ATI-2173 : A novel Active Site Polymerase Inhibitor Nucleotide (ASPIN)

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Disclosure

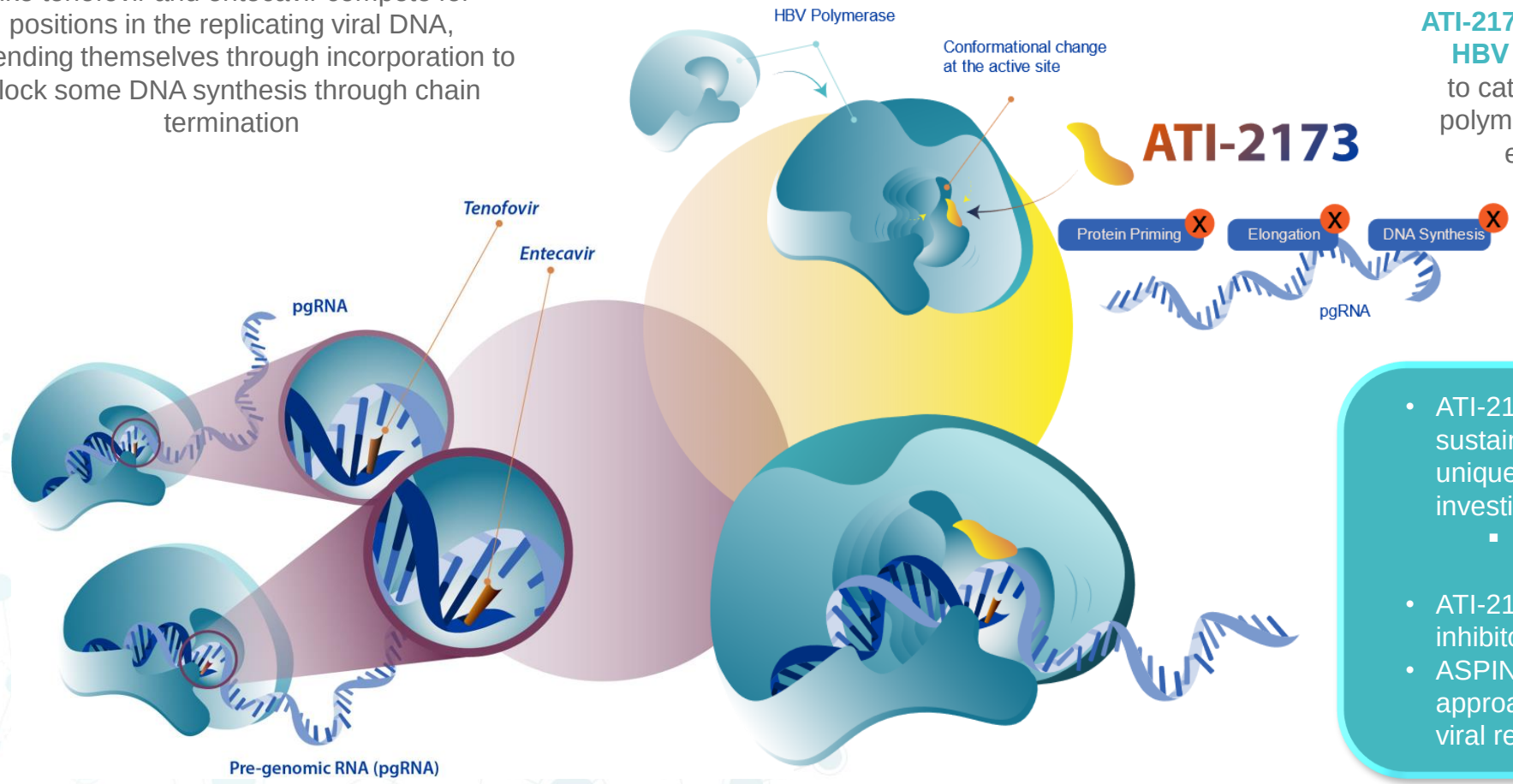
Douglas Mayers is a co-founder and Chief Medical Officer at Antios Therapeutics

Background: ATI-2173 and ASPIN Compounds

- ASPINs, such as ATI-2173 and clevudine, inhibit all HBV polymerase functions without being incorporated into HBV DNA, demonstrating a distinct MOA from traditional chain-terminating nucleos(t)ide analogues
- ATI-2173 is additive to synergistic with complementary anti-HBV MOAs
- ASPINs demonstrate potent anti-HBV activity and prolonged off-treatment viral suppression
  - Viral rebound following discontinuation of ASPIN treatment is slow, which may reduce the potential for hepatic flare
- Liver targeting of the next-generation ASPIN ATI-2173 resulted in lower extrahepatic exposure to the first-generation ASPIN clevudine, potentially reducing the risk of off-target effects observed with long-term clevudine treatment
- Combining ATI-2173 with a chain-terminating nucleos(t)ide analogue could more potently shut down the HBV polymerase, potentially leading to a higher functional cure rate
- Future combination regimens for HBV cure should include ASPINs because of their unique MOA and prolonged off-treatment responses

The Only ASPIN in Development Leverages a Unique Mechanism To Empower Combination Therapy

Chain-terminating nucleoside analogues like tenofovir and entecavir compete for positions in the replicating viral DNA, expending themselves through incorporation to block some DNA synthesis through chain termination

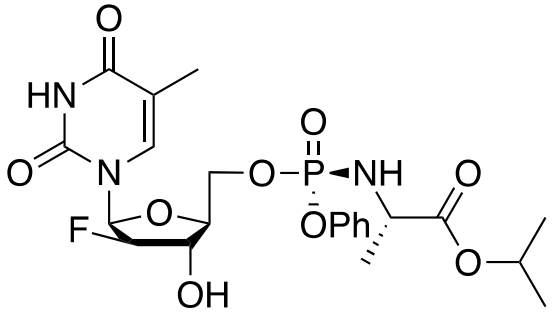


ATI-2173 actively binds to and distorts the HBV polymerase enzyme's active site to catastrophically disrupt ALL aspects of polymerase activity (protein priming, chain elongation, and DNA synthesis)

- ATI-2173 alone or combined with TDF results in sustained HBV DNA suppression off treatment, unique among approved nucleosides and investigational anti-HBV therapies
  - Could prevent rapid off-treatment viral rebound and associated ALT flares
- ATI-2173 is the only active site polymerase inhibitor nucleotide (ASPIN) in development
- ASPIN mechanism is complementary to all other approaches—potential to completely shut down viral replication and cure hepatitis B

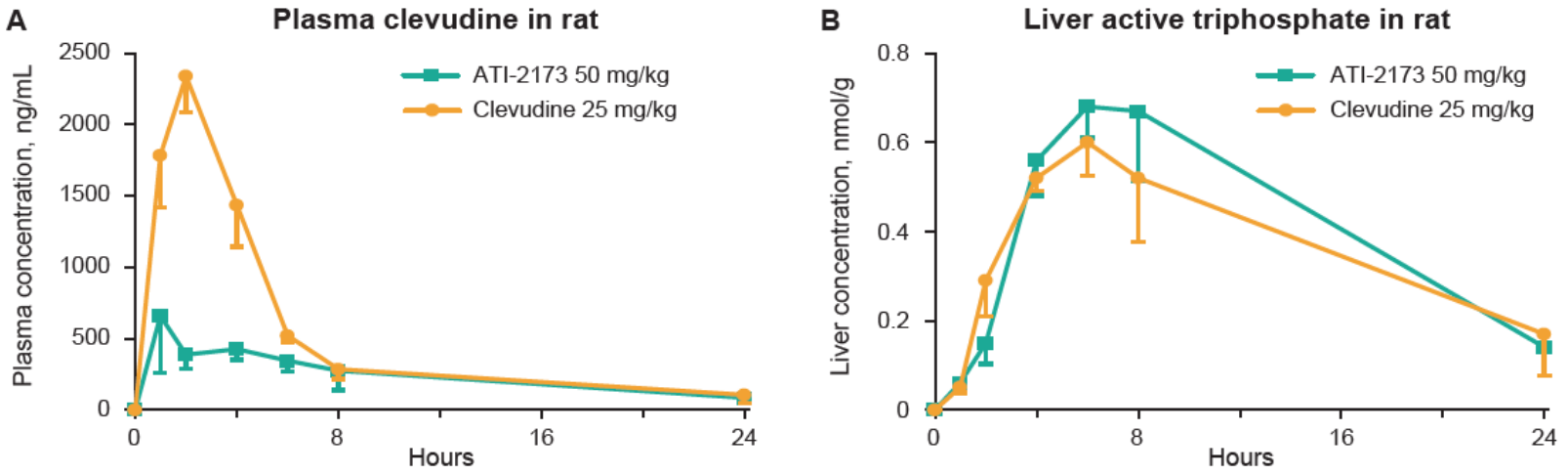
ATI-2173 Has Demonstrated Liver Targeting and Reduced Systemic Clevudine Exposure

- ATI-2173 is a liver-targeted phosphoramidate prodrug of clevudine
- ATI-2173 is ion-trapped in the liver as clevudine monophosphate, leading to:
  - High liver clevudine triphosphate levels
  - Low systemic clevudine exposure
- 1-year finite duration of therapy may reduce potential myopathy risk



ATI-2173

Mean concentrations of rat (A) plasma clevudine and (B) liver active triphosphate

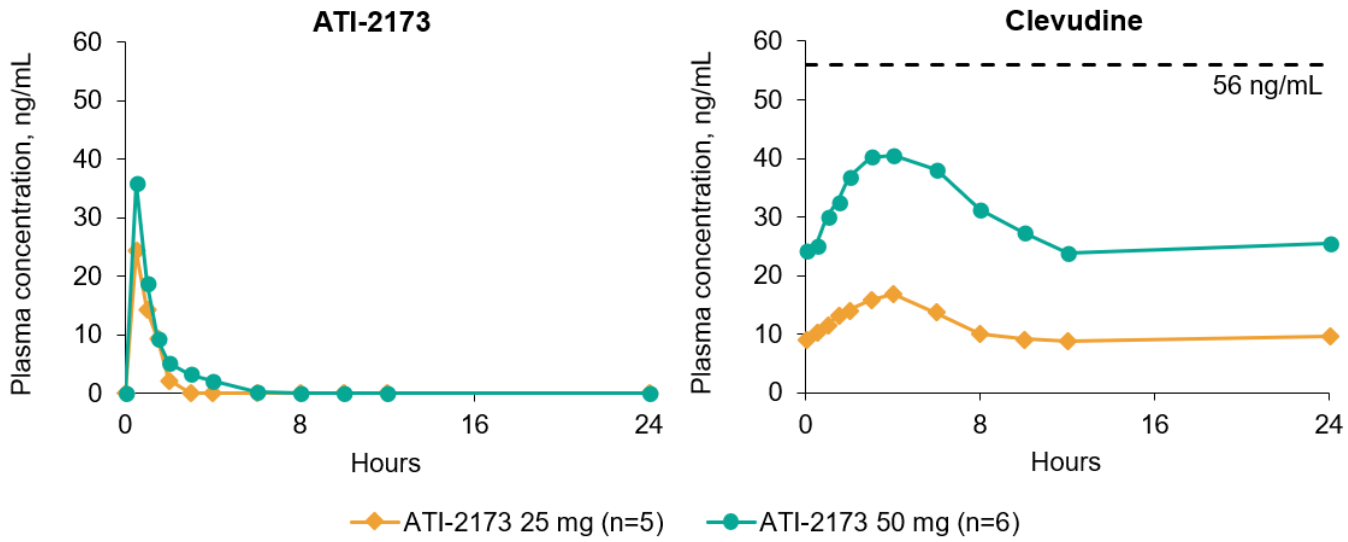


ASPIN, active site polymerase inhibitor nucleotide. Error bars represent standard error of the mean.

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

ATI-2173 Significantly Reduced Systemic Clevudine Exposure in Patients With Chronic HBV Infection

- ATI-2173 was rapidly cleared from the blood in 4 to 6 hours
- Clevudine exposure with ATI-2173 dosing was dose proportional and substantially reduced compared with historical values observed with clevudine administration



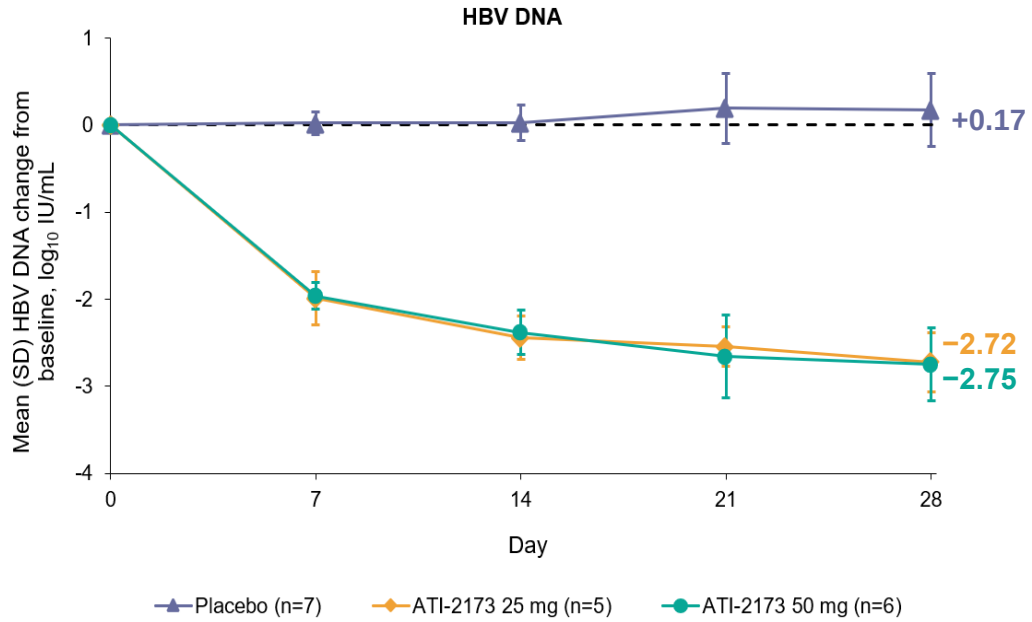
Mean (% historical value)[a]	C_{max}, ng/mL	C_{min}, ng/mL	AUC_{tau}, ng·h/mL
Historical clevudine 30 mg[1]	203	56	2010
ATI-2173 25 mg	17 (8)	9 (15)	257 (13)
ATI-2173 50 mg	42 (21)	22 (40)	691 (34)

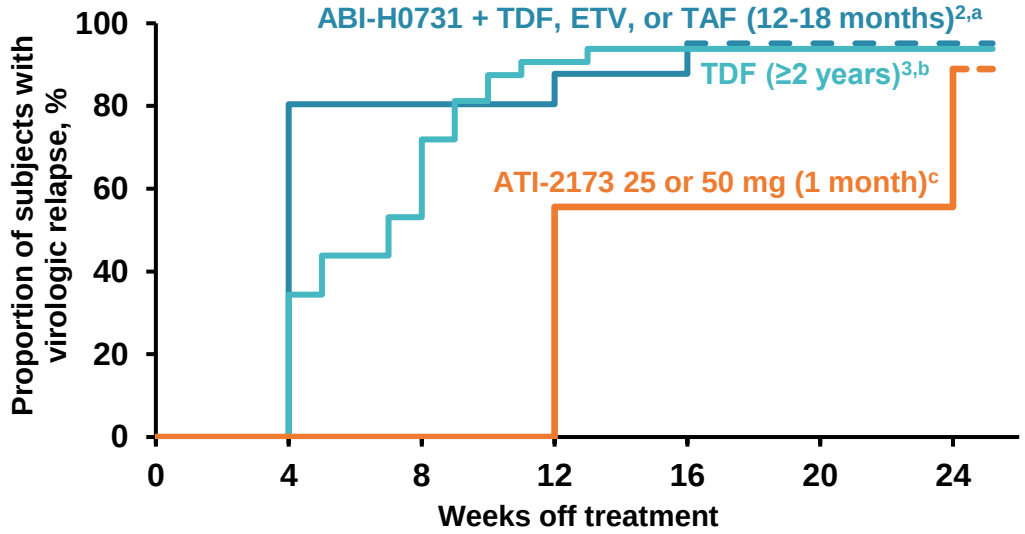
HBV, hepatitis B virus; PK, pharmacokinetic.
[a]Percent historical value was calculated by dividing the mean plasma clevudine PK parameter following administration of ATI-2173 for 14 days by the mean plasma clevudine PK parameter reported following administration of clevudine 30 mg for 12 weeks.[1]

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

All ATI-2173 Doses Demonstrated Potent Anti-HBV Activity

- Viral reductions with ATI-2173 were similar to those observed with 4 weeks of clevudine treatment (reduction of 2.5-3.0 log_{10} IU/mL)[1]
- 9 of 11 patients (82%) who received ATI-2173 were BLQ at the end of 28 days of treatment, of which 1 remained BLQ through 24 weeks post-treatment





		Off treatment		
	D28	W4	W12	W24
Active subjects, N	17	17	17	11
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; SD, standard deviation. [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.

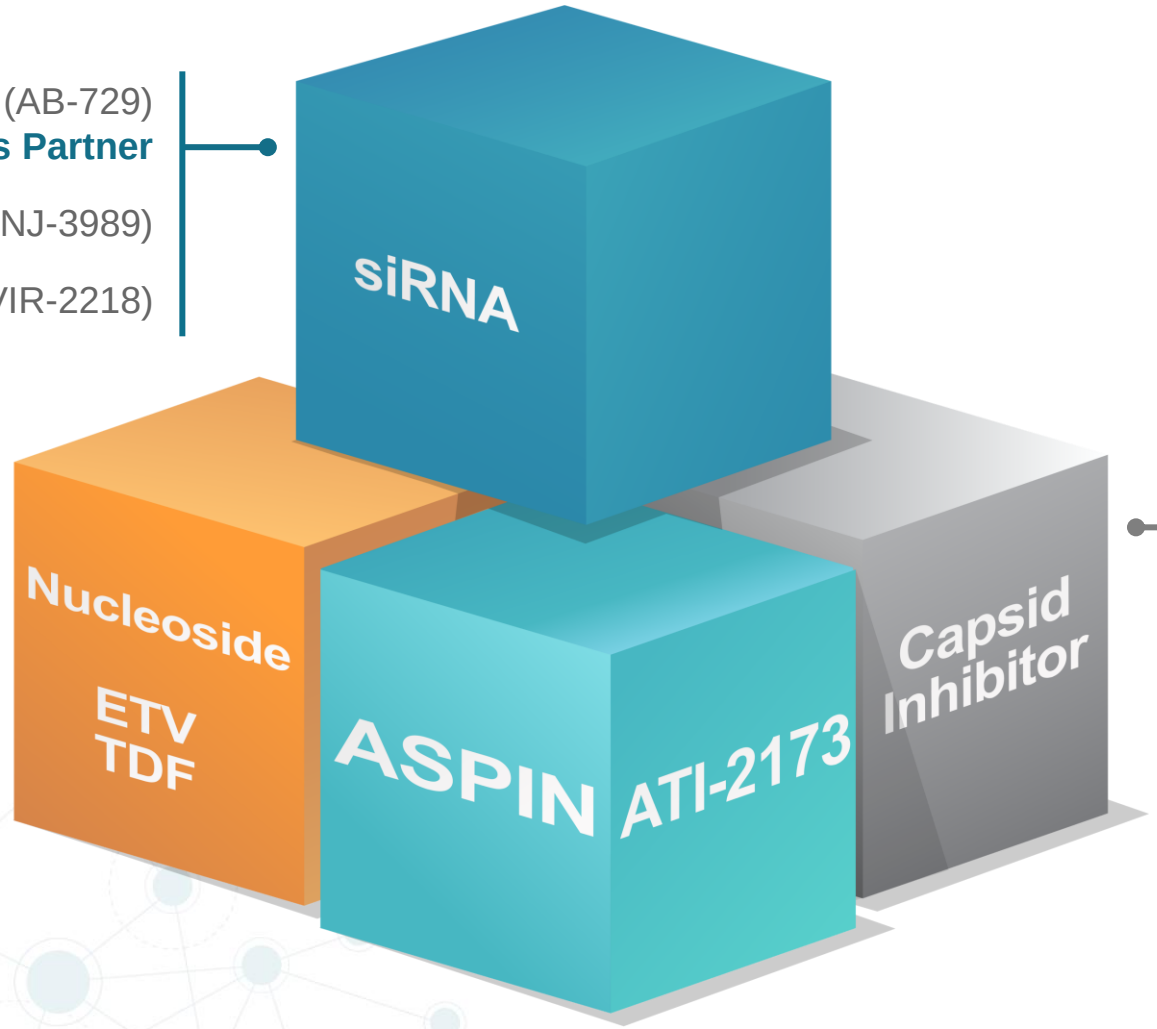
1. Marcellin et al. *Hepatology*. 2004;40:140-148. **2.** Assembly Biosciences [press release]. https://investor.assemblybio.com/news-releases/news-release-details/assembly-biosciences-provides-update-ongoing-phase-2-extens 021. **3.** Hall et al. Presented at: The Digital International Liver Congress; August 27-29, 2020.

ATI-2173 Creates Wide Opportunity for Powerful Combination Regimens

Arbutus Bio (AB-729)
Antios Partner

Arrowhead (JNJ-3989)

Vir Biotech (VIR-2218)



Assembly Bio (vebicorvir)
Antios Partner

Assembly Bio (ABI-H3733)

Arbutus Bio (AB-836)

Enanta (EDP-514)

Aligos Ther (ALG-00184)

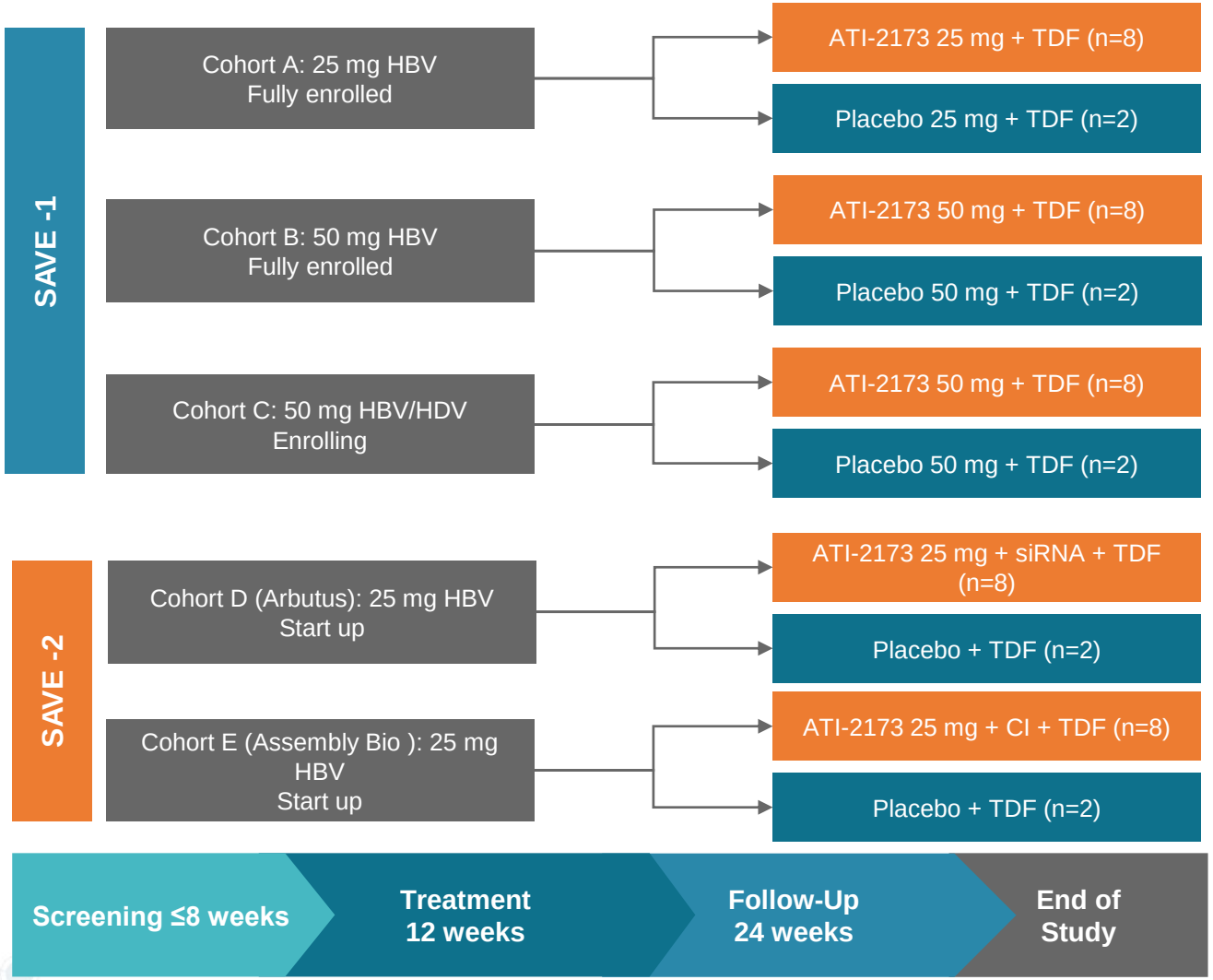
ETV, entecavir; siRNA, small/short interfering ribonucleic acid; TDF, tenofovir disoproxil fumarate.

Phase 2a Study Design

SAVE-1 and SAVE-2 (Sustained Antiviral Efficacy) Trial

Study Design

- ATI-2173 + TDF will be administered orally, once daily for 90 days in treatment-naive patients then stopped
- Treatment will be restarted for HBV-infected subjects during follow-up if viral rebound or a hepatic flare
- SVR24 data for HBV DNA will be available in mid-2022
- Addition of 2 cohorts, 1 with an siRNA and 1 with a core inhibitor in late-2021 (SAVE-2)



ATI-2173 Summary

- ATI-2173 is a novel ASPIN that inhibits all HBV polymerase functions without being incorporated into HBV DNA, demonstrating a distinct MOA from traditional chain-terminating nucleos(t)ide analogues
- Liver targeting of the next-generation ASPIN ATI-2173 results in lower extrahepatic exposure to clevudine, potentially reducing the risk of off-target effects observed with long-term clevudine treatment
- ATI-2173 demonstrated potent anti-HBV activity and prolonged off-treatment viral suppression after 1 month of dosing in patients with chronic HBV infection
  - ALT levels normalized on treatment
  - Markers of cccDNA activity in the blood (HBV RNA and HBcrAg) decreased both on and off treatment
  - Viral rebound following discontinuation of ASPIN treatment is slow, which may reduce the potential for hepatic flare
- Combining ATI-2173 with a chain-terminating nucleos(t)ide analogue could more potently shut down the HBV polymerase, potentially leading to a higher functional cure rate. The 25 and 50 mg doses of ATI-2173 combined with TDF and other novel HBV agents are being evaluated for 3 month dosing in ongoing phase 2a studies (SAVE 1 and SAVE 2)

Acknowledgements

- The Antios team would like to acknowledge all patients and investigators who participated in the ANTT101 study