The safety and pharmacokinetics of ABI-4334, a novel next-generation HBV core inhibitor: Interim results from a Phase 1 study in healthy volunteers

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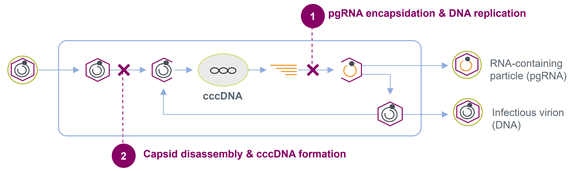
Edward J. Gane[1], Christian Schwabe[2], Jieming Liu[3], Luisa M. Stamm[3], Kathryn M. Kitrinos[3], Steven J. Knox[3], Michele Anderson[3], Grace Wang[3], Katie Zomorodi[3]

[1]University of Auckland, Auckland, New Zealand; [2]New Zealand Clinical Research, Auckland, New Zealand; [3]Assembly Biosciences, Inc., South San Francisco, CA, USA

Introduction

- Chronic hepatitis B virus infection (cHBV) is a significant global health problem
  - Worldwide, an estimated 296 million people have cHBV, resulting in approximately 820,000 deaths each year, mostly due to cirrhosis and hepatocellular carcinoma, which are long-term complications of cHBV[1-4]
- In most patients, nucleos(t)ide reverse transcriptase inhibitors (NrtIs) are well tolerated, but residual low-level viremia remains, resulting in the need for lifelong treatment[5-8]
- Novel combination approaches incorporating agents with complementary mechanisms of action (MOAs) may be required to further suppress viral replication and establish finite-duration regimens
- Core inhibitors 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
  - These agents have multiple MOAs that interfere with HBV replication, including inhibition of pregenomic (pg)RNA encapsidation, prevention of assembly and release of infectious viral particles, and disruption of incoming capsids, preventing covalently closed circular (ccc)DNA formation (**Figure 1**)[9]
  - In Phase 1b studies, first-generation core inhibitors demonstrated potent antiviral activity[10,11] and additive antiviral activity when combined with NrtIs compared with NrtIs alone in Phase 2 studies[12,13]
- ABI-4334 (4334) is a novel, next-generation core inhibitor that has demonstrated increased in vitro potency against HBV DNA and cccDNA formation compared with first-generation core inhibitors[14]
- Here we report the safety and pharmacokinetics (PK) from a first-in-human study of 4334 in healthy volunteers (HVs)

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 and PK of 4334 in HVs

Methods

- This study (NCT05569941) consists of single (SAD) and multiple (MAD) ascending doses of 4334 in HVs
- During the SAD phase, 8 HVs (6 active, 2 placebo [PBO]) were enrolled into each of 4 sequential dose cohorts, with an additional 6 HVs receiving 4334 in both fasted and fed states (Cohort 5) to evaluate the effect of a high-calorie meal (**Figure 2**)
- Following completion of the 200-mg SAD cohort, 8 HVs (6 active, 2 PBO) were enrolled into each of 2 sequential MAD cohorts receiving assigned treatment for 8 days

Figure 2. Study Design

Key inclusion criteria
- Male or female, aged 18-65 years (inclusive)
- BMI 18.0-30.0 kg/m^2 (inclusive)
- Female HVs must not be pregnant
- In good health (as determined by the investigator)

Key exclusion criteria
- Positive for HBV, HCV, or HIV
- History of illness that may confound the study results
- History of significant drug-related allergic reactions
- Persistent alcohol or illicit drug use within 3 years prior to Screening

[a]Food effect assessment was 2-period crossover; 1 dose with high-calorie food and 1 dose fasting in a randomized manner.
4334, ABI-4334; BMI, body mass index; HBV, hepatitis B virus, HCV, hepatitis C virus; HIV, human immunodeficiency virus; HV, healthy volunteer; MAD, multiple ascending dose; PBO, placebo; QD, once daily; SAD, single ascending dose.

- Safety was assessed by physical exams, vital signs, adverse event (AE) monitoring, and laboratory parameters
- Plasma concentrations of 4334 were measured by validated liquid chromatography mass spectrometry methodology with PK parameters estimated by noncompartmental analysis

Results

- In total, 32 HVs were enrolled in the SAD cohorts, 6 HVs in the food effect cohort, and 16 HVs in the MAD cohorts
- All HVs in the SAD cohorts completed the study; 1 HV each in the food effect cohort and the 100-mg 4334 MAD cohort were discontinued from the study due to protocol violations (receipt of prohibited medication; undisclosed cannabinoid use prior to study)

Table 1. Demographics

Characteristics	SAD Cohorts: 30 mg 4334 n=6	SAD Cohorts: 100 mg 4334 n=6	SAD Cohorts: 200 mg 4334 n=6	SAD Cohorts: 400 mg 4334 n=6	SAD Cohorts: All Cohorts PBO n=8	Food Effect Cohort: 200 mg Fed, Fasted n=3	Food Effect Cohort: 200 mg Fasted, Fed n=3	MAD Cohorts: 100 mg 4334[a] n=6	MAD Cohorts: 200 mg 4334[a] n=6	MAD Cohorts: All Cohorts PBO[a] n=4
Age, median (range), y	41 (21-61)	31 (20-50)	43 (19-61)	23 (20-30)	37 (23-60)	28 (23-41)	25 (21-27)	30 (21-45)	34 (30-56)	24 (23-27)
Sex, male, n (%)	4 (66.7)	4 (66.7)	2 (33.3)	4 (66.7)	7 (87.5)	3 (100.0)	2 (66.7)	6 (100.0)	4 (66.7)	4 (100.0)
Race, White, n (%)	5 (83.3)	4 (66.7)	4 (66.7)	5 (83.3)	3 (37.5)	2 (66.7)	0	3 (50.0)	4 (66.7)	3 (75.0)
BMI, median (range), kg/m^2	21.4 (18.9-25.4)	24.5 (20.3-26.4)	23.3 (20.0-25.7)	23.4 (18.9-25.6)	24.8 (21.4-29.6)	22.7 (18.8-24.9)	20.2 (19.0-26.9)	25.0 (19.5-27.1)	25.0 (19.8-29.4)	24.1 (20.7-26.2)

[a]QD for 8 days.
4334, ABI-4334; BMI, body mass index; MAD, multiple ascending dose; PBO, placebo; QD, once daily; SAD, single ascending dose.

- Overall, demographics were comparable between cohorts (**Table 1**)
- Most HVs were male and White, with age and body mass index ranging between 19-61 years and 18.8-29.6 kg/m^2, respectively

Table 2. Summary of Safety by Cohort

n (%) of HVs	SAD Cohorts: 30 mg 4334 n=6	SAD Cohorts: 100 mg 4334 n=6	SAD Cohorts: 200 mg 4334 n=6	SAD Cohorts: 400 mg 4334 n=6	SAD Cohorts: All Cohorts PBO n=8	Food Effect Cohort: 200 mg Fed, Fasted n=3	Food Effect Cohort: 200 mg Fasted, Fed n=3	MAD Cohorts: 100 mg 4334[a] n=6	MAD Cohorts: 200 mg 4334[a] n=6	MAD Cohorts: All Cohorts PBO[a] n=4
TEAEs	2 (33.3)	4 (66.7)	2 (33.3)	2 (33.3)	4 (50.0)	1 (33.3)	1 (33.3)	3 (50.0)	4 (66.7)	1 (25.0)
Grade 1	2 (33.3)	4 (66.7)	1 (16.7)	2 (33.3)	4 (50.0)	1 (33.3)	1 (33.3)	2 (33.3)	4 (66.7)	1 (25.0)
Grade 2	0	0	1 (16.7)[b]	0	0	0	0	1 (16.7)[c]	0	0
TEAEs related to 4334/PBO	0	0	0	0	1 (12.5)	0	0	0	0	0
TEAEs leading to study discontinuation	0	0	0	0	0	0	0	0	0	0
TE graded laboratory abnormalities	3 (50.0)	3 (50.0)	1 (16.7)	2 (33.3)	3 (37.5)	0	2 (66.7)	4 (66.7)	3 (50.0)	3 (75.0)
Grade 1	2 (33.3)	2 (33.3)	1 (16.7)	2 (33.3)	1 (12.5)	0	2 (66.7)	3 (50.0)	2 (33.3)	2 (50.0)
Grade 2	1 (16.7)	1 (16.7)	0	0	2 (25.0)	0	0	1 (16.7)	1 (16.7)	1 (25.0)
TE SAEs	0	0	0	0	0	0	0	0	0	0
Deaths	0	0	0	0	0	0	0	0	0	0

[a]QD for 8 days. [b]Pain in extremity. [c]Drug withdrawal syndrome.
4334, ABI-4334; HV, healthy volunteer; MAD, multiple ascending dose; PBO, placebo; QD, once daily; SAD, single ascending dose; TE, treatment-emergent; TEAE, treatment-emergent adverse event.

Table 3. Summary of TEAEs and Graded Laboratory Abnormalities by Cohort (>1 HV Overall)

n (%) of HVs	SAD Cohorts: 30 mg 4334 n=6	SAD Cohorts: 100 mg 4334 n=6	SAD Cohorts: 200 mg 4334 n=6	SAD Cohorts: 400 mg 4334 n=6	SAD Cohorts: All Cohorts PBO n=8	Food Effect Cohort: 200 mg Fed, Fasted n=3	Food Effect Cohort: 200 mg Fasted, Fed n=3	MAD Cohorts: 100 mg 4334[a] n=6	MAD Cohorts: 200 mg 4334[a] n=6	MAD Cohorts: All Cohorts PBO[a] n=4
TEAEs (all grades)										
Headache	1 (16.7)	1 (16.7)	0	1 (16.7)	1 (12.5)	0	1 (33.3)	0	1 (16.7)	0
Oropharyngeal pain	0	0	1 (16.7)	1 (16.7)	0	0	0	0	0	0
Catheter site bruise	0	0	0	0	0	0	0	0	2 (33.3)	0
Insomnia	0	1 (16.7)	0	0	0	0	0	1 (16.7)	0	0
Lab abnormalities										
Cholesterol[b] (Grade 1)	2 (33.3)	0	1 (16.7)	0	2 (25.0)	0	1 (33.3)	0	0	0
Grade 2	1 (16.7)	0	0	0	1 (12.5)	0	0	1 (16.7)	0	1 (25.0)
Amylase[b] (Grade 1)	0	1 (16.7)	0	0	0	0	0	3 (50.0)	0	0
Grade 2	0	1 (16.7)	0	0	1 (12.5)	0	0	0	0	0
Triglycerides[b] (Grade 1)	0	1 (16.7)	0	0	0	0	0	1 (16.7)	2 (33.3)	0
Bicarbonate[c] (Grade 1)	0	0	1 (16.7)	0	0	0	1 (33.3)	0	0	0
Urate[b] (Grade 1)	0	0	0	0	0	0	0	2 (33.3)	0	0
Creatinine[b] (Grade 1)	0	0	0	0	1 (12.5)	0	0	0	0	0
Grade 2	0	0	0	0	1 (12.5)	0	0	0	0	0
Glucose[b] (Grade 1)	0	0	0	1 (16.7)	0	0	1 (33.3)	0	0	0

[a]QD for 8 days. [b]Increased. [c]Decreased.
4334, ABI-4334; HV, healthy volunteer; MAD, multiple ascending dose; PBO, placebo; QD, once daily; SAD, single ascending dose; TEAE, treatment-emergent adverse event.

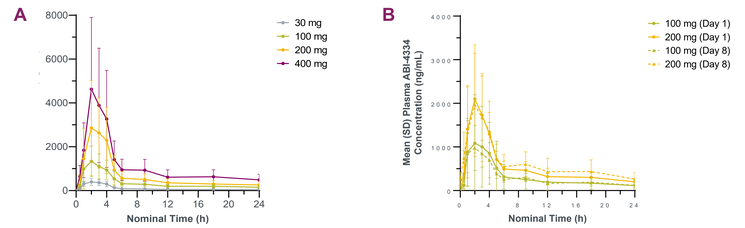
- 4334 was well tolerated, with no Grade ≥3 treatment-emergent adverse events (TEAEs), treatment-emergent serious AEs, TEAEs leading to study discontinuation, or deaths reported in any cohort (**Table 2**)
  - Grade 2 TEAEs were reported in 1 HV who received 4334 in the 200-mg SAD cohort (extremity pain) and 1 HV who received 4334 in the 100-mg MAD cohort (drug withdrawal syndrome). Among HVs who received 4334, headache was the most common TEAE in the SAD cohorts and catheter site bruise in the MAD cohorts
- No TEAEs related to 4334 were observed in the HVs (**Table 2**)
- There were no Grade ≥3 treatment-emergent graded laboratory abnormalities (**Table 3**)
  - The most common graded laboratory abnormalities reported in HVs who received 4334 were increases in cholesterol in the SAD cohorts and increases in amylase and triglycerides in the MAD cohorts
  - A Grade 2 increase in cholesterol was reported in 2 HVs who received placebo, 1 HV who received 4334 in the 30-mg SAD cohort, and another HV who received 4334 in the 100-mg MAD cohort

Table 4. Pharmacokinetic Parameters Following Single and Multiple Doses of 4334

Pharmacokinetic Parameters	SAD Cohorts: 30 mg 4334 n=6	SAD Cohorts: 100 mg 4334 n=6	SAD Cohorts: 200 mg 4334 n=6	SAD Cohorts: 400 mg 4334 n=6	Food Effect Cohort: 200 mg 4334 Fasted n=5	Food Effect Cohort: 200 mg 4334 Fed n=6	MAD Cohorts[a]: 100 mg 4334 Day 1 n=6	MAD Cohorts[a]: 100 mg 4334 Day 8 n=5	MAD Cohorts[a]: 200 mg 4334 Day 1 n=6	MAD Cohorts[a]: 200 mg 4334 Day 8 n=6
T_{max}, hours, median (range)	2.0 (1.0-3.0)	2.0 (1.0-4.0)	2.0 (1.0-4.0)	2.0 (2.0-4.0)	2.0 (1.0-4.0)	3.5 (2.0-5.0)	3.0 (1.0-4.0)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	2.0 (1.0-3.0)
$t_{1/2}$, hours, mean (CV%)	14.0 (25)	16.3 (21)	15.2 (16)	13.1 (16)	17.6 (41)	17.2 (55)	22.4 (63)[b]	12.5 (14)	16.1 (44)[c]	17.9 (39)
C_{max}, ng/mL, mean (CV%)	446 (28)	1376 (47)	3443 (62)	4878 (67)	4407 (72)	1876 (42)	1194 (94)	1061 (63)	2108 (58)	2013 (56)
$AUC_{0\text{-}24}$, ng•h/mL, mean (CV%)	2503 (29)	8772 (44)	16770 (56)	27590 (57)	20440 (56)	14240 (34)	7769 (87)	7419 (43)	13260 (39)	15430 (50)
$AUC_{0\text{-}inf}$, ng•h/mL, mean (CV%)	3183 (32)	11570 (47)	21230 (57)	35730 (55)	26110 (55)	18870 (35)	NA	NA	NA	NA
C_{24}, ng/mL, mean (CV%)	41 (40)	150 (53)	256 (60)	489 (53)	366 (59)	257 (36)	112 (77)	119 (51)	199 (29)	263 (59)
Accumulation ratio, $AUC_{0\text{-}24}$, mean (CV%)	NA	NA	NA	NA	NA	NA	NA	1.8 (75)	NA	1.2 (26)

Analysis is based on nominal times.
[a]QD for 8 days. [b]n=4. [c]n=3.
4334, ABI-4334; AUC, area under the curve; $AUC_{0\text{-}24}$, AUC from time 0 to 24 hours; $AUC_{0\text{-}inf}$, AUC from time 0 to infinity; C_{max}, maximum concentration; C_{24}, concentration 24 hours postdose; CV%, coefficient of variation percentage; MAD, multiple ascending dose; NA, not applicable; SAD, single ascending dose; $t_{1/2}$, elimination half-life; T_{max}, time to reach C_{max}; QD, once daily.

Figure 3. Mean (SD) Plasma Pharmacokinetic Profiles of 4334 Following (A) Single and (B) Multiple Doses (Linear Scale)



4334, ABI-4334; SD, standard deviation.

- In the SAD cohorts, 4334 was rapidly absorbed, with median time to maximum concentration of 2 hours
  - Mean elimination half-life estimates of 13-16 hours are supportive of once-daily (QD) dosing (**Table 4**)
  - Increases in 4334 exposure appeared to be near dose proportional in the 30-mg to 200-mg dose range and slightly less than dose proportional at the 400-mg dose (**Table 4**)
- Consumption of a high-fat meal appears to lower 4334 exposure and delay absorption (**Table 4**)
- In the MAD cohorts, mean profiles were similar on Day 1 and Day 8 (**Figure 3B**)
  - C_{24} levels of 4334 showed minimal to no accumulation in most HVs over 8 days of dosing, with Day 8 means of 119 and 263 ng/mL in the 100-mg and 200-mg cohorts, respectively (**Table 4**)

Table 5. Observed QD 4334 Exposures Relative to In Vitro Antiviral Activity

Parameters	4334: 100-mg Cohort Observed[a]	4334: 200-mg Cohort Observed[a]	4334: 300-mg Predicted[b]
C_{min}, ng/mL	119	263	376
HBV DNA EC_{50}, nM	0.5	0.5	0.5
C_{min}/pa HBV DNA EC_{50}	79	175	250
cccDNA EC_{50}, nM	2.6	2.6	2.6
C_{min}/pa cccDNA EC_{50}	15	34	48

EC_{50} values per Unchwaniwala N, et al. Poster presentation at EASL 2023. (Poster WED-114).
[a]Based on observed data on Day 8. [b]Based on 4334 at 100-mg/200-mg QD dose observed C_{min} and assumptions of PK dose proportionality and similar accumulation.
4334, ABI-4334; 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; PK, pharmacokinetics; QD, once daily.

- At steady state, C_{min} values following 100-mg 4334 QD administration were 79- and 15-fold above the paEC_{50}s of HBV DNA and cccDNA formation, respectively; at 200 mg QD, they were 175- and 34-fold above the paEC_{50}s of HBV DNA and cccDNA formation, respectively **(Table 5)**

Conclusions

- 4334, a novel next-generation core inhibitor, was well tolerated when administered orally up to 400 mg as a single dose and 200 mg as multiple QD doses for 8 days
- Plasma concentrations were higher than predicted by nonclinical models and C_{min} values were in multiple-fold excess of the in vitro paEC_{50} values for the inhibition of HBV DNA and cccDNA formation at all doses
- The data indicate the 4334 has the potential to provide potent inhibition of HBV with daily dosing. Potential best in class activity is projected, with a dose of 200 mg estimated to achieve 175× paEC_{50} for HBV DNA replication inhibition and 34× paEC_{50} for the prevention of cccDNA formation

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