The Second-Generation Hepatitis B Virus (HBV) Core Inhibitor (CI) ABI-H2158 is Associated with Potent Antiviral Activity in a 14-Day Monotherapy Study in HBeAg-positive Patients with Chronic Hepatitis B (CHB)

LP14

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Introduction

- Chronic Hepatitis B (CHB) infection remains a major cause of morbidity and mortality. The World Health Organization (WHO) estimates that approximately 257 million people worldwide are living with CHB (defined as HBsAg positive) among whom, 4.5 million are on treatment. HBV-related cirrhosis and hepatocellular carcinoma are the cause of approximately 880,000 deaths each year[1]
- HBV nucleos(t)ide polymerase inhibitors can maintain on-treatment viral suppression; however it is rarely sustained following treatment withdrawal. Therefore, novel therapeutic strategies are required in order to achieve off-treatment sustained virologic response
- The HBV core protein plays an integral role in multiple steps of the HBV lifecycle. ABI-H2158 is a second generation, potent and selective HBV core inhibitor (CI), that can suppress viral replication by preventing establishment of covalently-closed circular DNA (cccDNA)[2–4]
- *In vitro*, ABI-H2158 exhibits enhanced inhibitory potency over first-generation CIs against both viral replication (EC_{90} =0.069 µg/mL and surrogate markers (pgRNA, HBeAg and HBsAg) of cccDNA biosynthesis (EC_{90} = 0.242–0.288 µg/mL) in primary human hepatocyte infection assays
- Here we report the safety and antiviral activity from the initial cohort of CHB patients treated with oral ABI-H2158 100 mg QD or placebo for 14 days

Key Objectives

Primary

- To assess the dose-related safety and tolerability of orally administered ABI-H2158 in patients with CHB
- To evaluate ABI-H2158 changes in HBV DNA in patients with CHB

Secondary

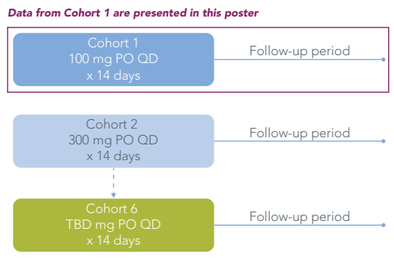
- To evaluate the pharmacokinetics (PK) of ABI-H2158 100 mg QD following 14-days of administration in patients with CHB

Exploratory

- To evaluate ABI-H2158 changes in HBV RNA in patients with CHB

Study Design

Figure 1. Design of Study ABI-H2158-101 Phase 1b



Day	1	2	8	14	15	22	29	57
PK[a]	X	X		X	X	X	X	
HBV DNA/ RNA	X	X	X	X	X	X	X	X
Safety	X	X	X	X	X	X	X	X

[a]AUC_{0-24}, C_{max}, T_{max}, $T_{1/2}$, and C_{max}, accumulation ratios and linearity factor

- In this phase 1b study, up to 6 cohorts of 9 patients with CHB will be enrolled to receive oral ABI-H2158. Within each cohort, eligible subjects will be randomized in a ratio of 7 (active):2 (placebo)
- A Safety Review Committee reviewed the safety, efficacy and PK data from each cohort versus prespecified criteria in order to support dosing in the next sequential cohort

Methods

- Safety monitoring includes physical examination, vital signs, 12-lead ECGs, collection of adverse events, and laboratory tests
- HBV DNA was measured using Roche Amplicprep COBAS® TaqMan® HBV Test v2.0; and HBV pgRNA was measured using an in-house RT-PCR method
- Plasma concentrations of ABI-H2158 are determined using a validated liquid chromatography tandem mass spectrometry method
- PK parameters are determined by non-compartmental analysis, using Phoenix™ WinNonLin®

Patient Population

Enrolled patients were recruited at 15 sites in 6 countries: New Zealand, UK, South Korea, Hong Kong, USA, and China. To be eligible for this study, patients had to meet the following criteria:

- Between 18 and 65 years of age
- BMI ≥18 and ≤34 kg/m² and a minimum weight of 45 kg
- No prior treatment within last 6 months with an investigational or approved therapy for CHB
- No prior treatment with a core protein targeted therapy
- Negative serology for HIV, HCV, or HDV
- Noncirrhotic (Metavir score F0–F2 or FibroScan® <8kPa)
- HBsAg-positive, HBeAg-positive
- HBV DNA ≥2× 10^5 IU/mL
- ALT and AST <5× upper limit of normal range

Results

Demographic and Disease Characteristics

- For Cohort 1, all patients have been randomized and have completed assigned dosing and all study visits

Table 1. Baseline Demographic and Disease Characteristics, Cohort 1

Characteristics	Placebo (N=2)	ABI-H2158 100 mg (N=7)
Age, years, mean (SD)	32.5 (0.7)	36.9 (10.8)
Sex, male; n (%)	2 (100)	5 (71)
Race; n (%) Asian Black or African American	 2 (100) 0	 6 (86) 1 (14)
BMI, kg/m², mean (SD)	20.8 (0.4)	22.6 (2.8)
HBV Genotype; n (%) B C E	 0 2 (100) 0	 1 (14) 5 (71) 1 (14)
HBV DNA at Baseline (Log_{10} IU/mL), mean (SD)	8.6 (0.3)	7.6 (1.0)
HBV pgRNA at Baseline (Log_{10} U/mL), mean (SD)	7.2 (0.4)	6.5 (1.1)
Baseline ALT (U/L), mean (SD)	55 (49.5)	38.1 (17.5)

Safety

- All treatment-emergent adverse events (TEAEs) were mild (Grade 1)
  - One patient assigned to placebo and 3 patients assigned to ABI-H2158 reported TEAEs that resolved without intervention: dizziness, fatigue, rash, headache, and upper abdominal pain
  - The rash reported by a patient receiving ABI-H2158 was mild (Grade 1), transient and resolved with no specific treatment within 24 hours of onset. There were no systemic signs or laboratory abnormalities associated with the event
  - No on-treatment moderate, severe, or serious AEs were reported
- No clinically significant ECG, vital signs, physical exam, or laboratory test abnormalities were observed
- No serious AEs, dose-limiting toxicities or premature discontinuations were reported
- Most treatment-emergent laboratory abnormalities were mild (Grade 1)
  - No clinically significant ALT/AST increase was reported
  - No trend in laboratory abnormality was observed

Table 2. Treatment-Emergent Adverse Events (TEAEs), Cohort 1

MedDRA Preferred Term	Placebo (N=2) n (%)	ABI-H2158 100 mg (N=7) n (%)
Any AE	1 (50.0)	3 (42.9)
Nervous System Disorders Grade 1 Headache Grade 1 Dizziness	 1 (50.0) 0	 1 (14.3) 1 (14.3)
Gastrointestinal Disorders Grade 1 Abdominal Pain Upper	 0	 1 (14.3)
Skin and Subcutaneous Tissue Disorders Grade 1 Rash	 0	 1 (14.3)
General Disorders Grade 1 Fatigue	 0	 1 (14.3)
AE leading to early discontinuation	0	0

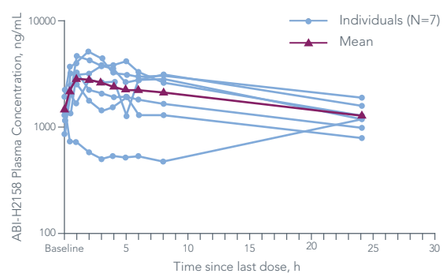
Table 3. Treatment-Emergent Laboratory Abnormalities[a]

Laboratory Abnormality	Grade	Placebo (N=2), n (%)	ABI-H2158 100 mg (N=7), n (%)
Elevated AST	1	0	2 (28.6)
Elevated ALT	1	0	2 (28.6)
Amylase	1	0	1 (14.3)
Cholesterol	1 3	1 (14.3) 0	0 1[b] (14.3)
Creatinine	1	1 (14.3)	0
Calcium	1	0	1 (14.3)
Uric acid	1	1 (14.3)	1 (14.3)
Glucose	1	0	1 (14.3)
Triglycerides	1 2	0 0	1 (14.3) 1[b] (14.3)

[a]Treatment-emergent laboratory abnormality is defined as worsened toxicity grade (DAIDS, July 2017, version 2.1) compared with Baseline
[b]The same patient had baseline Grade 2 cholesterol abnormality and baseline grade 1 triglycerides

Pharmacokinetics

Figure 2. PK at Day 14, Cohort 1



- The PK of ABI-H2158 in patients with HBV are similar to those previously reported in healthy volunteers[5]
- Steady-state exposures observed at the lowest dose level of 100 mg QD are in excess of the EC_{90} values for *in vitro* antiviral and cccDNA assays

Table 4. PK, Day 14, Cohort 1 (100 mg QD)

Dose	C_{max} ± SD, µg/mL	T_{max} ± SD, h	$T_{1/2}$* ± SD, h	AUC_{0-24} ± SD, h•µg/mL
100 mg	3.39 ± 1.23	2.3 ± 2.7	23.6 ± 8.1	46.1 ± 18.0
Dose	**C_{24} ± SD, µg/mL**	**C_{24} > EC_{90} (antiviral)[b]**		**C_{24} > EC_{90} (cccDNA)[b]**
100 mg	1.26 ± 0.360	+		+

[a]6 of 7 subjects
[b]*in vitro* primary human hepatocyte HBV infection assay

Antiviral Activity

- In patients receiving ABI-H2158, mean declines from Baseline to Day 15 in HBV DNA and pgRNA levels were 2.3 log_{10} IU/mL (range 1.7–3.0) and 2.1 log_{10} IU/mL (range 1.5–2.7), respectively

Figure 3. HBV DNA Change from Baseline, Cohort 1 (100 mg QD)

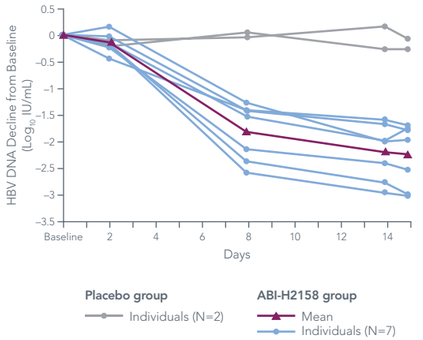
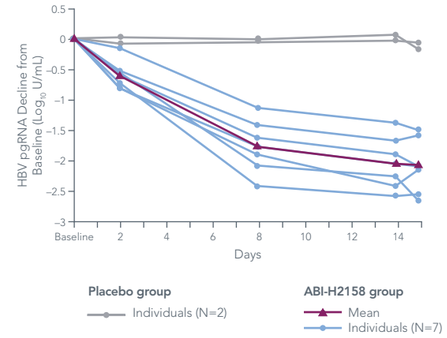


Figure 4. HBV pgRNA Change from Baseline, Cohort 1 (100 mg QD)



Conclusions

- At the time of the interim analysis, ABI-H2158 has been well-tolerated. The observed safety profile supports continued evaluation across the planned dose cohorts
- The initial ABI-H2158 dose level (100 mg QD PO) demonstrated potent antiviral activity as reflected by 2.3 log_{10} and 2.1 log_{10} reductions in HBV DNA and pgRNA over the 14-day dosing interval
- ABI-H2158 100 mg QD PK parameters support once-daily administration in patients with CHB
- Data from this interim analysis support the continued evaluation of ABI-H2158 in patients with CHB

References

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