Antiviral activity, pharmacokinetics, and safety of the second-generation hepatitis B core inhibitor ABI-H2158 in a phase 1b study of patients with HBeAg positive chronic hepatitis B infection

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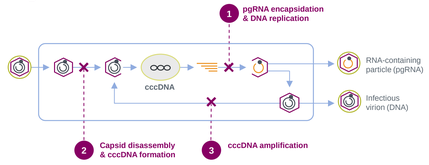
Background

- Worldwide, ~250 million people are chronically infected with hepatitis B virus (HBV) and 600,000–1 million die each year due to cirrhosis and hepatocellular carcinoma associated with chronic hepatitis B (CHB)[1–4]; of the ~94 million patients eligible for treatment, only ~4.8 million (5%) receive antiviral therapy[5]
- Nucleos(t)ide reverse transcriptase inhibitors (NrtIs) are safe and have a high barrier to resistance; however:
  - ~10%–30% of patients do not completely suppress HBV DNA after 48 weeks of treatment[6–9]
  - Of those who completely suppress HBV DNA by current assays, 70%–80% still have infectious virus[10,11]
  - Durable off-treatment virologic suppression is rare and treatment is indefinite for most patients
- New therapies are needed to provide deeper suppression of HBV replication and ultimately achieve sustained virologic response and allow for finite therapy
- Core inhibitors target multiple steps of the HBV life cycle to suppress HBV DNA, pregenomic RNA (pgRNA) and covalently closed circular DNA (cccDNA; **Figure 1**)
- Combination treatment with a core inhibitor and an NrtI, which have distinct mechanisms of action, has the potential to lead to deeper virologic suppression and to improve treatment outcomes of CHB

Figure 1. Core Inhibitor Mechanisms of Action



cccDNA, covalently closed circular DNA; pgRNA, pregenomic RNA.

ABI-H2158 (2158): A Novel Second-Generation Inhibitor of HBV Core Protein

- Disrupts HBV capsid formation by allosteric binding and interference with core protein dimerization
- Broad in vitro antiviral activity with 5- to 10-fold increased potency over first-generation core inhibitors[12]
  - Inhibits virion and pgRNA particle formation (Concentration of drug that gives half maximal response [EC_{50}] = 0.02 µM)
  - Inhibits de novo formation of cccDNA and downstream HBeAg and HBsAg production (EC_{50} = 0.21–0.72 µM)
  - Pangenotypic and fully active against NrtI-resistant HBV
- Orally administered once daily without regard to food
- Favorable clinical safety profile in Phase 1 studies to date

Figure 2. Study Design

Day	1	2	8	14	15	22	29	57
Safety	X	X		X	X	X	X	X
HBV DNA and pgRNA	X	X	X	X	X	X	X	X
PK	X	X	X	X	X	X	X	

Within each cohort, patients randomized in a ratio of 7 (active):2 (placebo).
HBV, hepatitis B virus; pgRNA, pregenomic RNA; PK, pharmacokinetics; PO, by mouth; QD, once daily.

Objectives

- In patients with CHB treated with oral placebo or 2158 100, 300, or 500 mg once daily (QD) for 14 days:
  - To assess the dose-related safety and tolerability
  - To evaluate changes in HBV DNA and HBV pgRNA
  - To evaluate the pharmacokinetics (PK)
- Enrolled patients were recruited at 15 sites in 6 countries: New Zealand, United Kingdom, South Korea, Hong Kong, United States of America, and China

Table 1. Patient Population

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/m^2 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 inhibitor
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

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHB, chronic hepatitis B; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; HIV, human immunodeficiency virus.

Methods

- Safety was assessed by physical examination, vital signs, 12-lead electrocardiogram (ECG), collection of adverse events (AEs), and laboratory parameters
- Efficacy was assessed through monitoring HBV nucleic acids and antigens
  - Roche Ampliprep COBAS® TaqMan® HBV DNA Test v2.0 (lower limit of quantification [LLOQ] = 20 IU/mL)
  - Assembly HBV pgRNA assay (LLOQ = 45 U/mL [250 copies/mL])
- 2158 plasma concentrations were determined using a validated liquid chromatography tandem mass spectrometry method
- PK parameters were determined by noncompartmental analysis using Phoenix™ WinNonLin®

Results

Table 2. Baseline Demographics and Disease Characteristics

	Placebo N = 6	2158 100 mg N = 7	2158 300 mg N = 7	2158 500 mg N = 7
Age, years, mean (SD)	35.7 (10.6)	36.9 (10.8)	38.6 (8.3)	32.0 (6.6)
Male, n (%)	4 (67)	5 (71)	2 (29)	5 (71)
Asian, n (%)	6 (100)	6 (86)	7 (100)	7 (100)
BMI, kg/m^2, mean (SD)	23.2 (3.1)	22.6 (2.8)	22.3 (2.9)	22.7 (2.9)
Genotype[a], n (%)				
B	2 (33)	1 (14)	3 (43)	3 (43)
C	4 (67)	5 (71)	4 (57)	4 (57)
HBV DNA, log_{10} IU/mL, mean (SD)	8.2 (0.6)	7.6 (1.0)	7.8 (1.4)	8.3 (0.2)
HBV pgRNA, log_{10} U/mL, mean (SD)	6.7 (0.7)	6.4 (1.0)	7.1 (0.7)	7.1 (0.6)
ALT, U/L, mean (SD)	63 (40)	38 (17)	30 (26)	33 (16)

[a]One patient taking the 100-mg dose had genotype E.
ALT, alanine aminotransferase; BMI, body mass index; HBV, hepatitis B virus; pgRNA, pregenomic RNA; SD, standard deviation.

Table 3. Overall Summary of Safety

TEAEs, n (%)	Placebo N = 6	2158 100 mg N = 7	2158 300 mg N = 7	2158 500 mg N = 7
Any TEAE	3 (50)	3 (43)	2 (29)	4 (57)
Grade 1	2 (33)	3 (43)	1 (14)	2 (29)
Grade 2	1 (17)	0	1 (14)	1 (14)
Grade 3	0	0	0	1 (14)
Grade 4	0	0	0	0
Serious AEs	0	0	0	0
AEs leading to discontinuation	0	0	0	0
Deaths	0	0	0	0

AE, adverse event; TEAE, treatment-emergent adverse event

Table 4. Treatment-Emergent Adverse Events

Events, n (%)	Placebo N = 6	2158 100 mg N = 7	2158 300 mg N = 7	2158 500 mg N = 7
Headache	1 (17)	1 (14)	1 (14)	0
Dizziness	1 (17)	1 (14)	0	0
Increased ALT	1 (17)	0	1 (14)	1 (14)
Increased AST	1 (17)	0	1 (14)	1 (14)
Upper abdominal pain	0	1 (14)	0	0
Hypertriglyceridemia	0	0	1 (14)	1 (14)
Fatigue	1 (17)	1 (14)	0	0
Dyspepsia	0	0	0	1 (14)
Insomnia	0	0	0	1 (14)
Neutrophil count decreased	0	0	0	1 (14)
Rash	0	1 (14)	0	0
Diarrhea	1 (17)	0	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

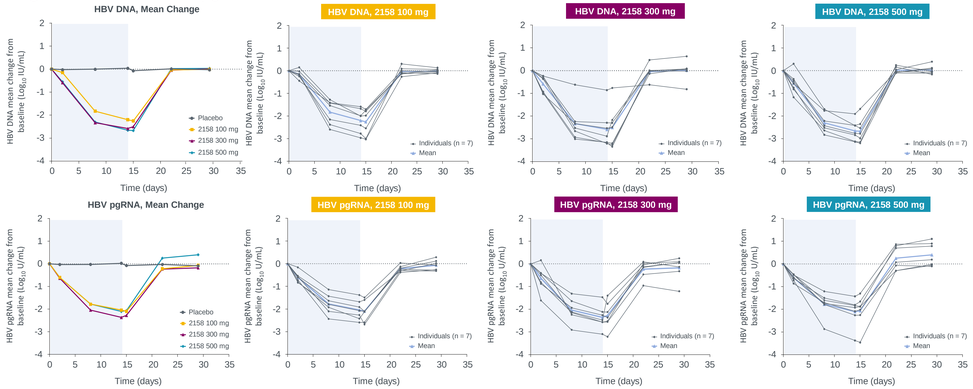
Table 5. Treatment-Emergent Laboratory Abnormalities

Laboratory abnormality, n (%)	Grade	Placebo N = 6	2158 100 mg N = 7	2158 300 mg N = 7	2158 500 mg N = 7
Elevated ALT	1	1 (17)	2 (29)	1 (14)	2 (29)
	3	1 (17)	0	0	0
Elevated AST	1	1 (17)	1 (14)	1 (14)	2 (29)
Elevated amylase	1	0	2 (29)	0	0
	2	0	0	0	1 (14)
Low calcium	1	0	1 (14)	0	0
High cholesterol	1	0	0	1 (14)	2 (29)
	2	0	0	2 (29)	0
	3	0	1 (14)	0	0
High creatinine	1	1 (17)	0	0	0
Low neutrophils	1	0	0	0	1 (14)
Low platelets	2	0	1 (14)	0	0
High triglycerides	1	0	0	1 (14)	0
	2	0	1 (14)	1 (14)	0
	3	0	0	0	1 (14)
High uric acid	1	1 (17)	1 (14)	0	0

ALT, alanine aminotransferase; AST, aspartate aminotransferase.

- Treatment-emergent adverse events (TEAEs) were similar across the treatment groups
  - There were no Grade 4 TEAEs, serious AEs, AEs leading to study drug discontinuation, or deaths (**Table 3**)
  - Most TEAEs were Grade 1 and no AE was reported by more than 1 patient in a treatment group (**Table 3 and Table 4**)
  - A single patient who received 2158 500 mg experienced a Grade 3 TEAE of hypertriglyceridemia (Grade 3 laboratory abnormality) reported on Day 29, which resolved by Day 36; the observation was considered unrelated to study drug
  - There were no clinically significant findings on physical examination or ECG
- Most treatment-emergent laboratory abnormalities were Grade 1 (**Table 5**)
  - All alanine aminotransferase (ALT) and aspartate aminotransferase elevations observed in patients receiving 2158 were Grade 1; a Grade 3 ALT elevation was observed in a patient who received placebo (**Table 5**)

Figure 3. HBV DNA and pgRNA



Blue shading indicates the time on treatment (14 days).
HBV, hepatitis B virus; pgRNA, pregenomic RNA.

Table 6. HBV DNA and pgRNA

Mean change from Baseline to Day 15	Placebo N = 6	2158 100 mg N = 7	2158 300 mg N = 7	2158 500 mg N = 7
HBV DNA (range), log_{10} IU/mL	−0.08 (−0.3 to 0.1)	−2.3 (−1.7 to −3.0)	−2.5 (−0.8 to −3.3)	−2.7 (−1.7 to −3.2)
HBV pgRNA (range), log_{10} U/mL	−0.08 (−0.2 to 0.1)	−2.1 (−1.5 to −2.7)	−2.3 (−1.4 to −3.2)	−2.1 (−1.3 to −3.5)

HBV, hepatitis B virus; pgRNA, pregenomic RNA.

- Patients receiving 2158 had rapid declines in HBV DNA and HBV pgRNA while on treatment (**Figure 3, Table 6**)
  - In a patient who received 2158 300 mg with a blunted HBV DNA response, the mean change from baseline was -0.74 log_{10} IU/mL; this patient had HBV genotype C and had no baseline variant in core protein region (**Figure 3**)
- As expected with this short duration of treatment, no meaningful changes in the levels of HBeAg, HBsAg, or HBcrAg were observed in the study

Figure 4. 2158 Plasma Concentration on Day 14

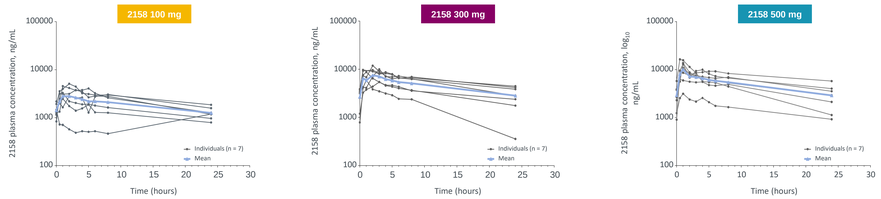


Table 7. PK Parameters at Day 14

Parameter	2158 100 mg N = 7	2158 300 mg N = 7	2158 500 mg N = 7
C_{max}, µg/mL, mean (SD)	3.39 (1.2)	8.80 (2.3)	10.42 (4.5)
T_{max}, hours, mean (SD)	2.29 (2.7)	1.8 (1.0)	0.79 (0.3)
$T_{1/2}$, hours, mean (SD)	23.63 (8.1)	19.35 (7.7)	17.42 (4.5)
$AUC_{0\text{-}24}$, h•µg/mL, mean (SD)	46.12 (18.0)	112.70 (40.7)	120.70 (50.0)
C_{24}, µg/mL, mean (SD)	1.26 (0.4)	2.84 (1.5)	2.9 (1.7)
Fold change/replication EC_{50}[a]	>50-fold	>100-fold	>100-fold
Fold change/cccDNA formation EC_{50}[b]	>10-fold	>20-fold	>20-fold

[a]C_{min} plasma concentrations/in vitro EC_{50} PHH measures of viral replication. [b]C_{min} plasma concentrations/in vitro EC_{50} PHH measures of cccDNA formation.
AUC, area under the curve; C_{24}, concentration at 24 hours; C_{max}, maximum serum concentration; cccDNA, covalently closed circular DNA; EC_{50}, concentration of drug that gives half maximal response; PHH, primary human hepatocytes; PK, pharmacokinetic; SD, standard deviation; $T_{1/2}$, half-life; T_{max}, time to reach C_{max}.

Conclusions

- 2158, a second-generation inhibitor of the HBV core protein, was selected for clinical development based on increased potency against cccDNA
- 2158 demonstrated a favorable safety profile when orally administered for 14 days at doses of 100, 300, and 500 mg QD
- Plasma concentrations of 2158 increased with dose, however, there was a less than dose proportional increase in PK between the 300-mg and 500-mg dose levels
- Dose-dependent reductions in HBV DNA and pgRNA were observed
  - In patients receiving the 300-mg dose, the mean decline from baseline to day 15 in HBV DNA and pgRNA levels were 2.5 log_{10} IU/mL and 2.3 log_{10} U/mL
- 2158 will be assessed with longer duration therapy in a Phase 2 study in which patients will receive 2158 300 mg in combination with NrtI

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