Pharmacokinetics of ATI-2173, a Novel Active Site Polymerase Inhibitor Nucleotide (ASPIN), in a Phase 1b Clinical Trial

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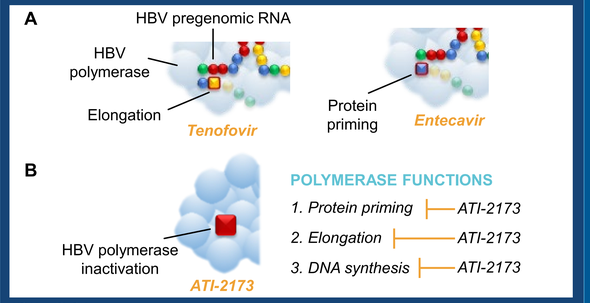
INTRODUCTION

- Current treatments for chronic hepatitis B virus (HBV) infection are not curative and require lifelong therapy to maintain viral suppression[1,2]
- Clevudine demonstrated promising efficacy in reducing HBV viral load, with sustained posttreatment effects in phase 2 and 3 studies, but high plasma clevudine exposure was associated with reversible clinical skeletal muscle myopathy in a small subset of subjects[3-5]
- ATI-2173 is a novel phosphoramidate nucleotide designed to deliver the 5'-monophosphate of clevudine directly to the liver for localized conversion to the active 5'-triphosphate
- Unlike chain-terminating nucleos(t)ide analogues, ATI-2173 is a novel active site polymerase inhibitor nucleotide (ASPIN) that noncompetitively distorts the active site of the HBV polymerase, resulting in complete inhibition of polymerase activity[6,7] (Figure 1)

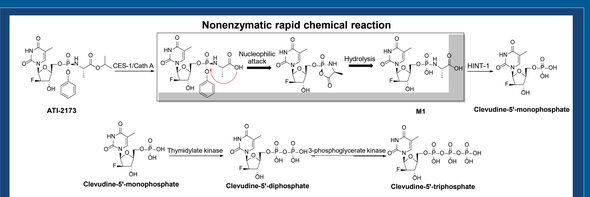
Figure 1. (A) Traditional chain-terminating nucleos(t)ide analogues inhibit DNA synthesis by competing for nucleotide positions with the HBV DNA chain. **(B)** ATI-2173 is the only nucleotide in development that inhibits all stages of DNA synthesis by distorting the HBV polymerase active site noncompetitively.



HBV, hepatitis B virus.

- The design of ATI-2173 targets the 5'-monophosphate to the liver, bypassing the first phosphorylation step and reducing systemic exposure to the circulating metabolite, clevudine, and the risk of toxicity[7] (Figure 2)

Figure 2. Metabolism of ATI-2173 to intermediate metabolite M1 and subsequently clevudine-5'-monophosphate.

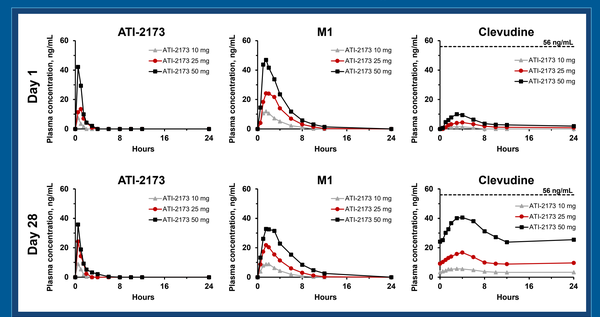


- ATI-2173 demonstrated favorable pharmacokinetics (PK) in animal models compared with clevudine dosing, with comparable 5'-triphosphate levels in the liver but much lower levels of systemic clevudine, including reduced skeletal muscle concentrations[7]
- Taken orally at doses of 10 to 50 mg per day, ATI-2173 demonstrated potent antiviral activity against chronic HBV, with mean viral load decreases of 2.7 to 2.8 $\log_{10}$ IU/mL on day 28 for each dose[8]
- Here we present the PK of ATI-2173 and its metabolites in subjects with HBV infection from the phase 1b portion of the ANTT101 study (NCT04248426)

RESULTS

- 24 subjects with HBV infection were administered 10-mg (n=6), 25-mg (n=5), or 50-mg (n=6) doses of ATI-2173 or placebo (n=7)
- ATI-2173 was rapidly absorbed, with median time to maximum concentration (T_{max}) observed at 0.5 hours post-dose, after which plasma levels rapidly declined
- At 6 hours post-dose, ATI-2173 was only measurable in 1 subject in the 50-mg group on day 28 at 1.5 ng/mL
- Plasma ATI-2173 was not detectable in any group by 8 hours post-dose
- Mean ATI-2173 plasma concentration was generally dose proportional with no indication of accumulation (Figure 3)

Figure 3. Mean plasma concentrations of ATI-2173, M1, and clevudine on days 1 and 28 of ATI-2173 dosing. Dashed line in clevudine panels represents historical steady-state clevudine minimum concentrations during treatment.[5]



- In contrast, clevudine was quantifiable in plasma through 24 hours post-dose on day 1 in the 25- and 50-mg ATI-2173 dosing groups, and on day 28 in all subjects, with higher total exposure on day 28 versus day 1
  - Clevudine was quantifiable in plasma through 6 hours post-dose on day 1 in the 10-mg ATI-2173 dosing group
  - Clevudine was detectable through 312 hours post-dose in all subjects on day 28
  - The maximum concentration of systemic clevudine with ATI-2173 administration remained below the minimum concentration observed in prior studies of clevudine administration[5]
- Plasma concentrations of M1 were similar to those of ATI-2173 but showed quantifiable mean concentrations through 3 to 12 hours post-dose in some subjects
- Clevudine 24-hour area under the plasma concentration-time curve (AUC_{24}) following daily dosing of ATI-2173 10, 25, and 50 mg for 28 days was 5%, 13%, and 34%, respectively, of the plasma exposure historically seen with the 30-mg dose of clevudine (Table 2)

Table 2. Pharmacokinetic Parameters of Clevudine Following ATI-2173 Administration Relative to Historical Clevudine Results

Drug	C_{max}, ng/mL	C_{min}, ng/mL	AUC_{24}, ng·h/mL
Historical clevudine 30 mg, mean[5]	203	56	2010
ATI-2173 10 mg, mean (% historical value)[a]	6 (3)	0	92 (5)
ATI-2173 25 mg, mean (% historical value)[a]	17 (8)	9 (15)	257 (13)
ATI-2173 50 mg, mean (% historical value)[a]	42 (20)	22 (40)	691 (34)

AUC_{24}, 24-hour area under the plasma concentration-time curve; C_{max}, maximum concentration; C_{min}, minimum concentration; PK, pharmacokinetic. [a]Percent historical value was calculated by dividing the mean plasma clevudine PK parameter following 28 days of ATI-2173 administration by the mean plasma clevudine PK parameter reported following administration of clevudine 30 mg for 12 weeks.[5]

- Exposure to ATI-2173 was characterized by an initial brief spike within the first hour of dosing, followed by rapid clearance from the blood (Table 3)
- The volume of distribution for ATI-2173 at steady state was 575 L (25-mg cohort) and 1500 L (50-mg cohort), indicating tissue targeting
  - Preclinical studies support targeting of the liver over other tissues

Table 3. Pharmacokinetic Parameters of ATI-2173, M1, and Clevudine on Day 28

Parameter, mean (% CV)	10 mg			25 mg			50 mg		
	ATI-2173	M1	Clevudine	ATI-2173	M1	Clevudine	ATI-2173	M1	Clevudine
C_{max}, ng/mL	10.26 (47.2)	9.91 (57.6)	5.86 (28.5)	26.39 (64.7)	22.93 (34.0)	16.92 (46.7)	38.70 (95.8)	39.66 (42.8)	41.99 (27.6)
C_{min}, ng/mL	0	0	3.08 (37.3)	0	0	8.62 (50.0)	0	0	22.33 (22.6)
T_{max}, median (range), h	0.50 (0-1.00)	1.50 (1.00-2.00)	2.50 (1.50-6.00)	0.50 (0.50-1.00)	1.50 (1.00-2.00)	4.00 (3.00-4.00)	0.50 (0.50-3.00)	1.50 (1.50-3.00)	3.00 (1.00-4.00)
$t_{1/2}$, h	NC	2.06 (29.4)	350.84 (9.5)	0.37 (8.2)	1.89 (23.1)	410.82 (83.9)	0.56 (46.9)	2.31 (13.7)	184.03 (11.3)
AUC_{tau}, ng·h/mL	8.89 (34.6)	35.07 (63.1)	92.17 (37.0)	28.32 (67.3)	92.24 (31.7)	256.69 (49.3)	41.27 (62.7)	198.20 (35.9)	691.01 (21.8)

AUC_{tau}, area under the plasma concentration-time curve over the dosing interval (24 hours); C_{max}, maximum concentration; C_{min}, minimum concentration; CV, coefficient of variance; NC, not calculable; $t_{1/2}$, half-life; T_{max}, time to maximum concentration.

- Clevudine exposure exhibited a delayed onset and extended half-life
- Exposure to M1 was similar to that of ATI-2173, which was characterized by a short T_{max} and half-life, and no accumulation over 28 days

METHODS

- The phase 1b portion of the ANTT101 study was a randomized, double-blind, placebo-controlled, multiple-ascending-dose trial of ATI-2173 once daily for 28 days in subjects with chronic HBV infection conducted in the Republic of Moldova and Ukraine
- Clinic visits were conducted both on and off treatment to measure the PK of ATI-2173; blood samples were collected through 24 hours post-dose on day 1 and 312 hours post-dose on day 28 (Table 1)

Table 1. Schedule of Pharmacokinetic Blood Sample Collection on Days 1 and 28

Study day	Hours post-dose																				
	Pre-dose	0.5	1	1.5	2	3	4	5	6	7	8	9	10	11	12	24	48	72	144	216	312
Day 1	X	X	X	X	X	X	X		X		X		X		X	X					
Day 28	X	X	X	X	X	X	X		X		X		X		X	X	X	X	X	X	X

- A validated ultra-high-performance liquid chromatography method with tandem mass spectrometry detection was used to measure plasma concentrations of ATI-2173 and clevudine between 1 and 1000 ng/mL and the intermediate metabolite, M1, between 1 and 500 ng/mL
- PK analysis was performed by noncompartmental methods using Phoenix WinNonlin 8.0
- Nominal timepoints were used for PK calculations

CONCLUSIONS

- ATI-2173 is a novel ASPIN in development as part of a potential curative combination treatment regimen for chronic HBV infection
- Mean plasma concentrations of ATI-2173 and its primary metabolite, M1, were generally dose proportional with no indication of accumulation
- Successful targeting of ATI-2173 to the liver greatly decreased systemic exposure to the circulating metabolite, clevudine; a 25-mg dose of ATI-2173 resulted in an AUC_{24} level roughly one-eighth of that reported with a 30-mg dose of clevudine
- ATI-2173 results in lower systemic exposure of clevudine, which may lead to increased safety and efficacy
- The 25- and 50-mg doses of ATI-2173 are currently being examined in combination with tenofovir in a phase 2a study in subjects with either HBV mono-infection or HBV/hepatitis D virus co-infection (NCT04847440)

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