Improving the pharmacokinetic profile of the hepatitis B virus core inhibitor ABI-H3733 following oral administration: results from new formulation activities

SAT-389

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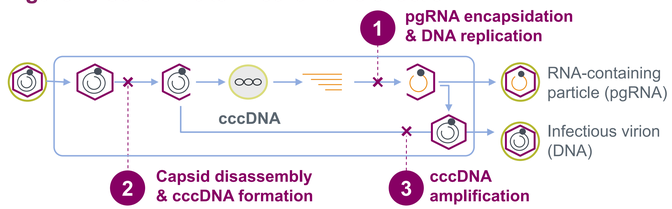
Background

- Core inhibitors are a novel class of antivirals with the potential to improve cure rates in patients with chronic hepatitis B virus infection (cHBV)
  These agents have:
  - Multiple mechanisms of action targeting the viral replication cycle, including inhibition of pregenomic RNA (pgRNA) encapsidation and DNA replication, preventing the assembly and release of new viral particles, and preventing the formation and amplification of covalently closed circular (ccc)DNA[1] (**Figure 1**)
  - Demonstrated potent antiviral activity in Phase 1 studies[2,3] and additive antiviral activity when combined with nucleos(t)ide reverse transcriptase inhibitors in Phase 2 studies[4–6]
- ABI-H3733 is a novel orally administered, next-generation inhibitor of HBV core protein
  - In a Phase 1a study (ABI-H3733-101; NCT04271592), ABI-H3733 demonstrated favorable systemic exposure with a half-life ($t_{½}$) of 21 hours using a Liquid formulation in healthy participants[7]
  - An initial prototype tablet formulation (T1) only achieved 30% exposure compared with the Liquid formulation in the Phase 1a study, with predicted trough concentrations (C_{min}) approximately 28- and 5.5-fold higher than the protein-adjusted half-maximal effective concentration ($paEC_{50}$) for HBV DNA formation and cccDNA formation, respectively[7]

Figure 1. Core inhibitor mechanisms of action



cccDNA, covalently closed circular DNA; pgRNA, pregenomic RNA.

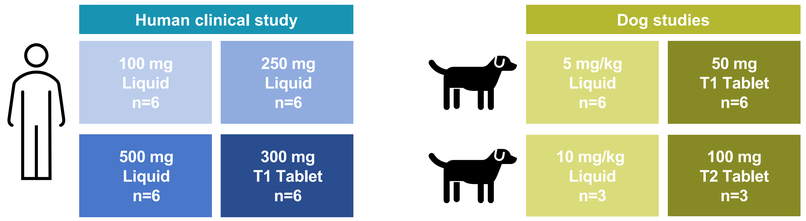
Objective of this analysis

- To assess the pharmacokinetic (PK) profile of a new tablet formulation (T2 Tablet) of ABI-H3733 in beagle dogs, a model predictive of relative exposures in humans

Methods

- The initial Liquid (5 mg/kg) and T1 Tablet (50 mg) formulations of ABI-H3733 were tested in dog PK studies (n=6 male beagles per group) and subsequently assessed in healthy human participants at doses of 100, 250, and 500 mg for the Liquid formulation and 300 mg for the T1 Tablet (n=6 per group). ABI-H3733 Liquid and T1 Tablet formulations were administered by mouth (PO) as single doses **(Figure 2)**
- Due to the low exposure of the ABI-H3733 T1 Tablet in dogs and humans, the T2 Tablet was designed to improve bioavailability and achieve comparable exposure to the Liquid formulation by improving the kinetic solubility and preventing precipitation in vivo
- The PK of the ABI-H3733 Liquid (10 mg/kg) and T2 Tablet (100 mg) formulations were evaluated in dog PK studies (n=3 male beagles per group). ABI-H3733 Liquid and T2 Tablet formulations were administered PO as single doses **(Figure 2)**
- Concentrations of ABI-H3733 were measured by validated liquid chromatography mass spectrometry methods

Figure 2. Evaluation of ABI-H3733 T1 and T2 Tablet vs Liquid formulations (PO, single dose)



PO, by mouth; T1, initial prototype tablet formulation; T2, new tablet formulation.

Results

Table 1. ABI-H3733 PK in humans and dogs, T1 Tablet vs Liquid formulation

	Humans				Dogs	
	Liquid			T1 Tablet	Liquid	T1 Tablet
PK Parameter	100 mg (n=6)	250 mg (n=6)	500 mg (n=6)	300 mg (n=6)	5 mg/kg (n=6)	50 mg (n=6)
T_{max}, hours, median (minimum, maximum)	1.00 (1.00, 3.00)	1.51 (1.00, 4.00)	3.50 (1.00, 5.00)	4.00 (2.00, 4.00)	1.58 (0.5, 2.00)	2.33 (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	9.7 ± 0.79	10.2 ± 2.04
C_{max}, ng/mL, geo mean (geo CV%)	2,121 (21.4)	3,656 (41.8)	4,156 (35.3)	1,346 (16.5)	6,000 (21.5)	1,748 (19.7)
$AUC_{0–inf}$, h·ng/mL, geo mean (geo CV%)	47,600 (14.9)	113,900 (31.6)	130,600 (41.3)	40,790 (21.7)	48,888 (23.0)	17,225 (37.9)
F%	NA	NA	NA	30	NA	35.2

AUC, area under the curve; $AUC_{0–inf}$, AUC from time 0 extrapolated to infinity; C_{max}, maximum concentration; CV, coefficient of variation; F, bioavailability; geo, geometric; NA, not available; PK, pharmacokinetics; SD, standard deviation; $t_{½}$, half-life; T_{max}, time to reach C_{max}.

- Human PK data from the Phase 1a study showed a relative bioavailability of 30% for the ABI-H3733 T1 Tablet compared to the Liquid formulation at 250 mg **(Table 1)**
- In dogs, the area under the curve (AUC) for the ABI-H3733 T1 Tablet 50 mg was approximately 35% compared to the Liquid formulation
- The relative bioavailability values of the T1 Tablet were comparable in human participants and dogs, indicating that the dog is a predictive model to evaluate the relative exposures for different formulations

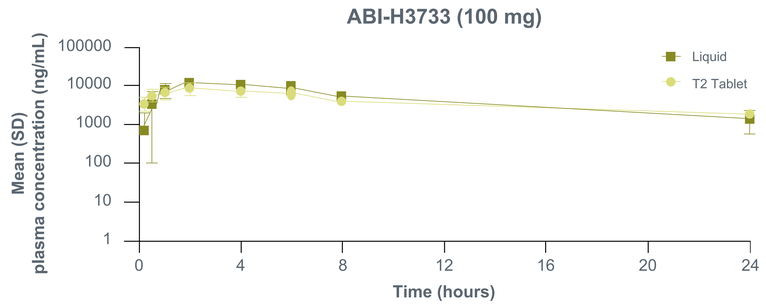
Table 2. ABI-H3733 PK in dogs, T2 Tablet vs Liquid formulation

	Dogs	
PK Parameter	Liquid, 10 mg/kg (n=3)	T2 Tablet , 100 mg (n=3)
T_{max}, hours, median (minimum, maximum)	2 (2, 2)	1.67 (1, 2)
$t_{½}$, hours, mean ± SD	11.9 ± 3.10	7.22 ± 2.00
C_{max}, ng/mL, geo mean (geo CV%)	8,603 (33.8)	12,100 (7.44)
$AUC_{0–inf}$, h·ng/mL, geo mean (geo CV%)	129,483 (12.1)	126,234 (26.0)
F%	NA	97.5

AUC, area under the curve; $AUC_{0–inf}$, AUC from time 0 extrapolated to infinity; C_{max}, maximum concentration; CV, coefficient of variation; F, bioavailability; geo, geometric; NA, not available; PK, pharmacokinetics; SD, standard deviation; $t_{½}$, half-life; T_{max}, time to reach C_{max}.

- The ABI-H3733 T2 Tablet was tested in the dog PK model at 100 mg and showed equivalent AUC compared to the Liquid formulation **(Table 2)**

Figure 3. Mean (SD) plasma concentration-time profiles of ABI-H3733 after single oral doses of the Liquid and T2 Tablet formulations in dogs



SD, standard deviation.

- The ABI-H3733 T2 Tablet was rapidly absorbed **(Figure 3)** and subsequently eliminated with a mean $t_{½}$ of 7.22 hours

Table 3. Projected T2 Tablet exposures[a]

	T2 Tablet					
Projected C_{min} (nM)	HBV DNA EC_{50} (nM)	HBV DNA $paEC_{50}$ (nM)	$C_{min}/paEC_{50}$	cccDNA EC_{50} (nM)[1]	cccDNA $paEC_{50}$ (nM)	$C_{min}/paEC_{50}$
17259	12	115	150	62	595	29

[a]These data are based on a 300-mg tablet.
cccDNA, covalently closed circular DNA; C_{min}, trough concentration; HBV, hepatitis B virus; EC_{50}, half-maximal effective concentration; $paEC_{50}$, protein-adjusted EC_{50}; T2, new tablet formulation.

- The improved T2 Tablet exposure, at a dose of 300 mg, is expected to result in C_{min} approximately 150- and 29-fold higher than the $paEC_{50}$ for HBV DNA formation and cccDNA formation, respectively **(Table 3)**

Conclusions

- Based on the relative PK data in male beagles, the T2 Tablet of ABI-H3733 is expected to achieve exposure equivalent to the Liquid formulation in humans, with predicted C_{min} at a dose of 300 mg approximately 150- and 29-fold higher than the $paEC_{50}$ for HBV DNA formation and cccDNA formation, respectively
- The T2 Tablet data from this study support once-daily dosing in patients with cHBV
  - This formulation will be used in an upcoming Phase 1b study to be conducted in patients with cHBV in the first half of 2022

References

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