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

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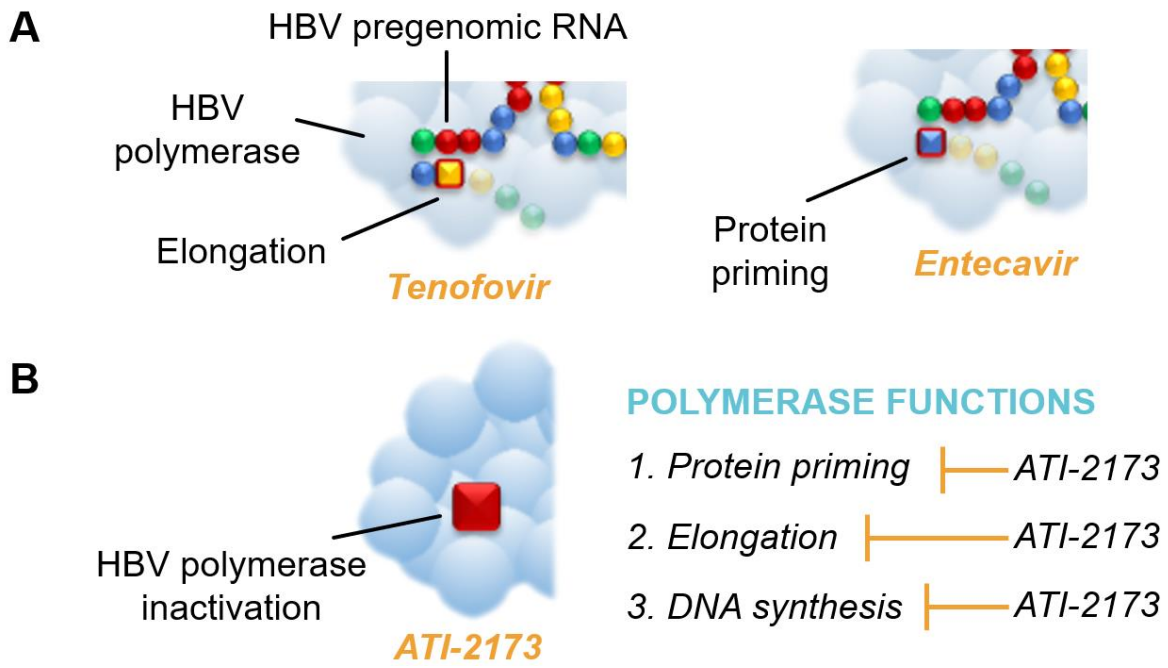
- ATI-2173 is a novel phosphoramidate nucleotide designed to deliver the 5'-monophosphate of clevudine directly to the liver for localized conversion to the active 5'-triphosphate, thereby reducing systemic exposure to clevudine and the risk of toxicity[1]
- Unlike chain-terminating nucleos(t)ide analogues, ATI-2173 is a novel ASPIN that noncompetitively distorts the active site of the HBV polymerase, resulting in complete inhibition of polymerase activity[1,2]
- ATI-2173 demonstrated favorable PK in animal models compared with clevudine dosing, with comparable 5'-triphosphate levels in the liver but much lower levels of systemic clevudine[1]
- The phase 1b portion of the ANTT101 study (NCT04248426) 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
- Here we present the PK of ATI-2173 and its metabolites in subjects with chronic HBV infection

Mechanism of action of (A) traditional chain-terminating nucleos(t)ide analogues and (B) the novel ASPIN ATI-2173



ASPIN, active site polymerase inhibitor nucleotide; HBV, hepatitis B virus; PK, pharmacokinetics.

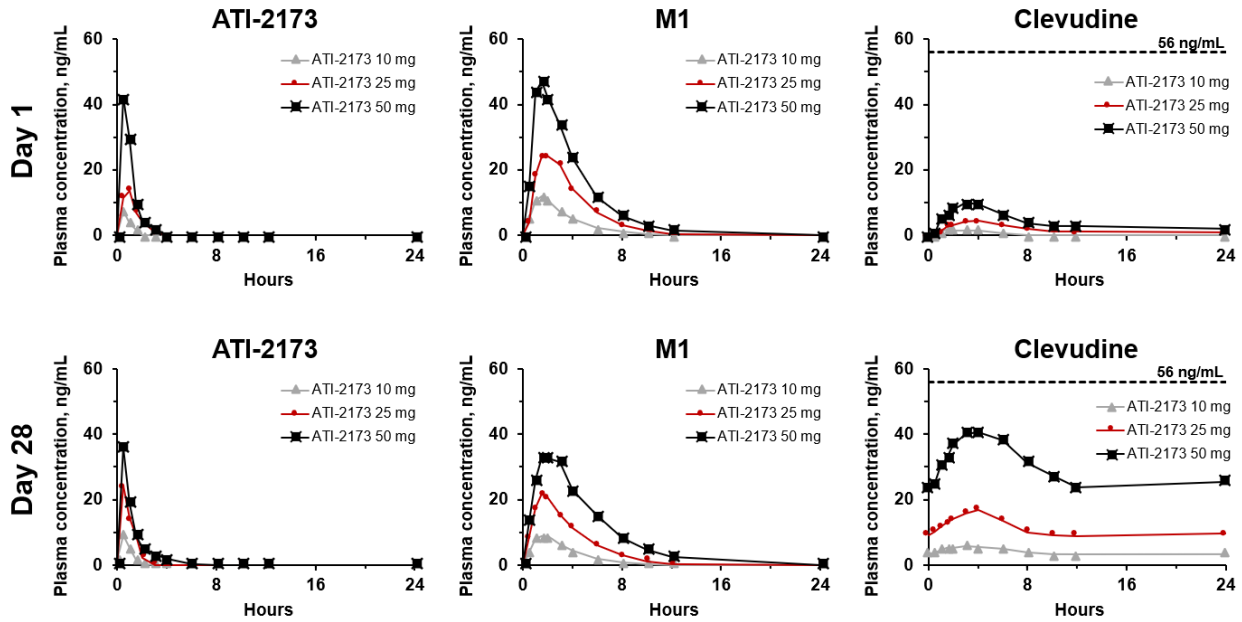
1. Squires et al. *Antimicrob Agents Chemother*. 2020;64:e00836-20. **2.** Jones et al. *Antimicrob Agents Chemother*. 2013;57:4181-4189.

Squires et al. The International Liver Congress; Virtual. Poster PO-1240.

Mean ATI-2173 Plasma Concentration Was Generally Dose Proportional With No Indication of Accumulation

- 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)
- Mean ATI-2173 plasma concentration was generally dose proportional with no indication of accumulation
  - Plasma ATI-2173 was not detectable in any group by 8 hours post-dose
- Clevudine was quantifiable in plasma through 24 hours post-dose on day 1 in the 25- and 50-mg groups, and on day 28 in all subjects, with higher total exposure on day 28 versus day 1
  - Clevudine was detectable through 312 hours post-dose on day 28 in all subjects
  - The maximum concentration of systemic clevudine with ATI-2173 administration remained below the minimum concentration observed in prior studies of clevudine administration at the marketed 30-mg dose[1]
- Plasma concentrations of M1 were similar to those of ATI-2173 but were quantifiable through 3 to 12 hours post-dose in some subjects

Mean plasma concentrations of ATI-2173, M1, and clevudine on days 1 and 28 of ATI-2173 dosing



HBV, hepatitis B virus.
Dashed line in clevudine panels represents historical steady-state clevudine minimum concentrations during treatment.[1]

1. Lim et al. *Aliment Pharmacol Ther*. 2008;27:1282-1292.

Squires et al. The International Liver Congress; Virtual. Poster PO-1240.

ATI-2173 Administration Greatly Decreased Systemic Clevudine Exposure

- Clevudine 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

Drug	C_{max}, ng/mL	C_{min}, ng/mL	AUC_{24}, ng·h/mL
Historical clevudine 30 mg, mean[1]	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.[1]

1. Lim et al. *Aliment Pharmacol Ther*. 2008;27:1282-1292.

ATI-2173 Was Rapidly Cleared From the Blood, With Distribution Volumes Indicating Tissue Targeting

- Exposure to ATI-2173 was characterized by an initial brief spike within the first hour of dosing, followed by rapid clearance from the blood
- 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
- Clevudine exposure exhibited a delayed onset and extended $t_{1/2}$
- Exposure to M1 was similar to that of ATI-2173, which was characterized by a short T_{max} and $t_{1/2}$, and no accumulation over 28 days

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.

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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)

AUC_{24}, 24-hour area under the plasma concentration-time curve; ASPIN, active site polymerase inhibitor nucleotide; HBV, hepatitis B virus.

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