ATI-2173, a Novel Active Site Polymerase Inhibitor Nucleotide (ASPIN), for HBV Cure Regimens Is Well Tolerated and Has Favorable Pharmacokinetics in Healthy Volunteers

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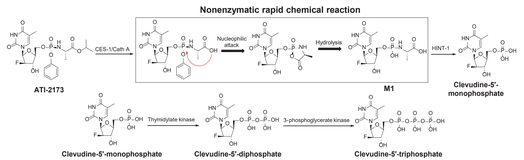
INTRODUCTION

- Current treatments for chronic hepatitis B virus (HBV) infection are not curative and require lifelong therapy to maintain viral suppression[1]
- Clevudine demonstrated extended posttreatment reductions in HBV viral load in phase 2 and 3 studies, but clinical development was stopped voluntarily by the sponsor when reversible skeletal muscle myopathy was observed in a small subset of subjects with clevudine exposure >8 months[2-6]
- ATI-2173, a novel liver-targeted phosphoramidate prodrug of clevudine-5′-triphosphate that functions as an active site polymerase inhibitor nucleotide (ASPIN), is in development as a potential curative agent for chronic HBV infection[7]
- ATI-2173 delivers the 5′-monophosphate of clevudine directly to the liver by bypassing the first phosphorylation step, thereby reducing systemic clevudine exposure and associated toxicities **(Figure 1)**[7]
  - ATI-2173 100 mg contains ~50 mg of clevudine
- Here we summarize the preclinical profile of ATI-2173 and report the safety and pharmacokinetics (PK) of ATI-2173 from a phase 1a study of healthy volunteers

Figure 1. Metabolism of ATI-2173.



METHODS

PRECLINICAL STUDIES

- In vitro studies of anti-HBV activity were conducted in HepG2/HepG2.2.15 cells and primary human hepatocytes
- Clevudine and active triphosphate concentrations were assessed in Sprague-Dawley rats receiving equimolar concentrations of oral ATI-2173 50 mg/kg or clevudine 25 mg/kg
  - Blood samples were collected at 1, 2, 4, 6, 8, or 24 hours post-dose, with tissue collection occurring immediately thereafter
- ATI-2173 and clevudine concentrations were determined in peripheral and portal plasma from jugular and portal vein–cannulated cynomolgus monkeys receiving oral ATI-2173 20 mg/kg

PHASE 1A STUDY

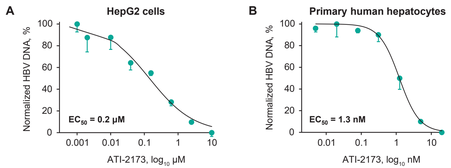
- The phase 1a, randomized, double-blind, placebo-controlled trial was conducted in Canada as part of the ANTT101 study (NCT04248426) and assessed the safety, tolerability, and PK of multiple ascending doses of ATI-2173 in healthy subjects
- Healthy adults aged 18 to ≤55 years with a body mass index of 18 to 32 kg/m^2 were randomized 6:1 to receive oral ATI-2173 doses of 10, 25, 50, or 100 mg or placebo once daily for 14 days
- Safety assessments included monitoring for adverse events (AEs)
- Blood samples for PK analysis were collected pre-dose and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours post-dose on days 1 and 14
  - Plasma ATI-2173 and clevudine concentrations were determined using validated liquid chromatography with tandem mass spectrometry methods with a range of 1 to 1000 ng/mL

RESULTS

ANTIVIRAL ACTIVITY IN VITRO

- ATI-2173 showed potent anti-HBV activity in HepG2 cells and primary human hepatocytes as well as across all HBV genotypes, with no evidence of cytotoxicity observed within the evaluated dose range **(Figure 2)**

Figure 2. In vitro anti-HBV activity in (A) HepG2 cells, (B) primary human hepatocytes, and (C) across all HBV genotypes.



C

	HBV genotype							
	A	B	C	D	E	F	G	H
Isolate	HE974371	JN406371	AB246345	U955551	AB091255	HE974369	AB064315	AB179747
EC_{50}, nM	416	212	227	234	427	328	230	718

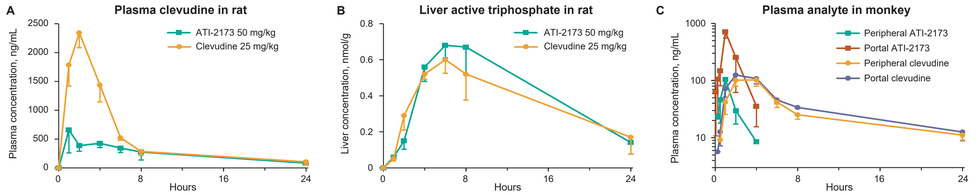
Error bars represent standard error of the mean. EC_{50}, 50% effective concentration; HBV, hepatitis B virus.

- ATI-2173 exhibited low serum protein binding, with minimal change in anti-HBV activity in the presence of increasing human serum concentrations
- When combined in vitro in primary human hepatocytes, ATI-2173 showed additive antiviral activity with tenofovir, lamivudine, and the capsid inhibitor GLS4
- Synergistic antiviral activity was demonstrated with adefovir, entecavir, and interferon-α
- ATI-2173 displayed in vitro cross-resistance with the nucleoside analogues lamivudine and entecavir, but not with the capsid inhibitors GLS4 or AT-130
  - Overlapping resistance with lamivudine was observed for the reverse transcriptase mutants M204I, V173L + M204I, and L180M + M204V, but not for M204V alone
  - Resistance with entecavir overlapped for the reverse transcriptase mutants S202G + M204I with and without M250V

PK IN PRECLINICAL MODELS

- ATI-2173 administration in rats significantly decreased plasma clevudine exposure while maintaining similar active triphosphate concentrations in the liver compared with clevudine dosing, demonstrating liver targeting of ATI-2173 **(Figure 3A, B)**
- Liver targeting of ATI-2173 was also demonstrated in cynomolgus monkeys, with an 82% hepatic extraction ratio after oral ATI-2173 dosing **(Figure 3C)**

Figure 3. Mean concentrations of (A) rat plasma clevudine, (B) rat liver active triphosphate, and (C) monkey plasma ATI-2173 and clevudine.



Error bars represent standard error of the mean.

SAFETY AND PK IN PHASE 1A STUDY OF HEALTHY ADULTS

- Of 28 healthy subjects randomized 6:1 to receive ATI-2173 or placebo, most (79%) were male, White (82%), and not Hispanic or Latino (75%; **Table 1**)

Table 1. Phase 1a Study Baseline Demographics

Parameter	Cohort[a]			
	10 mg (n=7)	25 mg (n=7)	50 mg (n=7)	100 mg (n=7)
Age, mean (range), y	32 (22-44)	32 (21-44)	39 (22-55)	39 (19-54)
Female, n (%)	2 (29)	0	3 (43)	1 (14)
Body mass index, mean (range), kg/m^2	25.5 (21.7-29.2)	26.5 (21.8-30.7)	27.0 (22.6-32.4)	24.3 (20.7-30.6)
Race and ethnicity, n (%)				
White[b]	5 (71)	6 (86)	7 (100)	5 (71)
Not Hispanic or Latino	5 (71)	5 (71)	6 (86)	5 (71)

[a]Includes 1 placebo and 6 active subjects per cohort. [b]The remaining participants were Asian (n=1 each in the 10- and 100-mg cohorts) and other race (n=1 each in the 10-, 25-, and 100-mg cohorts). No participants were Black or African American.

- The most common treatment-emergent AE was headache, reported in 33% of subjects (8/24) receiving ATI-2173 **(Table 2)**
- All AEs resolved and no serious AEs or ATI-2173 dose-limiting toxicities were reported

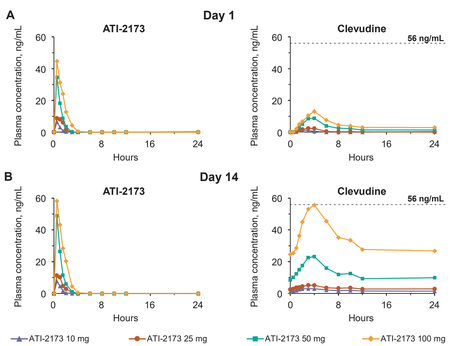
Table 2. Phase 1a Study TEAEs in >1 Subject

Preferred term, n (%)	Placebo (n=4)	ATI-2173 10 mg (n=6)	ATI-2173 25 mg (n=6)	ATI-2173 50 mg (n=6)	ATI-2173 100 mg (n=6)
Subjects with any TEAE[a]	3 (75)	0	5 (83)	2 (33)	4 (67)
Headache	0	0	5 (83)	2 (33)	1 (14)
Pruritus	0	0	2 (33)	1 (17)	0
Dizziness	0	0	0	0	2 (33)
Epistaxis	0	0	1 (17)	1 (17)	0
Erythema	0	0	1 (17)	1 (17)	0

TEAE, treatment-emergent adverse event. [a]TEAEs reported in 1 subject were abdominal distension, lower abdominal pain, feeling hot, and muscle spasms (placebo group); folliculitis and extremity pain (25-mg group); asthenia, constipation, diarrhea, premenstrual headache, toothache, and tremor (50-mg group); and decreased appetite, fatigue, nausea, and procedural dizziness (100-mg group).

- Following single- and repeated-dose administration, ATI-2173 was rapidly absorbed, with mean time to maximum plasma concentration at <1 hour post-dose and rapidly declining thereafter **(Figure 4; Table 3)**
- ATI-2173 exposure was approximately dose proportional at the 10- and 25-mg doses and approached saturation at the 50- and 100-mg doses, with no appreciable accumulation after 14 days
- Mean concentration of systemic clevudine for each ATI-2173 dose was below the minimum exposure reported for the 30-mg marketed dose of clevudine[5]

Figure 4. Phase 1a study mean plasma ATI-2173 and clevudine concentrations on (A) day 1 and (B) day 14.



Dashed lines represent the steady-state minimum plasma clevudine concentration observed with clevudine 30 mg in subjects with hepatitis B virus.[5]

Table 3. Phase 1a Study Plasma Pharmacokinetic Parameters on Day 14

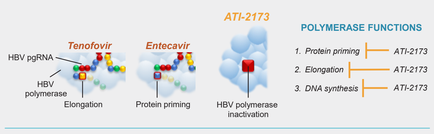
Parameter, mean (SD)	ATI-2173 10 mg (n=6)	ATI-2173 25 mg (n=6)	ATI-2173 50 mg (n=6)	ATI-2173 100 mg (n=6)
ATI-2173				
t_{max}, h	0.58 (0.20)	0.83 (0.41)	0.58 (0.20)	0.75 (0.42)
C_{max}, ng/mL	9.82 (2.74)	14.88 (6.68)	49.61 (32.54)	62.07 (30.50)
AUC_{0-24}, ng•h/mL	7.85 (2.05)[a]	17.81 (10.69)[a]	47.22 (20.73)	82.12 (38.88)
Clevudine				
t_{max}, h	2.33 (0.98)	3.25 (0.99)	3.57 (0.52)	3.67 (0.52)
C_{max}, ng/mL	3.41 (1.44)	5.58 (1.70)	23.37 (17.42)	57.68 (14.55)
% historical value[b]	2	3	12	28
AUC_{0-24}, ng•h/mL	43.60 (20.72)	79.05 (24.40)	296.19 (179.25)	803.58 (244.17)
% historical value[b]	2	4	15	40

AUC_{0-24}, area under the plasma concentration-time curve from time 0 to 24 hours; C_{max}, maximum observed concentration; SD, standard deviation; t_{max}, time to maximum concentration. [a]n=4. [b]Percent historical value was calculated by dividing the mean plasma clevudine PK parameter following 14 days of ATI-2173 administration by the mean plasma clevudine PK parameter reported following administration of clevudine 30 mg for 12 weeks.[5]

CONCLUSIONS

- The novel ASPIN ATI-2173 has promising preclinical and clinical profiles to support its development as part of a potential curative combination regimen for chronic HBV infection (Figure 5)

Figure 5. Summary of ATI-2173 preclinical and clinical profiles.



PRECLINICAL PROFILE

- ASPIN with novel mechanism of action
- Synergistic or additive anti-HBV activity with chain-terminating nucleos(t)ides or capsid inhibitors
- Liver targeting reduced systemic clevudine exposure in animal models

CLINICAL PROFILE

- Dose-proportional PK
- Significantly reduced systemic clevudine exposure compared with marketed dose of clevudine
- Safe, with headache being the most common AE

AE, adverse event; ASPIN, active site polymerase inhibitor nucleotide; HBV, hepatitis B virus; pgRNA, pregenomic RNA; PK, pharmacokinetics.

- **ATI-2173 25- and 50-mg doses are being evaluated in combination with tenofovir in an ongoing phase 2a study in subjects with either HBV mono-infection or HBV/hepatitis D virus co-infection (NCT04847440)**

REFERENCES / DISCLOSURES

1. Seto et al. *Lancet*. 2018;392:2313-2324. **2.** Marcellin et al. *Hepatology*. 2004;40:140-148. **3.** Lee et al. *Hepatology*. 2006;43:982-988. **4.** Yoo et al. *Hepatology*. 2007;46:1041-1048. **5.** Lim et al. *Aliment Pharmacol Ther*. 2008;27:1282-1292. **6.** Seok et al. *Hepatology*. 2009;49:2080-2086. **7.** Squires et al. *Antimicrob Agents Chemother*. 2020;64:e00836-20.

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