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

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- ATI-2173, a novel liver-targeted phosphoramidate prodrug of clevudine-5'-triphosphate that functions as an ASPIN, is in development as part of a potential combination curative regimen for HBV infection[1]
- 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[1]
- 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 HBsAg were randomized 6:2 to receive oral ATI-2173 doses of 10, 25, or 50 mg or placebo once daily for 28 days
- Here we report the safety, tolerability, and antiviral activity of ATI-2173 monotherapy for 28 days in subjects with HBV infection

ASPIN, active site polymerase inhibitor nucleotide; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

1. Squires et al. *Antimicrobial Agents Chemother*. 2020;64:e00836-20.

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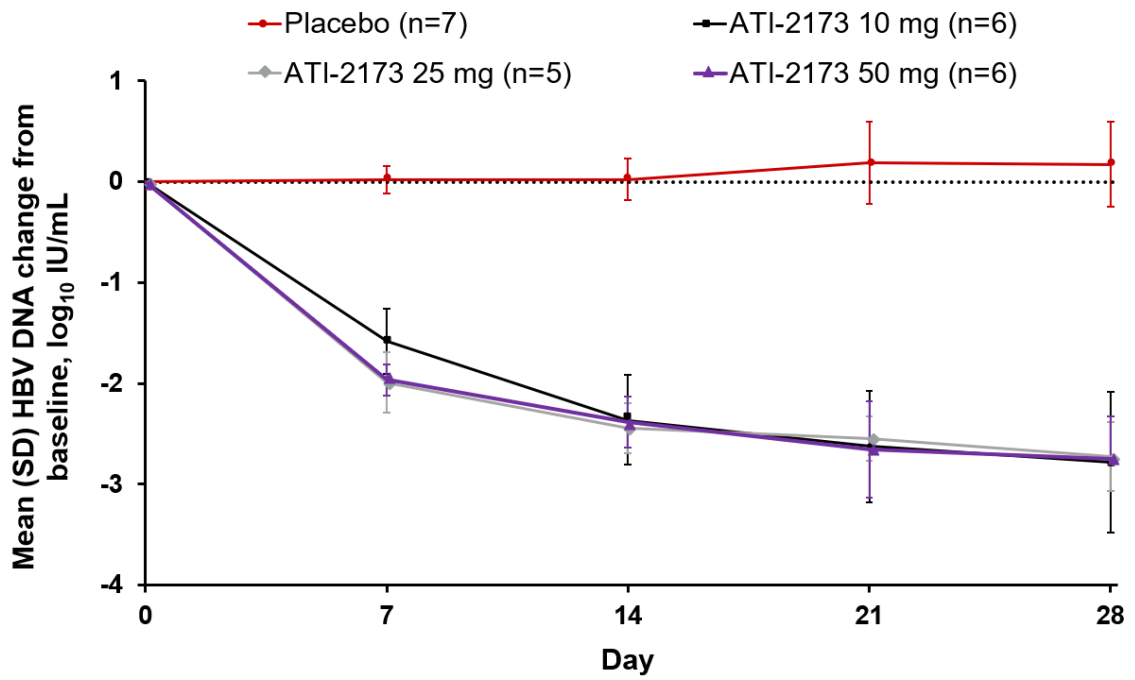
ATI-2173 Had Potent Anti-HBV Activity and Was Well Tolerated After 28 Days of Treatment

- Mean HBV DNA decreased from baseline with each ATI-2173 dose, with decreases of 2.7 to 2.8 $\log_{10}$ IU/mL on day 28 in each ATI-2173 group
  - A similar antiviral effect (2.5-3.0 $\log_{10}$ IU/mL reduction) was reported with 1 month of clevudine treatment[1]
- ALT levels normalized with the ATI-2173 10-mg dose and remained stable and normal with the 25- and 50-mg doses
- TEAEs were reported in 47% of subjects (8/17) receiving ATI-2173 and 71% (5/7) receiving placebo, with headache being the most common
- No apparent ATI-2173 dose-related AEs, serious AEs, or AEs leading to drug withdrawal were reported

On-treatment mean change from baseline in HBV DNA



AE, adverse event; ALT, alanine aminotransferase; HBV, hepatitis B virus; TEAE, treatment-emergent adverse event.

1. Marcellin et al. *Hepatology*. 2004;40:140-148.

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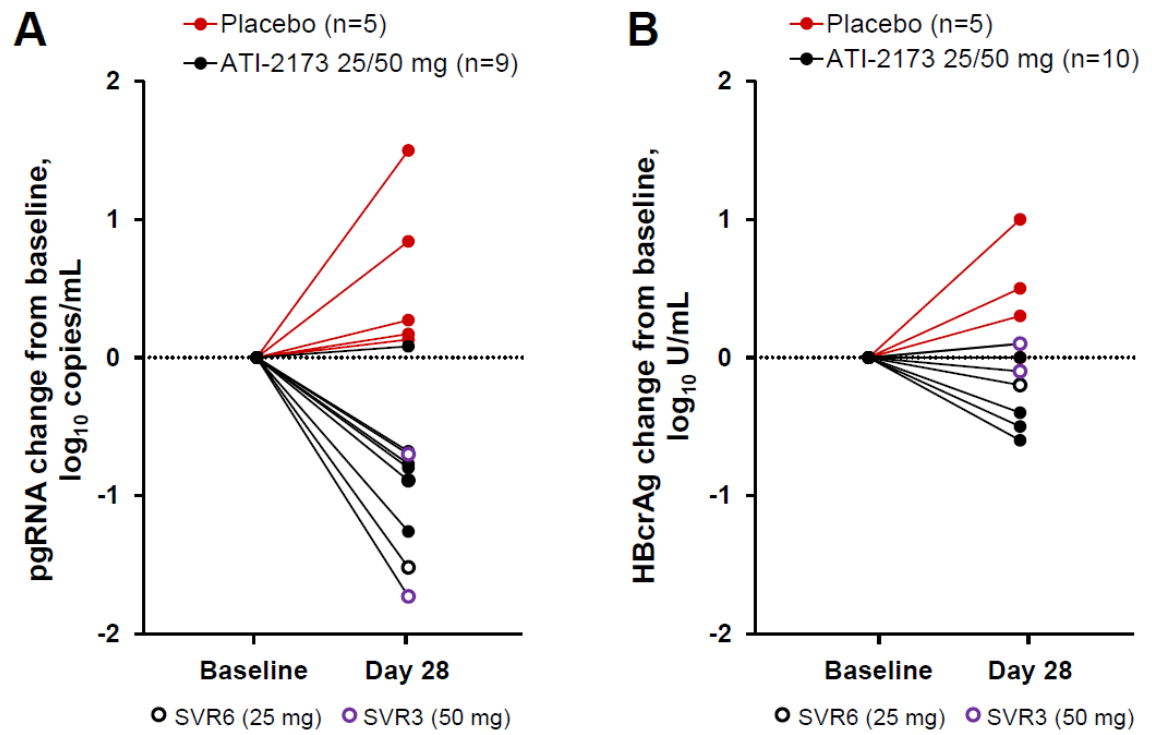
ATI-2173 Treatment for 28 Days Decreased HBV cccDNA Markers

- 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
  - 1 subject in the 50-mg group and 1 in the 25-mg group with SVR3 or 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

On-treatment change from baseline in (A) pgRNA and (B) HBcrAg



cccDNA, covalently closed circular DNA; HBcrAg, hepatitis B core-related antigen; HBV, hepatitis B virus; pgRNA, pregenomic RNA; SVR3, sustained virologic response for 3 months; SVR6, sustained virologic response for 6 months.

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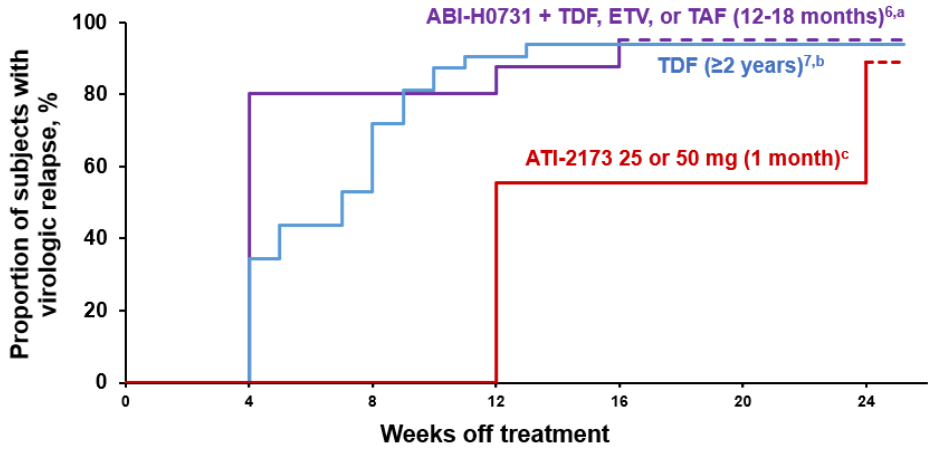
ATI-2173 Treatment for 28 Days Led to Sustained Off-Treatment Responses

- 1-month monotherapy with ATI-2173 25 or 50 mg led to prolonged off-treatment undetectable HBV DNA, including 1 subject who achieved SVR for 6 months, and no occurrences of ALT flares
- 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 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[1,2]

Off-treatment virologic relapse with ATI-2173 vs nucleos(t)ide analogue or nucleos(t)ide analogue + capsid inhibitor treatment[1,2]



		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)

ALT, alanine aminotransferase; 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.

1. Assembly Biosciences [press release]. https://investor.assemblybio.com/news-releases/news-release-details/assembly-biosciences-provides-update-ongoing-phase-2-extension. Accessed April 12, 2021. **2.** Hall et al. Presented at: The Digital International Liver Congress; August 27-29, 2020.

Mayers et al. The International Liver Congress; Virtual. Poster PO-1251.

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[1]
- Sustained off-treatment responses were noted 1 to 6 months after ATI-2173 discontinuation, with 1 subject in the 25-mg group achieving SVR for 6 months 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

AE, adverse event; ASPIN, active site polymerase inhibitor nucleotide; BLQ, below the limit of quantification; HBV, hepatitis B virus; SVR, sustained virologic response.

1. Marcellin et al. *Hepatology*. 2004;40:140-148.