Safety and pharmacokinetics of ABI-H3733, a novel second-generation HBV core inhibitor: Results from a Phase 1a study in healthy volunteers

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INTRODUCTION

- Chronic hepatitis B virus (HBV) infection is a significant public health problem. Worldwide, approximately 250 million people are chronically infected with HBV with approximately 887,000 deaths annually, primarily from complications of cirrhosis and/or hepatocellular carcinoma[1–4]
- Current standard of care nucleos(t)ide reverse transcriptase inhibitors are effective in reducing HBV DNA but are unable to fully suppress viral replication or prevent the establishment of covalently closed circular (ccc)DNA[5–6]
- ABI-H3733 (3733) is a second-generation core inhibitor that can target multiple steps of the HBV replication cycle, including prevention of the establishment of cccDNA
- In vitro, 3733 has increased potency compared with first-generation core inhibitors against HBV replication and inhibition of cccDNA formation[7]

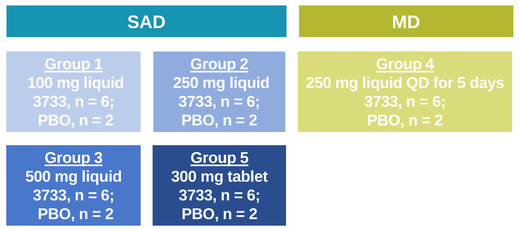
OBJECTIVE

- To report the dose-related safety and pharmacokinetics (PK) of 3733 administered to healthy volunteers following single and multiple oral doses

METHODS

- Forty healthy volunteers were enrolled in the study in 5 groups. In each group, 6 healthy volunteers received 3733, while 2 received placebo (PBO)
  - Groups 1, 2, and 3 were administered orally a single dose of 3733 at 100 mg, 250 mg, and 500 mg, respectively, as a liquid formulation
  - Group 4 was administered orally multiple doses of 250 mg once daily (QD) for 5 days, as a liquid formulation
  - Group 5 was administered orally a single dose of 3733 at 300 mg, as a prototype tablet (**Figure 1**)
- Safety was assessed by physical exams, treatment-emergent adverse events (TEAEs), and laboratory parameters
- Concentrations of 3733 were measured by validated liquid chromatography mass spectrometry methods

Figure 1. Phase 1a study groups



3733, ABI-H3733; MD, multiple dose; PBO, placebo; QD, once daily; SAD, single ascending dose.

RESULTS

- All 40 healthy volunteers completed the study
- Overall, baseline demographics were similar between treatment groups
- Thirty-three (83%) healthy volunteers were male, and 20 (50%) were white
- Age ranged from 20–61 years; body mass index was 19–30 kg/m^2 (**Table 1**)

Table 1. Baseline demographics

	SAD						MD	
	Liquid			Tablet			Liquid	
Characteristic	100 mg (n = 6)	250 mg (n = 6)	500 mg (n = 6)	300 mg (n = 6)	All 3733 (n = 24)	All PBO (n = 8)	250 mg (n = 6)	All PBO (n = 2)
Male, n (%)	5 (83)	6 (100)	5 (83)	5 (83)	21 (88)	5 (63)	5 (83)	2 (100)
Age, years, median (range)	44.0 (23–61)	42.5 (25–53)	29.0 (21–31)	36.0 (26–58)	33.5 (21–61)	24.5 (20–38)	41.5 (24–48)	40.0 (32–48)
Race, n (%)								
White	5 (83)	4 (67)	2 (33)	2 (33)	13 (54)	3 (38)	2 (33)	2 (100)
Asian	0	2 (33)	1 (17)	1 (17)	4 (17)	1 (13)	1 (17)	0
Other[a]	1 (17)	0	3 (50)	3 (50)	7 (29)	4 (50)	3 (50)	0
BMI, kg/m^2, median (range)	24.4 (19–30)	26.3 (22–28)	22.3 (19–24)	25.7 (21–27)	24.4 (19–30)	23.8 (19–29)	27.1 (24–29)	25.3 (25–26)

[a]Includes Pacific Islander, Native Hawaiian, Persian, Latin American, Māori, or Chinese.
3733, ABI-H3733; BMI, body mass index; MD, multiple dose; PBO, placebo; SAD, single ascending dose.

Safety

- 3733 was generally well tolerated with no serious adverse events (SAEs) or deaths
- 12/30 (40%) 3733 recipients and 3/10 (30%) PBO recipients reported a TEAE, all Grade 1 in severity (**Table 2**)
  - The most frequent TEAEs were nausea and headache
- TE laboratory abnormalities were observed in most treatment arms and were Grade 1 or Grade 2 in severity. There were no Grade 3 or Grade 4 TE lab abnormalities (**Table 2**)
  - The most frequently reported TE lab abnormality was elevated fasting cholesterol

Table 2. 3733 safety summary

	SAD						MD	
	Liquid			Tablet			Liquid	
Healthy Volunteers, n (%)	100 mg (n = 6)	250 mg (n = 6)	500 mg (n = 6)	300 mg (n = 6)	All 3733 (n = 24)	All PBO (n = 8)	250 mg (n = 6)	All PBO (n = 2)
With ≥1 TEAE	3 (50)	2 (33)	5 (83)	0	10 (42)	2 (25)	2 (33)	1 (50)
Nausea	2 (33)	0	1 (17)	0	3 (13)	0	0	0
Headache	1 (17)	1 (17)	0	0	2 (8)	1 (13)	1 (17)	0
With any TE lab abnormality	5 (83)	2 (33)	3 (50)	2 (33)	12 (50)	6 (75)	5 (83)	1 (50)
Fasting cholesterol, high[a]	4 (67)	1 (17)	1 (17)	0	6 (25)	2 (25)	1 (17)	0
Fasting LDL cholesterol, high[a]	3 (50)	1 (17)	0	1 (17)	5 (21)	1 (13)	2 (33)	0
eGFR, low[a]	1 (17)	1 (17)	0	0	2 (8)	1 (13)	2 (33)	0
Creatinine, high[a]	1 (17)	0	1 (17)	0	2 (8)	0	1 (17)	0

[a]Lab results were graded according to DAIDS criteria Version 2.1.
3733, ABI-H3733; DAIDS, division of AIDS; eGFR, estimated glomerular filtration rate; LDL, low-density lipoprotein; MD, multiple dose; PBO, placebo; SAD, single ascending dose; TE, treatment-emergent; TEAE, TE adverse event.

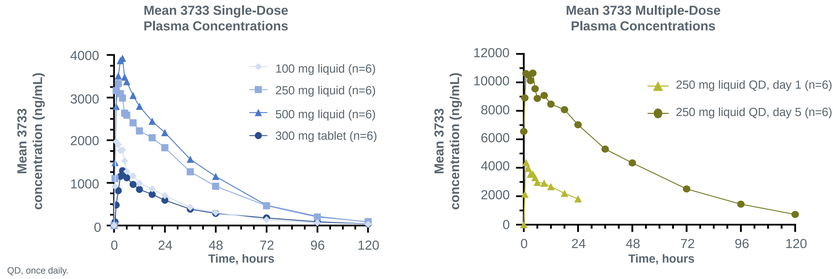
PK from current Phase 1a study

- 3733 was rapidly absorbed and subsequently eliminated with a half-life of 18.4–23.8 hours (**Figure 2, Table 3**)
- With the liquid formulation, exposure increased proportionally between the 100 mg and 250 mg single doses, with a less than proportional increase at the 500 mg single dose
- The accumulation ratio was 3.3 after 5 days of dosing (**Table 4**), and approximately 21% of the dose was recovered in the urine as parent drug
- 300 mg as a prototype tablet had lower exposures than 250 mg in the liquid formulation, with a relative bioavailability of approximately 30%
- The predicted minimum concentration for the prototype tablet is 1,190 ng/mL (2,454 nM), which is 28-fold and 5.5-fold higher than the protein-adjusted (pa) half-maximal concentration (EC_{50}) for inhibition of HBV DNA formation (89 nM) and cccDNA formation (444 nM), respectively **(Table 5)**

New tablet development

- A new 3733 tablet formulation has been developed showing comparable exposure to the liquid formulation in a dog PK study
- The predicted C_{min} for the new tablet formulation is approximately 150- and 29-times higher than the $paEC_{50}$ for inhibition of HBV DNA formation and cccDNA formation, respectively

Figure 2. Mean concentration profiles of 3733 following single and multiple doses



QD, once daily.

Table 3. Single-dose PK of 3733 in healthy volunteers

	SAD			
	Liquid			Tablet
PK Parameter	100 mg (n = 6)	250 mg (n = 6)	500 mg (n = 6)	300 mg (n = 6)
T_{max}, hours, median (range)	1.00 (1.00–3.00)	1.51 (1.00–4.00)	3.50 (1.00–5.00)	4.00 (2.00–4.00)
$T_{½}$, hours, mean ± SD	23.78 ± 6.52	20.56 ± 5.03	18.44 ± 3.07	22.63 ± 5.11
C_{max}, ng/mL, mean (CV%)	2,121 (21.4)	3,656 (41.8)	4,156 (35.3)	1,346 (16.5)
$AUC_{0–24}$, h·ng/mL, mean (CV%)	26,600 (7.9)	54,190 (22.8)	63,470 (38.6)	19,890 (12.6)
$AUC_{0–inf}$, h·ng/mL, mean (CV%)	47,600 (14.9)	113,900 (31.6)	130,600 (41.3)	40,790 (21.7)

3733, ABI-H3733; AUC, area under the curve; $AUC_{0–24}$, AUC from time 0 to 24 hours; $AUC_{0–inf}$, AUC from time 0 extrapolated to infinity; C_{max}, maximum concentration; CV, coefficient of variation; PK, pharmacokinetics; SAD, single ascending dose; SD, standard deviation; $T_{½}$, half-life; T_{max}, time to reach C_{max}.

Table 4. Multiple-dose PK of 3733 in healthy volunteers

	MD	
PK Parameter	Day 1, 250 mg liquid QD n = 6	Day 5, 250 mg liquid QD n = 6
T_{max}, hours, median (range)	1.00 (1.00–4.00)	2.00 (1.00–4.00)
$T_{½}$, hours, mean ± SD	24.22 (5.91)	27.84 (9.15)
C_{max}, ng/mL, mean (CV%)	4,576 (18.2)	11,270 (21.0)
$AUC_{0–24}$, h·ng/mL, mean (CV%)	63,580 (13.2)	206,100 (13.3)
RA AUC_{tau}	NA	3.3 (0.3)

3733, ABI-H3733; AUC, area under the curve; $AUC_{0–24}$, AUC from time 0 to 24 hours; C_{max}, maximum concentration; CV, coefficient of variation; MD, multiple dose; NA, not applicable; PK, pharmacokinetics; QD, once daily; RA, accumulation ratio; SD, standard deviation; $T_{½}$, half-life; T_{max}, time to reach C_{max}.

Table 5. Projected prototype tablet exposure at 300 mg QD and HBV $paEC_{50}$

Projected C_{min} (nM)	HBV DNA EC_{50} (nM)	HBV DNA $paEC_{50}$ (nM)[1]	C_{min}/$paEC_{50}$	cccDNA EC_{50} (nM)[1]	cccDNA $paEC_{50}$ (nM)	C_{min}/$paEC_{50}$
2454	12	89	28	62	444	6

[1]Data first reported in Cai D, et al. Presented at: EASL 2021; June 23–26, 2021; Virtual.
ccc, covalently closed circular; C_{min}, trough concentration; EC_{50}, half maximal effective concentration; HBV, hepatitis B virus; pa, protein-adjusted; QD, once a day.

CONCLUSIONS

- 3733, a novel second-generation core inhibitor, was safe and well tolerated, with a favorable PK profile following single and multiple oral doses
- PK profile supports once daily, oral dosing regimens in patients with cHBV
- Plasma concentrations exceeded in vitro protein-adjusted EC_{50} values for inhibition of cccDNA formation, and potent inhibition of HBV with QD dosing is projected
- An improved tablet formulation is projected to provide exposures comparable to those observed with the liquid formulation and will be evaluated in a Phase 1b study

References

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