Safety, pharmacokinetics, and antiviral activity of the next-generation hepatitis B core inhibitor ABI-H3733 in patients with hepatitis B e antigen negative chronic hepatitis B infection: Preliminary results from a randomized, blinded, Phase 1b study

SAT-168

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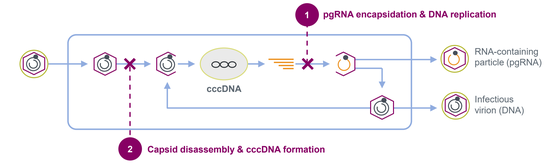
Background

- Chronic hepatitis B virus infection (cHBV) is a significant global health problem affecting an estimated 296 million people worldwide and resulting in approximately 820,000 deaths yearly, largely due to cirrhosis and hepatocellular carcinoma[1-4]
- In most patients, nucleos(t)ide reverse transcriptase inhibitors (NrtIs) are well tolerated and provide adequate on-treatment viral suppression. However, for the majority of patients, virologic responses are not maintained after stopping NrtIs, thus requiring lifelong treatment[5-7]
- Novel combination approaches may provide durable virologic outcomes following finite treatment durations and reduce the number of patients requiring lifelong therapy
- Core inhibitors are a novel class of antivirals that interfere with multiple steps of the HBV lifecycle
  - These agents work through inhibition of pregenomic (pg)RNA encapsidation, preventing assembly and release of infectious viral particles, and disruption of incoming capsids, preventing covalently closed circular (ccc)DNA formation (**Figure 1**)[8]
  - In Phase 1b studies, core inhibitors have demonstrated potent antiviral effects[9-11] and in Phase 2 studies, additive antiviral activity when combined with NrtIs compared to NrtIs alone[12,13]
- ABI-H3733 (3733) is a novel, next-generation core inhibitor that has demonstrated increased in vitro potency against HBV DNA replication and cccDNA formation compared with first-generation agents[14-15]

Figure 1. HBV Core Inhibitor Mechanisms of Action



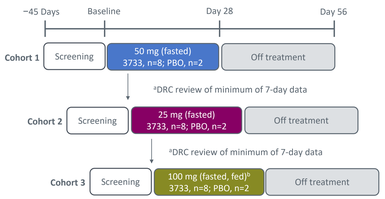
cccDNA, covalently closed circular DNA; HBV, hepatitis B virus; pgRNA, pregenomic RNA.

Objective

- The objective of this analysis is to describe the safety, pharmacokinetics (PK), and antiviral activity of 3733 in hepatitis B e antigen (HBeAg) negative patients with cHBV from a 28-day randomized, blinded, multiple-dose escalation study (NCT05414981)

Methods

Figure 2. Study Design



[a]Data Review Committee (DRC) review of minimum 7-day safety, PK, and antiviral data from 5 patients before the next cohort starts. [b]Fasted through Day 27; food-effect evaluation was conducted on Day 28.
3733, ABI-H3733; BMI, body mass index; BW, body weight; cHBV, chronic hepatitis B virus infection; HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; HIV, human immunodeficiency virus; PBO, placebo; PK, pharmacokinetics.

Key inclusion criteria

- Male or nonpregnant female, aged 18-65 years
- BMI ≥18.0 kg/m^2 and <35.0 kg/m^2 and BW ≥45 kg
- Documented cHBV ≥6 months
- HBeAg positive or negative
- Treatment naïve or off antiviral therapy for ≥24 weeks
- Lack of bridging fibrosis or cirrhosis

Key exclusion criteria

- Coinfection with HIV, HCV, HDV, HAV, or HEV
- History of liver transplant, advanced liver disease, cirrhosis, hepatic decompensation, or HCC
- Clinically significant diseases or conditions
- Current or prior cHBV treatment

- This study planned to enroll up to 5 cohorts each consisting of approximately 10 patients, for a maximum of 50 patients total. Three cohorts have completed enrollment and treatment (**Figure 2**)
- In each cohort, patients were to be randomized 8:2 to 3733 or placebo once daily for 28 days with an off-treatment follow-up period of 28 days
- Safety assessments included physical exams, vital signs, adverse events (AEs), lab parameters, and electrocardiogram testing
- 3733 PK parameters and viral biomarkers were assessed throughout
- HBV DNA values below the lower limit of quantification (LLOQ; <20 IU/mL) were imputed as 10 IU/mL (1.0 $\log_{10}$ IU/mL) for analysis of change from baseline
- The presented data summarizes HBeAg negative patients from the 3 completed cohorts assessing 25-mg, 50-mg, and 100-mg doses of 3733

Results

Table 1. Demographics and Baseline Characteristics

Characteristics	25-mg Cohort		50-mg Cohort		100-mg Cohort	
	3733 n=7	PBO n=2	3733 n=8	PBO n=1	3733 n=7	PBO n=2
Age, years	42.0 (5.1)	41.0 (15.6)	40.0 (5.2)	36.0 (NA)	43.0 (9.5)	39.0 (7.8)
Sex, n (%)						
Male	4 (57.1)	2 (100.0)	6 (75.0)	1 (100.0)	6 (85.7)	2 (100.0)
Female	3 (42.9)	0	2 (25.0)	0	1 (14.3)	0
Race, n (%)						
White	6 (85.7)	2 (100.0)	7 (87.5)	1 (100.0)	6 (85.7)	2 (100.0)
Asian	1 (14.3)	0	1 (12.5)	0	1 (14.3)	0
BMI, kg/m^2	27.1 (4.2)	27.3 (2.5)	22.1 (3.6)	30.9 (NA)	27.1 (3.3)	30.0 (1.3)
Time HBV Positive,[a] years	13.9 (10.7)	8.6 (11.2)	9.0 (7.6)	6.0 (NA)	12.3 (9.0)	3.8 (4.6)
HBV DNA, $\log_{10}$ IU/mL	4.5 (1.0)	4.3 (0.3)	4.3 (0.8)	3.3 (NA)	4.0 (0.7)	4.1 (1.4)
HBV pgRNA, $\log_{10}$ U/mL	1.9 (0.9)	1.4 (0)	1.7 (0.7)	1.4 (NA)	1.7 (0.6)	1.8 (0.7)
<LLOQ, n (%)	5 (71.4)	2 (100.0)	6 (75.0)	1 (100.0)	5 (71.4)	1 (50.0)
HBsAg, $\log_{10}$ IU/mL	3.8 (0.6)	3.2 (0.2)	3.6 (0.7)	3.9 (NA)	3.6 (0.8)	3.8 (0.9)
HBcrAg, $\log_{10}$ kU/mL	0.4 (0.8)	-0.1 (0.2)	0.2 (0.6)	−0.3 (NA)	0.0 (0.5)	0.3 (0.9)
<LLOQ, n (%)	3 (42.9)	1 (50.0)	4 (50.0)	1 (100.0)	4 (57.1)	1 (50.0)
ALT, U/L	42 (23.7)	32 (3.5)	26 (10.3)	31 (NA)	39 (34.4)	42 (17.7)

Data shown are mean (SD) unless otherwise indicated.
[a]Patient reported. HBV DNA measured by COBAS TaqMan with LLOQ=20 IU/mL, LOD=20 IU/mL. HBV pgRNA measured by Assembly in-house assay with LLOQ=45 U/mL. HBcrAg measured by Fujirebio Lumipulse G with LLOQ=1 kU/mL. HBsAg measured by Abbott Architect i2000SR with LLOQ=0.05 IU/mL. HBeAg measured by Abbott Architect i2000SR with LLOQ=0.59 PEI Units/mL.
3733, ABI-H3733; ALT, alanine aminotransferase; BMI, body mass index; HBcrAg, hepatitis B core-related antigen; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; LOD, limit of detection; NA, not applicable; PBO, placebo; PEI, Paul Ehrlich Institute; pgRNA, pregenomic RNA; SD, standard deviation.

- Overall, 27 HBeAg negative patients were included in this analysis; all patients completed treatment with study drug
- Baseline characteristics were comparable between cohorts (**Table 1**)
- Most patients were male, White, and 30-50 years of age
- Baseline viral parameters were consistent with an HBeAg negative population
  - HBV DNA and HBV pgRNA ranged from 3.1-6.1 $\log_{10}$ IU/mL and 1.4-3.5 $\log_{10}$ U/mL, respectively
  - Hepatitis B surface antigen (HBsAg) and hepatitis B core-related antigen (HBcrAg) ranged from 2.3-4.7 $\log_{10}$ IU/mL and −0.3 to 1.8 $\log_{10}$ kU/mL, respectively
  - 74% and 52% of patients had HBV pgRNA and HBcrAg below LLOQ, respectively

Table 2. Any Treatment-Emergent Adverse Events (Safety Population)

	25-mg Cohort		50-mg Cohort		100-mg Cohort	
	3733 n=7	PBO n=2	3733 n=8	PBO n=1	3733 n=7	PBO n=2
TEAE	2 (28.6)	1 (50.0)	1 (12.5)	0	2 (28.6)	1 (50.0)
Grade 1	2 (28.6)	0	1 (12.5)	0	1 (14.3)	0
Grade 2	0	1 (50.0)	0	0	1 (14.3)	1 (50.0)
TEAE Related to 3733/PBO	1 (14.3)	0	1 (12.5)	0	1 (14.3)	1 (50.0)
TEAE by Preferred Term						
Headache	2 (28.6)	0	0	0	0	0
Abdominal discomfort	0	0	0	0	1 (14.3)	0
Blood cholesterol increased	0	0	0	0	0	1 (50.0)
Dry mouth	0	0	0	0	1 (14.3)	0
Fatigue	0	0	0	0	1 (14.3)	0
Flatulence	0	0	1 (12.5)	0	0	0
Influenza	0	0	0	0	1 (14.3)	0
Nasopharyngitis	0	0	0	0	1 (14.3)	0
Upper respiratory tract infection	0	1 (50.0)	0	0	0	0
TE SAE	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

Data shown are n (%).
3733, ABI-H3733; PBO, placebo; SAE, serious adverse event; TE, treatment-emergent; TEAE, treatment-emergent adverse event.

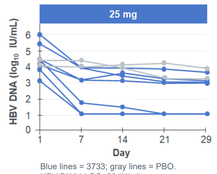
Table 3. Graded laboratory Abnormalities Observed in >1 Patient (Safety Population)

	25-mg Cohort		50-mg Cohort		100-mg Cohort	
	3733 n=7	PBO n=2	3733 n=8	PBO n=1	3733 n=7	PBO n=2
Cholesterol (Increased)	1 (14.3)	1 (50.0)	4 (50.0)	1 (100.0)	2 (28.6)	2 (100.0)
Grade 1	0	0	4 (50.0)	1 (100.0)	1 (14.3)	0
Grade 2	1 (14.3)	1 (50.0)	0	0	1 (14.3)	2 (100.0)
Triglycerides (Increased)	1 (14.3)	2 (100.0)	1 (12.5)	0	3 (42.9)	1 (50.0)
Grade 1	1 (14.3)	2 (100.0)	1 (12.5)	0	3 (42.9)	1 (50.0)
Bilirubin (Increased)	0	0	1 (12.5)	0	2 (28.6)	0
Grade 1	0	0	1 (12.5)	0	1 (14.3)	0
Grade 2	0	0	0	0	1 (14.3)	0
Glucose (Increased)	2 (28.6)	0	0	0	1 (14.3)	0
Grade 1	2 (28.6)	0	0	0	1 (14.3)	0
Phosphate (Decreased)	1 (14.3)	0	1 (12.5)	0	1 (14.3)	0
Grade 1	1 (14.3)	0	1 (12.5)	0	1 (14.3)	0
Glucose (Decreased)	0	1 (50.0)	1 (12.5)	0	0	0
Grade 1	0	0	1 (12.5)	0	0	0
Grade 2	0	1 (50.0)	0	0	0	0
Lipase (Increased)	0	1 (50.0)	0	0	1 (14.3)	0
Grade 1	0	1 (50.0)	0	0	0	0
Grade 2	0	0	0	0	1 (14.3)	0
Urate (Increased)	0	0	0	1 (100.0)	1 (14.3)	0
Grade 1	0	0	0	1 (100.0)	1 (14.3)	0
Coagulation (Increased)	1 (14.3)	1 (50.0)	1 (12.5)	0	0	0
Grade 1	1 (14.3)	1 (50.0)	1 (12.5)	0	0	0
Urinalysis Protein (Increased)	0	0	0	0	1 (20.0)[a]	1 (50.0)
Grade 1	0	0	0	0	1 (20.0)[a]	1 (50.0)

Data shown are n (%).
[a]n=5.
3733, ABI-H3733; ALT, alanine aminotransferase; PBO, placebo.

- 3733 was well tolerated, with no serious AEs, deaths, or AEs leading to study drug discontinuation reported
- AEs were reported in 5 patients receiving 3733, with only headache occurring in >1 patient; all were Grade 1/2 in severity (**Table 2**)
- Most graded laboratory abnormalities were Grade 1 in severity, with no reports of Grade 3 or 4 abnormalities
- No patients had alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increases

Figure 3. Observed HBV DNA Levels From Baseline to Day 29



Dose	Day 1	Day 7	Day 14	Day 21	Day 29
25 mg	4.19	3.22	3.14	2.99	2.98
	4.43	1.72	1.43	<LLOQ	<LLOQ
	5.52	3.99	3.99	3.86	3.66
	4.51	3.20	3.57	3.25	3.06
	3.12	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	6.06	3.89	3.44	3.07	3.11
	3.88	<LLOQ	<LLOQ	<LLOQ	<LLOQ
PBO	4.10	3.99	4.13	4.26	3.93
	4.47	4.40	3.95	3.26	3.26

TD
<LLOQ, TD
<LLOQ, TND

- 3733: 3/7 (43%) achieved <LLOQ
  - 1/3 (33%)=TND
  - 2/3 (66%)=TD

Dose	Day 1	Day 7	Day 14	Day 21	Day 29
50 mg[a]	5.74	3.59	2.91	2.37	1.53
	4.26	1.40	<LLOQ	<LLOQ	<LLOQ
	3.35	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	4.30	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	4.94	1.69	<LLOQ	<LLOQ	<LLOQ
	3.56	1.90	1.49	<LLOQ	<LLOQ
	4.51	ND	2.25	1.93	1.81
PBO	3.41	2.00	1.51	<LLOQ	<LLOQ
	3.31	3.33	2.82	2.99	2.75

TD
<LLOQ, TD
<LLOQ, TND

- 3733: 6/8 (75%) achieved <LLOQ
  - 2/6 (33%)=TND
  - 4/6 (66%)=TD

Dose	Day 1	Day 7	Day 14	Day 21	Day 29
100 mg	3.59	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	3.37	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	3.63	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	3.92	<LLOQ	<LLOQ	<LLOQ	<LLOQ
	4.00	1.95	<LLOQ	<LLOQ	<LLOQ
	4.20	1.65	<LLOQ	<LLOQ	<LLOQ
	5.48	2.13	1.59	<LLOQ	<LLOQ
PBO	3.18	3.37	3.30	3.39	3.26
	5.12	5.03	5.12	5.09	5.24

TD
<LLOQ, TD
<LLOQ, TND

- 3733: 7/7 (100%) achieved <LLOQ
  - 4/7 (57%)=TND
  - 3/7 (43%)=TD

Lines show individual patient absolute HBV DNA by study visit; gray lines represent placebo-treated patients. HBV DNA values below the lower limit of quantification (LLOQ=20 IU/mL) were imputed as 10 IU/mL for calculation of mean values. <LLOQ, TD defined as <LLOQ (<20 IU/mL) and DNA detected; <LLOQ, TND defined as <LLOQ (<20 IU/mL) and DNA not detected.
[a]One patient receiving 50 mg 3733 missed the Day 7 visit.
3733, ABI-H3733; HBV, hepatitis B virus; LLOQ, lower limit of quantification; PBO, placebo; TD, target detected; TND, target not detected.

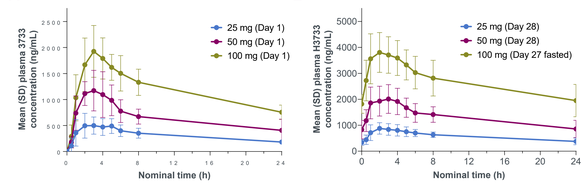
- Mean HBV DNA change from baseline at Day 29 was –2.3 $\log_{10}$ IU/mL, –3.1 $\log_{10}$ IU/mL, and –3.0 $\log_{10}$ IU/mL for 25-mg, 50-mg, and 100-mg doses of 3733, respectively (**Figure 3**)
  - The mean change in HBV DNA from baseline for each dose level is limited by the respective Baseline values and the proportion of patients achieving <LLOQ
- At Day 29, the number of patients with HBV DNA below the LLOQ of 20 IU/mL was 3 (43.0%), 6 (75.0%), and 7 (100.0%) in the 25-mg, 50-mg, and 100-mg cohorts, respectively (**Figure 3**)
- The rate at which HBV DNA <LLOQ was achieved was dose proportional, with 28.6%, 25.0%, and 57.1% of patients <LLOQ at Day 7, and 28.6%, 50.0%, and 85.7% of patients <LLOQ at Day 14 for the 25-mg, 50-mg, and 100-mg cohorts, respectively
- There was no change in HBsAg from baseline across all 3 cohorts, as expected with only 28 days of dosing

Table 4. Pharmacokinetics Parameters of ABI-H3733 on Day 1 and Day 27/28

Pharmacokinetic Parameters	3733 25 mg n=7		3733 50 mg n=8		3733 100 mg n=7		
	Day 1, fasted	Day 28, fasted	Day 1, fasted	Day 28, fasted	Day 1, fasted	Day 27, fasted	Day 28, fed
T_{max}, hours, median (range)	4.0 (2.0-5.0)	2.0 (1.0-6.0)	2.0 (1.0-4.0)	2.0 (1.0-5.0)	4.0 (2.0-5.0)	2.0 (1.0-4.0)	4.0 (2.0-6.0)
$t_{1/2}$, hours, mean (CV%)	17.1 (23)	22.8[a](44)	17.4[b](19)	23.9 (34)	19.1 (9)	31.5 (38)	29.9[c] (23)
C_{max}, ng/mL, mean (CV%)	555 (33)	902 (25)	1261 (30)	2188 (21)	2016 (26)	3929 (22)	3741 (32)
AUC_{0-24}, h·ng/mL, mean (CV%)	7518 (29)	13890 (21)	15480 (29)	31510 (25)	28220 (20)	64420 (23)	67400 (32)
C_{24}, ng/mL, mean (CV%)	182 (24)	379 (31)	408 (53)	858 (39)	756 (18)	1951 (32)	2301 (40)
Accumulation ratio, AUC_{0-24}, mean (CV%)	NA	1.9 (18)	NA	2.1 (25)	NA	2.3 (18)	NA

Analysis is based on nominal times.
[a]n=6; [b]n=7; [c]n=5.
3733, ABI-H3733; AUC_{0-24}, area under the curve from time 0 to 24 hours; C_{max}, maximum concentration; C_{24}, concentration 24 hours postdose; CV%, coefficient of variation percentage; NA, not applicable; $t_{1/2}$, elimination half-life; T_{max}, time to reach C_{max}.

Figure 4. Mean (SD) Plasma Pharmacokinetic Profiles of 3733 Following (A) Single Dose on Day 1 and (B) Multiple Doses on Day 27/28 (Linear Scale)



3733, ABI-H3733; SD, standard deviation.

Table 5. Observed QD 3733 Exposures Relative to In Vitro Antiviral Activity

Parameter	25-mg Cohort	50-mg Cohort	100-mg Cohort
C_{min}, ng/mL	379	858	1951
HBV DNA EC_{50}, nM	8.8	8.8	8.8
C_{min}/pa HBV DNA EC_{50}	9	21	48
cccDNA EC_{50}, nM	61	61	61
C_{min}/pa cccDNA EC_{50}	1.3	3	7

EC_{50} values per Unchwaniwala N, et al. Poster presentation at EASL 2023. (Poster WED-114).
3733, ABI-H3733; C_{min}, steady-state minimum (trough) concentration; cccDNA, covalently closed circular DNA; EC_{50}, half-maximal effective concentration; HBV, hepatitis B virus; pa, protein adjusted; QD, once daily.

- 3733 was rapidly absorbed, with a median T_{max} of 2.0 hours across all cohorts at Day 27/28 (**Table 4**)
- 3733 PK was consistent from Day 1 to Day 27/28 with a 2-fold accumulation, and exposure increases appeared to be near dose proportional between the 25-mg, 50-mg, and 100-mg doses (**Figure 4**)
- Mean steady-state C_{max} and AUC_{0-24} values were 902 ng/mL and 13,890 h·ng/mL after the 25-mg dose, 2188 ng/mL and 31,510 h·ng/mL after the 50-mg dose, and 3929 ng/mL and 64,420 h·ng/mL after the 100-mg dose (**Table 4**)
- Consumption of a high fat meal had no effect on exposure but appeared to delay absorption (**Table 4**)
- The C_{min} values for once-daily administration are in multiple-fold excess of in vitro protein-adjusted EC_{50}s for HBV DNA at the 25-mg, 50-mg, and 100-mg doses and for cccDNA formation at the 50-mg and 100-mg doses (**Table 5**)

Conclusions

- 3733, a novel next-generation core inhibitor, was well tolerated when administered orally at doses of 25 mg, 50 mg, and 100 mg once daily for 28 days
- All AEs were Grade 1 or 2, with no serious AEs, AEs leading to treatment discontinuation, or deaths
- Increases in 3733 dose level led to more rapid and consistent declines in HBV DNA, and greater proportions of patients achieving HBV DNA '<LLOQ, Target Not Detected' by the end of treatment
- PK characteristics of 3733 support daily dosing with C_{min} in multiple-fold excess of the protein-adjusted half-maximal inhibitory concentration for HBV DNA and cccDNA formation
- Overall, the PK profile and antiviral activity demonstrated by 3733 reflect the improved potency of next-generation core inhibitors against both mechanisms of action and potential to advance finite treatment regimens for cHBV

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