Phase 1 Results for ATI-2173, a Novel Active Site Polymerase Inhibitor Nucleotide (ASPIN), in HBV-Infected Subjects

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INTRODUCTION

- Current nucleos(t)ide analogues for treatment of chronic hepatitis B virus (HBV) infection effectively control viral replication but are not curative and require lifelong therapy to maintain virologic suppression[1]
- 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 part of a potential combination curative regimen for HBV infection[2]
- Liver targeting of ATI-2173 enhanced HBV antiviral activity and improved the safety profile by reducing systemic exposure to clevudine, while retaining comparable or improved levels in the liver[2]
  - 25 mg of ATI-2173 contains ~12.5 mg of clevudine
- Here we report the safety, tolerability, and antiviral activity of ATI-2173 monotherapy for 28 days in subjects with HBV infection

METHODS

- The phase 1b portion of the ANTT101 study (NCT04248426) was a randomized, double-blind, placebo-controlled, multiple-ascending-dose trial of ATI-2173 for 28 days in subjects with chronic HBV infection conducted in the Republic of Moldova and Ukraine
- Treatment-naive subjects positive for hepatitis B surface antigen (HBsAg) were randomized 6:2 to receive oral ATI-2173 doses of 10, 25, or 50 mg or placebo once daily for 28 days
  - Subjects positive for hepatitis B e antigen (HBeAg) with HBV DNA ≥20,000 IU/mL or negative for HBeAg with HBV DNA ≥2000 IU/mL at screening were included
- Safety assessments included monitoring for adverse events (AEs) and clinical laboratory parameters, including alanine aminotransferase (ALT) levels
- Antiviral activity was evaluated at baseline; days 7, 14, 21, and 28 on treatment; and days 4 and 10 and months 1, 3, and 6 off treatment
  - HBV DNA was measured using a Roche Cobas 6800 (lower limit of quantification [LLOQ] = 10 IU/mL)
  - HBsAg was measured using a Roche Elecsys (LLOQ = 0.05 IU/mL)
  - HBV RNA was assessed using the van Bömmel method (LLOQ = 4.04 $\log_{10}$ copies/mL; limit of detection [LOD] = 2.49 $\log_{10}$ copies/mL)[3]
    - Pregenomic RNA (pgRNA) levels in the predominantly HBeAg-negative population were low at baseline and all values were accepted as quantitative; any value not detected was imputed as 0.7 $\log_{10}$ copies/mL, as previously published[4]
- Hepatitis B core-related antigen (HBcrAg) was assessed at baseline and end of treatment using the Fujirebio Lumipulse G HBcrAg assay (LLOQ = 3 $\log_{10}$ U/mL; LOD = 2 $\log_{10}$ U/mL); HBcrAg levels were low at baseline and all values were accepted as quantitative

RESULTS

Baseline characteristics

- Of 24 subjects who completed the dosing period, all were white and not Hispanic or Latino and 22 (92%) were negative for HBeAg, reflective of the populations in the Republic of Moldova and Ukraine (Table 1)
- Women were well represented among the study population (57%-67% of subjects in each group)

Table 1. Baseline Demographics and HBV Characteristics

Parameter	Placebo (n=7)	ATI-2173 10 mg (n=6)	ATI-2173 25 mg (n=5)	ATI-2173 50 mg (n=6)
Age, mean (range), y	38 (27-53)	38 (25-56)	41 (29-63)	38 (25-48)
Female, n (%)	4 (57)	4 (67)	3 (60)	4 (67)
Body mass index, mean (range), kg/m^2	23.5 (19.8-27.6)	22.9 (19.9-26.3)	18.9 (18.3-34.0)	23.9 (18.3-32.5)
HBeAg negative, n (%)	6 (86)	5 (83)	5 (100)	6 (100)
HBV DNA, median (range), IU/mL	194,695 (6241-478,000,000)	23,176 (3160-3,180,000)	6710 (2093-33,614)	6104 (2020-41,729)
HBV genotype D, n[a]	4	4	5	4

HBeAg, hepatitis B e antigen; HBV, hepatitis B virus. [a]Two subjects had HBV genotype A (50-mg group), 2 had HBV genotype B (10-mg group), and 3 had an undetermined/undetectable HBV genotype (placebo group).

Safety

- Treatment-emergent AEs were reported in 47% of subjects (8/17) receiving ATI-2173 and 71% (5/7) receiving placebo, with headache being the most common (Table 2)
- No apparent ATI-2173 dose-related AEs, serious AEs, or AEs leading to drug withdrawal were reported

Table 2. Treatment-Emergent Adverse Events in >1 Subject

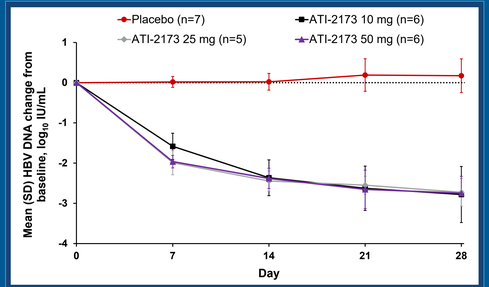
Preferred term, n (%)	Placebo (n=7)	ATI-2173 10 mg (n=6)	ATI-2173 25 mg (n=5)	ATI-2173 50 mg (n=6)
Subjects with any TEAE[a]	5 (71)	1 (17)	3 (60)	4 (67)
Headache	1 (14)	0	2 (40)	1 (17)
Coronavirus infection	0	0	1 (20)	1 (17)
ALT/AST high	2 (29)	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event. [a]TEAEs reported in only 1 subject were inflammation, common cold, and blood creatinine phosphokinase increased (placebo group); thrombocytosis (10-mg group); fatigue and bone pain (25-mg group); and secondary thrombocytopenia, external ear pain, nausea, and flu (50-mg group).

Antiviral activity

- Viral load decreased from baseline with each ATI-2173 dose, with decreases in mean HBV DNA of 2.7 to 2.8 $\log_{10}$ IU/mL on day 28 in each ATI-2173 group compared with a mean increase of 0.2 $\log_{10}$ IU/mL in the placebo group (Figure 1)
  - A similar antiviral effect (2.5-3.0 $\log_{10}$ IU/mL reduction) was reported with 1 month of clevudine treatment[5]
- After 28 days of treatment, 3 of 6 subjects in the 10-mg group, 4 of 5 in the 25-mg group, 5 of 6 in the 50-mg group, and 0 of 7 in the placebo group had HBV DNA below the limit of quantification (BLQ; <10 IU/mL); 1 of the 5 subjects in the 50-mg group achieved BLQ on day 10 posttreatment

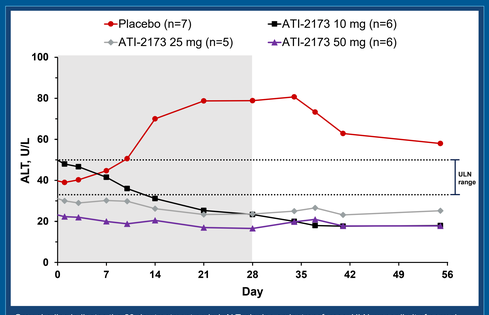
Figure 1. On-treatment mean change from baseline in HBV DNA.



HBV, hepatitis B virus; SD, standard deviation.

- HBsAg levels did not change during 28 days of treatment with any ATI-2173 dose or placebo
- ALT levels normalized with the ATI-2173 10-mg dose and remained stable and normal with the 25- and 50-mg doses (Figure 2)

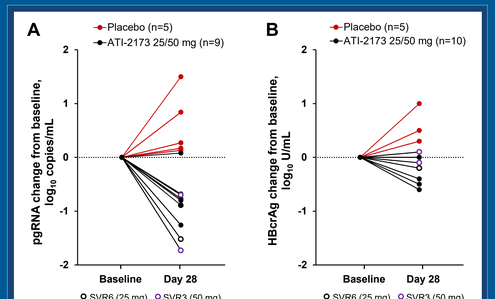
Figure 2. On- and off-treatment ALT levels.



Gray shading indicates the 28-day treatment period. ALT, alanine aminotransferase; ULN, upper limit of normal.

- After 28 days of treatment with ATI-2173 25 or 50 mg, pgRNA exhibited a mean decrease of 0.9 $\log_{10}$ copies/mL from baseline compared with a mean increase of 0.6 $\log_{10}$ copies/mL in the placebo group (Figure 3A)
  - 1 subject in the 50-mg group and 1 in the 25-mg group with sustained virologic response for 3 months (SVR3) or 6 months (SVR6) after ending treatment, respectively, had an undetectable pgRNA value on day 28
- Similar trends in HBcrAg changes from baseline were observed, with a mean decrease of 0.2 $\log_{10}$ U/mL on day 28 with ATI-2173 and a mean increase of 0.4 $\log_{10}$ U/mL with placebo (Figure 3B)

Figure 3. On-treatment change from baseline in **(A)** pgRNA and **(B)** HBcrAg.



HBcrAg, hepatitis B core-related antigen; pgRNA, pregenomic RNA; SVR3, sustained virologic response for 3 months off treatment; SVR6, sustained virologic response for 6 months off treatment.

- 1-month monotherapy with ATI-2173 25 or 50 mg led to prolonged off-treatment undetectable HBV DNA, including 1 subject who achieved SVR6, and no occurrences of ALT flares (Figure 4)

Figure 4. Individual on- and off-treatment viral load responses and ALT flares.

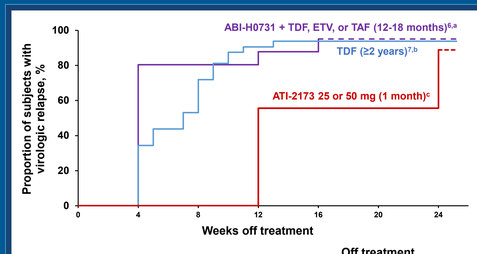
		On treatment					Off treatment				
	BL	D7	D14	D21	D28	D4	D10	W4	W12	W24[a]
Placebo	446000	592000	536000	1290000	1150000	1430000	799000	745000	3000	64200
	5115	3750	3930	4170	3080	5550	8800	8250	7760	1500
	114000	106000	93900	123000	155000	168000	157000	137000	87100	41400
	19650	19500	22500	50900	51700	46800	60400	55500	75600	78000
	879.5	1650	2110	6070	6140	11600	29400	166000	833000	854000
	1.23E+09	1.12E+09	1.58E+09	1.35E+09	1.2E+09	1.38E+09	1.3E+09	1.3E+09	1.3E+09	1.3E+09
	8E+08	7.05E+08	4.27E+08	3.41E+08	3.39E+08	3.27E+08	2.76E+08	4.87E+08	5.4E+08	
ATI-2173 10 mg	38250	709	57	35	12	11	69	2340	5210	
	12000	144	21	BLQ	BLQ	437	BLQ	BLQ	208	
	1230000	16200	2390	750	346	BLQ	120	54	196	
	1385	56	18	BLQ	BLQ	BLQ	50	174	1690	
	731500	22700	6130	3280	2440	2650	13700	20000	289000	
	849.5	73	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	21	
ATI-2173 25 mg	17700	171	44	25	BLQ	BLQ	BLQ	BLQ	79	2800
	145000	4480	1260	674	219	328	173	132	2600	113000
	2690	28	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	52[b]
	5205	40	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ
	2560	12	BLQ	BLQ	BLQ	b	BLQ	BLQ	27	196
ATI-2173 50 mg	9325	58	29	19	23	17	26	16	125	1630
	4870	39	17	BLQ	BLQ	BLQ	BLQ	BLQ	BLQ	15[b]
	20650	313	116	46	20	20	BLQ	BLQ	BLQ	704[b]
	3765	44	25	BLQ	BLQ	BLQ	BLQ	BLQ	674	1400
	25500	335	42	BLQ	BLQ	BLQ	BLQ	BLQ	430	4590
	1540	22	12	19	BLQ	BLQ	BLQ	BLQ	110	527

BLQ (<10 IU/mL) | Rebound (detectable DNA) after BLQ | ALT flare

Each row represents 1 subject. Numbers in each box represent HBV DNA (IU/mL). ALT, alanine aminotransferase; BL, baseline; BLQ, below the limit of quantification; D, day; HBV, hepatitis B virus; W, week. [a]Subjects in the 10-mg group have not yet reached W24 off treatment. [b]HBV DNA to be confirmed.

- Subjects whose HBV DNA relapsed off treatment had a gradual increase in HBV DNA levels without associated ALT flares
- ATI-2173 25 or 50 mg for 1 month resulted in a decreased rate of virologic relapse (detectable HBV DNA >10 IU/mL) that was delayed compared with other studies in subjects with HBV infection who discontinued nucleos(t)ide analogues and/or capsid inhibitors after ≥1 year of treatment[6,7] (Figure 5)

Figure 5. Off-treatment virologic relapse with ATI-2173 vs nucleos(t)ide analogue or nucleos(t)ide analogue + capsid inhibitor treatment.[6,7]



	Off treatment			
	D28	W4	W12	W24
Active subjects, N	17	17	17	11
10 mg with BLQ, n (% of D28)[d]	3	2 (66)	0	—
25/50 mg with BLQ, n (% of D28)[d,e]	9	9 (100)	4 (44)	1 (11)
SVR, n (% of N)	12 (71)	11 (65)	4 (24)	1 (9)

BLQ, below the limit of quantification; D, day; ETV, entecavir; HBeAg; hepatitis B e antigen; HBV, hepatitis B virus; SVR, sustained virologic response; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; W, week. [a]Subjects were positive (n=18) or negative (n=23) for HBeAg and had undetectable HBV DNA at the end of 12-18 months of treatment. [b]Subjects were negative for HBeAg (n=32) and had undetectable HBV DNA after ≥24 months of treatment. [c]Subjects were negative for HBeAg (n=9). [d]BLQ = HBV DNA <10 IU/mL. [e]Four subjects in the 25-mg group and 4 in the 50-mg group were BLQ at D28; the fifth subject in the 50-mg group was BLQ at D10 posttreatment.

CONCLUSIONS

- ATI-2173 is a novel ASPIN with potent anti-HBV activity (decreases ≥2.7 $\log_{10}$ IU/mL) after 28 days of treatment
  - 71% of subjects treated with ATI-2173 who were active at the end of treatment were BLQ
  - The antiviral effect was similar to that previously reported with clevudine 50 mg, with approximately one-fourth of the equivalent oral dose[5]
- Sustained off-treatment responses were noted 1 to 6 months after ATI-2173 discontinuation, with 1 subject in the 25-mg group achieving SVR6 and a slow increase in HBV DNA levels in subjects who relapsed
- No ATI-2173 dose-related AEs were reported, with mild headache being the most common AE observed in the ATI-2173 and placebo groups
- ATI-2173 25- and 50-mg doses have been advanced into a phase 2a study for evaluation in combination with tenofovir in subjects with either HBV mono-infection or HBV/hepatitis D virus co-infection

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