Safety, Pharmacokinetics, and Antiviral Activity of the Next-Generation Hepatitis B Capsid Assembly Modulator ABI-4334 in Patients With HBeAg-Negative Chronic Hepatitis B Infection Not Suppressed on Nucleoside Analogues: Results From a Randomized, Blinded, Phase 1b Study

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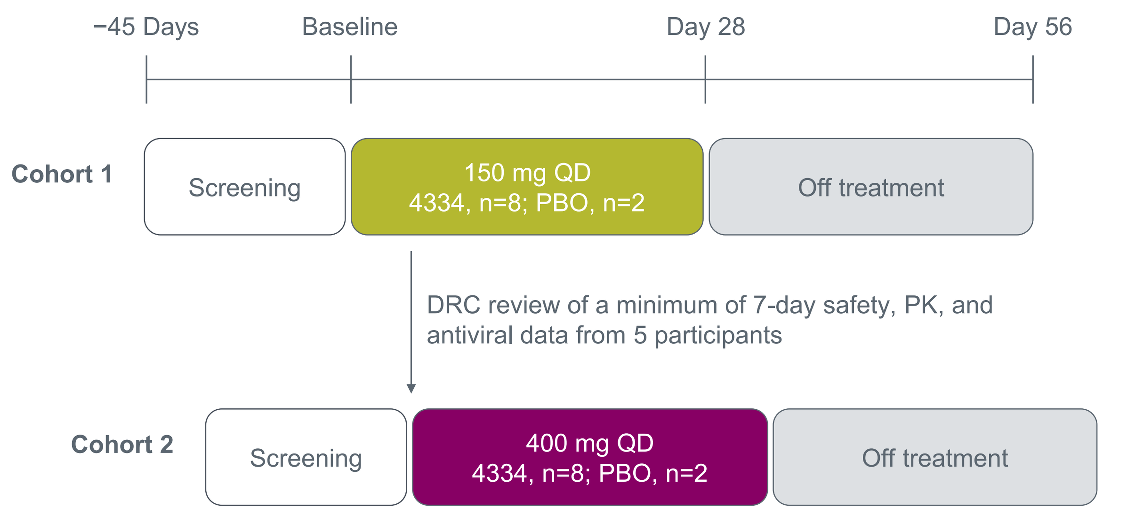
Background

- Worldwide, an estimated 254 million people have chronic hepatitis B virus infection (cHBV), which results in approximately 1.1 million deaths annually, predominantly due to cirrhosis and hepatocellular carcinoma[1-4]
- Suppressive therapy with nucleos(t)ide reverse transcriptase inhibitors is generally well tolerated, but low-level viremia persists, necessitating lifelong treatment[5-8]
- Novel combination treatment regimens incorporating agents with complementary mechanisms of action (MOAs) have the potential to further suppress viral replication and are being explored as finite-duration treatment regimens
- Capsid assembly modulators (CAMs) are a novel class of antivirals with the potential to increase on-treatment responses and functional cure rates after finite-duration treatments in patients with cHBV
- CAMs have multiple MOAs, including inhibition of pregenomic RNA (pgRNA) encapsidation, prevention of assembly and release of infectious viral particles, and disruption of incoming capsids, preventing covalently closed circular DNA (cccDNA) formation[9]
- ABI-4334 (4334) is a novel, investigational, next-generation CAM with increased *in vitro* potency against HBV DNA and cccDNA formation compared with first-generation CAMs[10]
- In healthy volunteers, 4334 was well tolerated as single oral doses up to 400 mg and multiple oral doses up to 200 mg once daily (QD) for 8 days. The observed plasma concentrations were in multi-fold excess of the *in vitro* protein-adjusted half-maximal effective concentration ($paEC_{50}$) values for the inhibition of HBV DNA and cccDNA formation at all doses tested[11]
- Here we report the safety, pharmacokinetics (PK), and antiviral activity of 4334 after QD administration for 28 days in participants with predominantly hepatitis B e antigen (HBeAg)-negative cHBV

Methods

- ABI-4334-102 (NCT06384131) is a randomized, blinded, multiple-dose escalation study evaluating the safety, PK, and antiviral activity of 4334 in participants with HBeAg-negative or HBeAg-positive cHBV
- Ten participants, 8 receiving 4334 and 2 receiving placebo (PBO), were enrolled into sequential dose cohorts with assigned treatment administered orally, QD for 28 days (**Figure 1**)
- Up to 4 dose cohorts were planned dependent upon emergent data from previous cohorts
- Safety was assessed by physical exams, vital signs, adverse events (AEs), and laboratory parameters
- Plasma concentrations of 4334 were measured by liquid chromatography mass spectrometry and PK parameters estimated by noncompartmental analysis

Figure 1. Study Design



Key Inclusion Criteria

- Male or nonpregnant female, aged ≥18 and ≤65 years
- BMI ≥18.0 and <35.0 kg/m^2
- Documented cHBV for ≥6 months
- HBeAg-negative or -positive
  - HBeAg-negative with HBV DNA ≥2×10^3 IU/mL
  - HBeAg-positive with HBV DNA ≥2×10^4 IU/mL
- Off antiviral therapy for ≥24 weeks
- Lack of bridging fibrosis or cirrhosis; FibroScan <9 kPa, Metavir F0–F2

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 treatment with HBV CAM, siRNA, or other oligonucleotide

4334, ABI-4334; BMI, body mass index; CAM, capsid assembly modulator; cHBV, chronic hepatitis B virus infection; DRC, data review committee; HAV, hepatitis A virus; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HDV, hepatitis D virus; HEV, hepatitis E virus; PBO, placebo; PK, pharmacokinetics; QD, once daily; siRNA, small interfering RNA.

Results

Participant Disposition

- Twenty participants (15 HBeAg-negative, 5 HBeAg-positive) were enrolled in 2 dose cohorts:
  - Cohort 1 (150 mg QD):
    - Eight participants received 4334 (6 HBeAg-negative, 2 HBeAg-positive)
    - Two participants received PBO (1 HBeAg-negative, 1 HBeAg-positive)
  - Cohort 2 (400 mg QD):
    - Eight participants received 4334 (7 HBeAg-negative, 1 HBeAg-positive)
    - Two participants received PBO (1 HBeAg-negative, 1 HBeAg-positive)
- All randomized participants completed treatment and follow-up per protocol

Analysis Population

- The focus of the analysis is the predominant HBeAg-negative population; however, data for the enrolled HBeAg-positive participants are displayed for completeness. For safety and PK analyses, data from HBeAg-negative and -positive participants are combined. Similarly, safety data for PBO recipients are pooled for analysis purposes

Table 1a. Baseline Demographics

	HBeAg-Negative Participants			HBeAg-Positive Participants		
Demographic Characteristic	PBO QD n=2	150 mg QD 4334 n=6	400 mg QD 4334 n=7	PBO QD n=2	150 mg QD 4334 n=2	400 mg QD 4334 n=1
Age, mean (SD), y	45 (9.9)	48 (4.3)	50 (7.5)	42 (8.5)	38 (7.1)	24 (NA)
Sex at birth						
Male, n (%)	2 (100.0)	3 (50.0)	4 (57.1)	0	1 (50.0)	1 (100.0)
Female, n (%)	0	3 (50.0)	3 (42.9)	2 (100.0)	1 (50.0)	0
Race						
White, n (%)	1 (50.0)	5 (83.3)	7 (100.0)	2 (100.0)	2 (100.0)	1 (100.0)
Native Hawaiian or other Pacific Islander, n (%)	1 (50.0)	0	0	0	0	0
Asian, n (%)	0	1 (16.7)	0	0	0	0
BMI, mean (SD), kg/m^2	26.2 (2.45)	26.4 (5.76)	27.8 (3.74)	27.2 (7.22)	24.5 (0.37)	25.4 (NA)

4334, ABI-4334; BMI, body mass index; HBeAg, hepatitis B e antigen; NA, not applicable; PBO, placebo; QD, once daily; SD, standard deviation; y, years.

Table 1b. Baseline Disease Characteristics

	HBeAg-Negative Participants			HBeAg-Positive Participants		
HBV Disease Characteristic	PBO QD n=2	150 mg QD 4334 n=6	400 mg QD 4334 n=7	PBO QD n=2	150 mg QD 4334 n=2	400 mg QD 4334 n=1
Duration positive for HBV, mean (SD), y	7.2 (4.53)	6.7 (5.72)	6.4 (3.89)	3.0 (0.92)	0.7 (0.20)	0.9 (NA)
HBV genotype, n (%)						
A	0	1 (16.7)	0	0	0	0
B	0	1 (16.7)	0	0	0	0
D	2 (100.0)	4 (66.7)	6 (85.7)	2 (100.0)	2 (100.0)	1 (100.0)
Missing	0	0	1 (14.3)	0	0	0
HBV DNA, mean (SD), log_{10} IU/mL	4.2 (1.27)	5.2 (2.45)	4.4 (1.04)	7.1 (1.57)	6.2 (2.99)	9.0 (NA)
HBV pgRNA						
Mean (SD), log_{10} U/mL	1.9 (0.75)	3.1 (2.64)	2.0 (1.09)	5.6 (1.35)	4.1 (3.45)	7.1 (NA)
<LLOQ, n (%)	1 (50.0)	3 (50.0)	5 (71.4)	0	0	0
HBsAg, mean (SD), log_{10} IU/mL	3.4 (0.18)	3.8 (0.79)	3.5 (0.40)	4.6 (0.26)	4.6 (0.29)	5.1 (NA)
FibroScan, mean (SD), kPa	6.3 (2.76)	6.2 (1.63)	6.4 (1.67)	4.9 (0.71)	6.8 (0.49)	6.0 (NA)
ALT, mean (SD), U/L	63 (53.7)	42 (24.0)	73 (97.3)	30 (7.1)	98 (94.8)	42 (NA)

4334, ABI-4334; ALT, alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable; LLOQ, lower limit of quantification; PBO, placebo; pgRNA, pregenomic RNA; QD, once daily; SD, standard deviation; y, years.

- Overall, demographics and disease characteristics were comparable across treatments (**Tables 1a** and **1b**)
  - For HBeAg-negative participants:
    - Most were male (9/15, 60%) and White (13/15, 87%), with a mean age range of 45 to 50 years
    - Predominantly HBV genotype D (12/15, 80%)
    - Mean HBV DNA and hepatitis B surface antigen (HBsAg) levels ranged from 4.2 to 5.2 and 3.4 to 3.8 log_{10} IU/mL, respectively
    - Mean HBV pgRNA levels ranged from 1.9 to 3.1 log_{10} U/mL, and 9/15 (60%) participants had HBV pgRNA less than the lower limit of quantification at Baseline
    - Mean alanine aminotransferase (ALT) levels ranged from 42 to 73 U/L

Table 2. Summary of Safety

	PBO QD n=4	150 mg QD 4334 n=8	400 mg QD 4334 n=8
Any TEAE	2 (50.0)	5 (62.5)	6 (75.0)
TEAE by maximum toxicity grade			
Grade 1	0	2 (25.0)	1 (12.5)
Grade 2	2 (50.0)	2 (25.0)	5 (62.5)
Grade 3	0	1 (12.5)[a]	0
TEAE related to treatment	1 (25.0)	5 (62.5)	1 (12.5)
TEAE leading to study discontinuation	0	0	0
TE graded laboratory abnormalities Grade ≥1	3 (75.0)	6 (75.0)	8 (100.0)
Grade 1	3 (75.0)	5 (62.5)	8 (100.0)
Grade 2	3 (75.0)	3 (37.5)	4 (50.0)
Grade 3	1 (25.0)[b]	1 (16.7)[a]	0
TE SAE	0	0	0
Deaths	0	0	0

For safety analyses, data from HBeAg-negative and HBeAg-positive participants are combined. Data for PBO recipients are pooled for analysis purposes. Data shown as n (%).
[a]Grade 3 TEAE and TE laboratory abnormality of increased alanine aminotransferase considered treatment related; resolved with continued treatment.
[b]Grade 3 TE laboratory abnormality of increased total bilirubin; resolved on study.
4334, ABI-4334; HBeAg, hepatitis B e antigen; PBO, placebo; QD, once daily; SAE, serious adverse event; TE, treatment-emergent; TEAE, treatment-emergent adverse event.

Table 3. Summary of Grade 3 or Higher Treatment-Emergent Laboratory Abnormalities

	PBO QD n=4	150 mg QD 4334 n=8	400 mg QD 4334 n=8
Any laboratory abnormality Grade ≥3	1 (25.0)	1 (12.5)	0
Grade 3	1 (25.0)	1 (12.5)	0
Grade 4	0	0	0
Alanine aminotransferase (increased)			
Grade 3	0	1 (12.5)[a]	0
Grade 4	0	0	0
Bilirubin (increased)			
Grade 3	1 (25.0)[b]	0	0
Grade 4	0	0	0

For safety analyses, data from HBeAg-negative and HBeAg-positive participants are combined. Data for PBO recipients are pooled for analysis purposes. Data shown as n (%).
[a]Grade 3 TE laboratory abnormality of increased alanine aminotransferase considered treatment related; resolved with continued treatment.
[b]Grade 3 TE laboratory abnormality of increased total bilirubin; resolved on study.
4334, ABI-4334; HBeAg, hepatitis B e antigen; PBO, placebo; QD, once daily; TE, treatment-emergent.

Table 4. Summary of Treatment-Emergent Adverse Events by Preferred Term Occurring in ≥2 Participants

	PBO QD n=4	150 mg QD 4334 n=8	400 mg QD 4334 n=8
Participants with any TEAE	2 (50.0)	5 (62.5)	6 (75.0)
Alanine aminotransferase increased	1 (25.0)	1 (12.5)	1 (12.5)
Aspartate aminotransferase increased	0	2 (25.0)	1 (12.5)
Blood cholesterol increased	0	1 (12.5)	1 (12.5)
Headache	0	0	2 (25.0)
International normalized ratio increased	0	2 (25.0)	0
Prothrombin time prolonged	0	2 (25.0)	0

For safety analyses, data from HBeAg-negative and HBeAg-positive participants are combined. Data for PBO recipients are pooled for analysis purposes. Data shown as n (%).
4334, ABI-4334; HBeAg, hepatitis B e antigen; PBO, placebo; QD, once daily; TEAE, treatment-emergent adverse event.

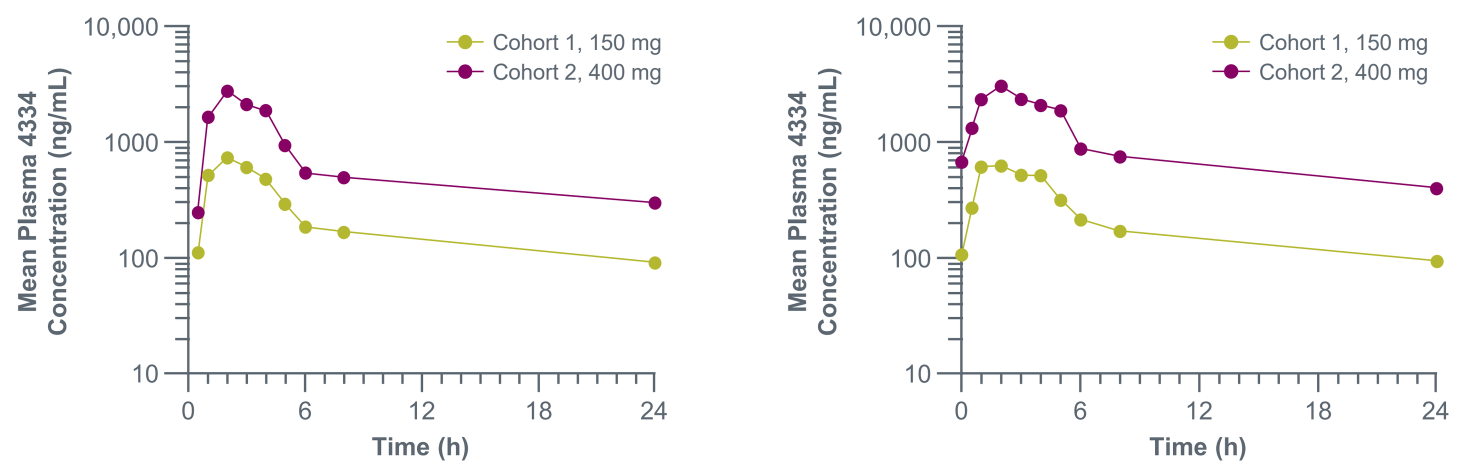
- Overall, 4334 was well tolerated with no treatment-emergent AEs (TEAEs) leading to study drug discontinuation and no serious AEs (**Table 2**)
- The majority of TEAEs and laboratory abnormalities were Grade 1 or 2 in severity (**Table 2**)
  - Increased ALT was reported in an HBeAg-negative participant receiving 150 mg 4334. The Grade 3 ALT increase was considered related to treatment but resolved with continued study drug administration (**Table 2, Table 3**)
- The most commonly reported TEAEs and laboratory abnormalities (reported in ≥2 participants) included increased ALT, increased aspartate aminotransferase, increased cholesterol, headache, increased international normalized ratio, and prolonged prothrombin time (**Table 4**)
  - A Grade 3 elevation in total bilirubin was reported in a PBO recipient, which resolved on study (**Table 2, Table 3**)

Table 5. Summary of Plasma 4334 PK Parameters After Multiple Dosing (Day 28)

PK Parameters	150 mg QD 4334 n=8	400 mg QD 4334 n=8
AUC_{24h}, h·ng/mL	5161 (77.9)	23,140 (42.1)
$C_{max,ss}$, ng/mL	723.1 (89.6)	3080 (46.1)
C_{24h}, ng/mL	93.3 (75.3)	403.7 (48)
$T_{max,ss}$, median (min, max), h	2 (1, 4)	2 (2, 4)
$t_{1/2}$, hours	27.5 (106.6)[a]	17.5 (27.1)
Accumulation ratio AUC_{24h}	1.6 (76)	2.1 (94)[b]

All parameters are presented as mean (CV%), unless otherwise stated. PK parameter calculations include both HBeAg-negative and HBeAg-positive 4334 recipients.
[a]n=6. [b]n=7.
4334, ABI-4334; AUC_{24h}, area under the curve over 24 hours at steady state; $C_{max,ss}$, maximum concentration at steady state; C_{24h}, concentration at 24 hours postdose; CV%, coefficient of variation percentage; HBeAg, hepatitis B e antigen; max, maximum; min, minimum; PK, pharmacokinetics; QD, once daily; $t_{1/2}$, elimination half-life; $T_{max,ss}$, time to reach C_{max} at steady state.

Figure 2. Mean Plasma 4334 Concentration vs Time Profile – Day 1 and 28, Semi-Log Scale



4334, ABI-4334.

- 4334 was rapidly absorbed, with mean elimination half-life estimates of 17.5 to 27.5 hours and minimal accumulation from Day 1 to Day 28 (**Table 5**)
- Mean steady-state concentrations at 24 hours postdose at the 150 mg and 400 mg dose levels were approximately 62- to 269-fold above the target concentration for HBV DNA inhibition and approximately 12- to 52-fold above the target concentration for inhibition of cccDNA formation based on the *in vitro* potency data[11]
- Intensive PK sampling was performed following dosing on Days 1 and 28. Plasma concentration profiles for 4334 are presented in **Figure 2**

- Individual participant HBV DNA and HBV pgRNA results by visit according to HBeAg status are shown for 150 mg (**Table 6**) and 400 mg (**Table 7**)

Table 6. 150 mg/PBO: Individual Participant HBV DNA and HBV pgRNA Levels From Baseline to Day 28

HBV DNA (log_{10} IU/mL)						
Dose	HBeAg Status[a]	Day 1	Day 7	Day 14	Day 21	Day 28
150 mg	Negative	3.44	<1	<1	1.11	<1
	Negative	3.05	<1	<1	<1	<1
	Negative	7.43	5.60	5.18	4.81	4.70
	Negative	>9	7.44	7.27	7.21	7.00
	Negative	3.70	1.52	1.72	1.18	1.26
	Negative	4.39	<1	<1	<1	<1
	Positive	8.27	5.86	5.53	4.97	4.44
	Positive	4.05	1.95	<1	<1	<1
PBO	Negative	3.26	3.21	3.19	3.05	3.06
	Positive	8.23	8.15	8.1	8.25	8.24

<LLOQ: TD, TND

TD defined as <LLOQ (<10 IU/mL; <1 log_{10} IU/mL) and HBV DNA detected.
TND defined as <LLOQ (<10 IU/mL; <1 log_{10} IU/mL) and HBV DNA not detected.

HBV pgRNA (log_{10} U/mL)						
Dose	HBeAg Status[a]	Day 1	Day 7	Day 14	Day 21	Day 28
150 mg	Negative	1.87	<1.65	<1.65	<1.65	<1.65
	Negative	<1.65	<1.65	<1.65	<1.65	<1.65
	Negative	5.39	4.17	3.62	2.99	2.25
	Negative	7.46	5.22	4.88	4.76	4.52
	Negative	<1.65	<1.65	<1.65	<1.65	<1.65
	Negative	<1.65	<1.65	<1.65	<1.65	<1.65
	Positive	6.53	4.53	4.17	3.64	3.08
	Positive	1.65	<1.65	<1.65	<1.65	<1.65
PBO	Negative	<1.65	<1.65	<1.65	<1.65	<1.65
	Positive	6.55	6.48	6.52	6.54	6.44

<LLOQ:

LLOQ = 45 U/mL; <1.65 log_{10} U/mL.

[a]HBeAg status at Baseline. 4334, ABI-4334; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; PBO, placebo; pgRNA, pregenomic RNA; TD, target detected; TND, target not detected.

Table 7. 400 mg/PBO: Individual Participant HBV DNA and HBV pgRNA Levels From Baseline to Day 28

HBV DNA (log_{10} IU/mL)						
Dose	HBeAg Status[a]	Day 1	Day 7	Day 14	Day 21	Day 28
400 mg	Negative	3.93	1.51	1.20	<1	1.18
	Negative	5.93	3.67	3.32	3.06	2.73
	Negative	3.71	<1	<1	<1	<1
	Negative	3.95	<1	<1	<1	<1
	Negative	3.38	<1	<1	<1	<1
	Negative	4.02	2.03	1.52	1.00	1.30
	Negative	5.83	2.74	2.10	1.88	1.46
	Positive	8.98	6.40	5.70	5.53	5.45
PBO	Negative	5.05	5.13	5.31	5.27	5.14
	Positive	6.01	6.22	5.99	6.01	5.86

<LLOQ: TD, TND

TD defined as <LLOQ (<10 IU/mL; <1 log_{10} IU/mL) and HBV DNA detected.
TND defined as <LLOQ (<10 IU/mL; <1 log_{10} IU/mL) and HBV DNA not detected.

HBV pgRNA (log_{10} U/mL)						
Dose	HBeAg Status[a]	Day 1	Day 7	Day 14	Day 21	Day 28
400 mg	Negative	<1.65	<1.65	<1.65	<1.65	<1.65
	Negative	4.09	<1.65	<1.65	<1.65	<1.65
	Negative	<1.65	<1.65	<1.65	<1.65	<1.65
	Negative	<1.65	<1.65	<1.65	<1.65	<1.65
	Negative	<1.65	<1.65	<1.65	<1.65	<1.65
	Negative	<1.65	<1.65	<1.65	<1.65	<1.65
	Negative	2.80	<1.65	<1.65	<1.65	<1.65
	Positive	7.15	5.49	4.71	4.45	4.35
PBO	Negative	2.42	2.54	2.58	2.89	2.93
	Positive	4.64	4.69	4.72	4.70	4.83

<LLOQ:

LLOQ = 45 U/mL; <1.65 log_{10} U/mL.

[a]HBeAg status at Baseline. 4334, ABI-4334; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus; LLOQ, lower limit of quantification; PBO, placebo; pgRNA, pregenomic RNA; TD, target detected; TND, target not detected.

Table 8. Mean Change From Baseline in Viral Parameters

HBeAg Status at Baseline	Mean (SD) [n] Change From Baseline to Day 28								
	HBV DNA (log_{10} IU/mL)			HBV pgRNA (log_{10} U/mL)			HBsAg (log_{10} IU/mL)		
	150 mg QD	400 mg QD	PBO QD	150 mg QD	400 mg QD	PBO QD	150 mg QD	400 mg QD	PBO QD
HBeAg-negative	−2.7 (0.58) [n=6]	−3.1 (0.59) [n=7]	−0.1 (0.20) [n=2]	−1.1 (1.52) [n=6]	−0.6 (1.09) [n=7]	0.3 (0.36) [n=2]	−0.1 (0.11) [n=6]	0.0 (0.06) [n=7]	0.0 (0.05) [n=2]
HBeAg-positive	−3.6 (0.35) [n=2]	−3.5 (NA) [n=1]	−0.1 (0.11) [n=2]	−1.9 (2.23) [n=2]	−2.8 (NA) [n=1]	0.0 (0.20) [n=2]	−0.1 (0.02) [n=2]	−0.2 (NA) [n=1]	0.0 (0.10) [n=2]
Combined HBeAg-negative and -positive	−2.9 (0.66) [n=8]	−3.2 (0.56) [n=8]	−0.1 (0.13) [n=4]	−1.3 (1.57) [n=8]	−0.9 (1.27) [n=8]	0.1 (0.27) [n=4]	−0.1 (0.10) [n=8]	0.0 (0.08) [n=8]	0.0 (0.06) [n=4]

HBV DNA values below the lower limit of quantification (10 IU/mL; 1 log_{10} IU/mL) were imputed as 5 IU/mL (0.7 log_{10} U/mL) for calculation of mean values.
HBV pgRNA values below the lower limit of quantification (45 U/mL; 1.65 log_{10} U/mL) were imputed as 22.5 U/mL (1.35 log_{10} U/mL) for calculation of mean values.
HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, not applicable; PBO, placebo; pgRNA, pregenomic RNA; QD, once daily; SD, standard deviation.

- In HBeAg-negative participants, the mean changes from Baseline at Day 28 were as follows:
  - HBV DNA: −2.7 and −3.1 log_{10} IU/mL for 150 mg and 400 mg, respectively (**Table 8**)
  - HBV pgRNA: −1.1 and −0.6 log_{10} U/mL for 150 mg and 400 mg, respectively (**Table 8**)
  - No changes in HBsAg were observed (**Table 8**)

Conclusions

- 4334, a novel, **next-generation, investigational** HBV CAM, was safe and well tolerated when administered orally up to 400 mg QD for 28 days
- Most TEAEs and lab abnormalities were mild to moderate (Grade 1 or 2). No serious AEs or study drug discontinuations occurred
- Increased *in vitro* potency of 4334 relative to first-generation CAMs was reflected in multi-log declines in HBV DNA
- Safety and PK data support QD oral dosing, achieving exposures in multi-fold excess of those anticipated to inhibit HBV DNA replication and cccDNA formation
- The findings support continued development of 4334 as part of combination regimens with agents of complementary MOAs

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