulceration, and Dizziness [x2])
  - One Grade 3 Rash occurred in a 46 year old Asian male on Day 10 of dosing, after a seafood meal. The subject had not previously experienced allergies to seafood, and the rash was deemed probably related to study drug; treatment was discontinued and the rash resolved rapidly over subsequent visits without additional medical intervention, and no new AEs nor associated laboratory abnormalities
  - With possible exception of the isolated patient with rash, no relationship was seen between ABI-H0731 dose or duration for any AE across either study
  - Most common AEs (≥2 subjects, inclusive of placebo) independent of relatedness were Diarrhea (x2), Dizziness (x2), Fatigue (x2), Headache (x3), Hypertension (x2), Influenza-like Illness (x3), Pruritus (x3), and Oropharyngeal Pain (x3)

Treatment-Emergent Laboratory Abnormalities*

- There were no clinical chemistry, hematology, or coagulation abnormalities deemed treatment related and clinically significant in either study
- The majority of treatment-emergent laboratory abnormalities were low grade (1-2) and/or deemed spurious
- Lab abnormalities were scattered with no apparent target body system pattern, there was no clear relationship seen between clinical laboratory abnormalities and treatment, duration, or dose across either study
- Among those CHB patients in ABI-H0731-101(B) who entered the study with abnormal liver function tests (LFTs) and received ABI-H0731, most were either stable or showed improvement or resolution of liver function during the study
  - No subjects developed a new liver "flare" on or post study
  - One subject in Study ABI-H0731-101(B) had normal ALT on treatment, had transient Grade 1 ALT elevation (52) at Day 29 (post treatment)
  - One subject in Study ABI-H0731-102 noted to have elevated ALT to 117 at Day 1 (pre-dose), which resolved on treatment
  - One subject in Study ABI-H0731-101(B) (HBeAg positive, 200 mg) had a severe ALT elevation (ALT = 399) on Day 1 (prior to dosing), with associated elevations noted in both AST and Bilirubin; the lab abnormalities were deemed most likely due to a pre-treatment virus-induced flare, and the subject continued on treatment. The subject LFTs declined, accompanied by a 2.3 log decline in HBV DNA and ~0.5 log reduction in HBsAg that rebounded soon after the subject stopped therapy



Pooled Safety Summary*

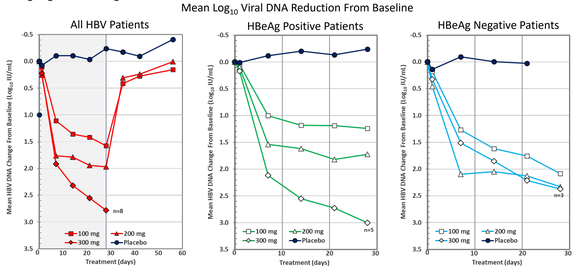
QD Dose	100 mg (n=20)	200 mg (n=20)	300 mg (n=20)	400 mg (n=2)	Placebo (n=12)
Total[a] TEAEs (ABI-H0731-101(B)/-102)	24 (24/0)	15 (12/3)	12 (10/2)	5 (5/0)	9 (8/1)
Grade 1 AEs (possibly or probably related)	24 (6)	15 (1)	12 (1)	4 (1)	9
Grade 2 AEs (possibly or probably related)	0	0	0	0	0
Grade 3 AEs (possibly or probably related)	0	0	0	1 (1)[b]	0
Most Common AEs (≥2 subjects)[c]					
Influenza-like Illness	3	0	0	0	0
Headache	2	3	0	0	0
Fatigue	1	1	0	1	0
Pruritus	2	0	1	0	0
Hypertension	1	1	0	0	0
Dizziness	0	2	1	0	0
Diarrhea	1	0	0	0	1
Oropharyngeal Pain	0	0	1	0	2

*Study is ongoing, results shown are interim data at the time of poster generation
[a]AE Preferred Term: unique count, highest severity scored; [b]Rash leading to discontinuation; [c]In either study

Overall Antiviral Efficacy*

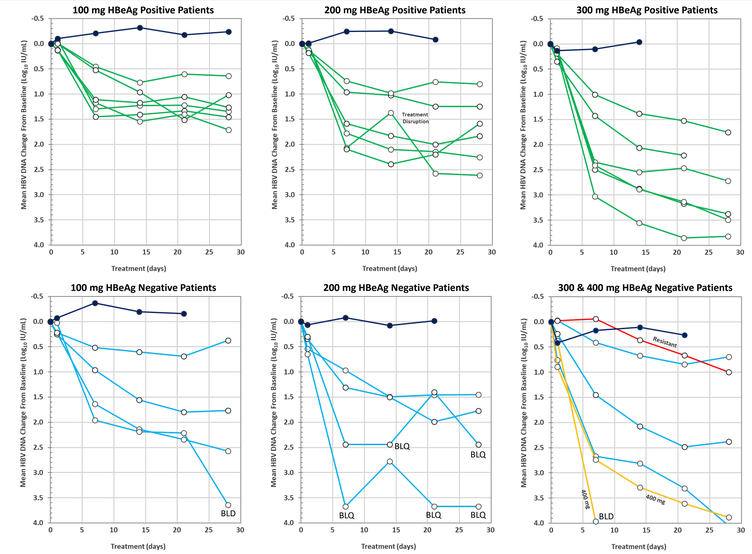
- Cohorts composed of 6 HBeAg positive and 4 HBeAg negative patients were treated with ABI-H0731 for up to 28 days
- At time of data cutoff, 100 mg QD and 200 mg QD cohorts have been fully enrolled and completed dosing, dosing is ongoing in the 300 mg cohort

Mean Log_{10} Viral DNA Reduction From Baseline



*Study is ongoing, results shown are at the time of this poster generation

Antiviral Efficacy



- In this ongoing Phase 1B study ABI-H0731-101(B), ABI-H0731 demonstrated significant antiviral effects at all dose levels tested
- Overall HBV viral DNA reductions increased with increasing dose
- HBV DNA levels <LLOQ were noted in four HBeAg negative patients (1 at 100 mg, 2 at 200 mg, 1 at 300 mg and 1 at 400 mg)
- Three HBeAg negative patients (1 in 100 mg and 2 in 300 mg cohorts) had unexpectedly weak responses
  - 1 patient (300 mg cohort) harbored a known CpAM-resistant variant (T109M) at Baseline and still exhibited a 1.0 log decline
  - 2 patients have no evidence of known resistance mutations and are being evaluated for the possibility of uneven compliance or reduced susceptibilities
- Ongoing resistance monitoring has not identified any other patients with evidence of pre-existing or emerging CpAM-resistant mutations (data not shown)
- All patients had quantitative RNA levels evaluated at Baseline and on treatment; the majority of HBeAg negative subjects had RNA viral loads that were the limits of reproducible quantitation at Baseline and on treatment, while HBeAg Positive patients showed consistent HBV RNA reductions of proportional magnitude to their HBV DNA reductions (data not shown)
- Other than the individual subject who began with an ALT flare, no significant changes were seen in serum HBsAg, HBeAg, or HBV core-related antigen over 28 days on monotherapy

Summary Statistics of HBV DNA Reductions[a]

Cohort (QD Dose)	Number of Subjects Who Completed Treatment		Mean Change from Baseline Log_{10} IU/mL (Range)			Median Change from Baseline Log_{10} IU/mL (Range)		
	HBeAg Positive	HBeAg Negative	Overall Cohort	HBeAg Positive	HBeAg Negative	Overall Cohort	HBeAg Positive	HBeAg Negative
100 mg	6	4	1.7 (0.7 - 3.6)	1.3 (0.8 - 1.7)	2.2 (0.7 - 3.6)	1.5 (0.7 - 3.6)	1.4 (0.8 - 1.7)	2.2 (0.7 - 3.6)
200 mg	6	4	2.1 (1.0 - 3.7)	1.9 (1.0 - 2.6)	2.4 (1.5 - 3.7)	2.1 (1.0 - 3.7)	2.1 (1.0 - 2.6)	2.2 (1.5 - 3.7)
300 mg	5	4	≥2.8[b] (0.8 - 4.0)	≥2.9 (1.8 - 3.9)	2.5[b] (0.8 - 4.0)	≥2.7[b] (0.8 - 4.0)	≥3.0 (1.8 - 3.9)	2.5[b] (0.8 - 4.0)
400 mg	0	2	NA	NA	3.9 (3.9 – 4.0)	NA	NA	3.9 (3.9 – 4.0)

[a]Study is ongoing, results shown are at the time of this poster generation
[b]Excludes patient with resistance mutation at Baseline
NA = Not applicable

Summary and Conclusions

- ABI-H0731 is a novel CpAM with selective and potent activity against all major HBV genotypes
- Four dose levels (100 mg, 200 mg, 300 mg and 400 mg) of ABI-H0731 were or are being evaluated in volunteers and/or CHB patients
- ABI-H0731 PK is similar in healthy volunteers and non-cirrhotic CHB patients, with steady state exposures achieved in ≤5 days, and approximately 2-fold accumulation observed following prolonged daily exposure, with no evidence of induced elimination
- ABI-H0731 was generally safe and well tolerated
  - No SAEs or dose-limiting toxicities were identified
  - No pattern of treatment-emergent clinical or laboratory abnormalities was observed
  - Among the 62 patients and volunteers treated in these two studies, all TEAEs were observed to be minor (Grade 1), with the exception of an isolated Grade 3 Rash that resolved rapidly without intervention other than treatment discontinuation
- All doses of ABI-H0731 administered in the ongoing ABI-H0731-101(B) efficacy study demonstrated potent overall antiviral activity, with the Mean Maximal HBV DNA reductions from Baseline of ≥2.8 Log_{10} IU/mL, and maximal declines from Baseline of up to 4.0 log_{10} IU/mL in patients treated at both the 300 mg (treatment ongoing) and 400 mg dose levels
- Where measurable, reductions in HBV RNA were (as expected by MOA), proportional to those seen in HBV DNA (data not presented)
- These data support the advancement of ABI-H0731 into Phase 2A clinical POC studies in combination with Nuc therapy in 2018