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Phase 1a Study of the Safety, Tolerability and Pharmacokinetics of ABI-H2158, a Novel Second-Generation HBV Core Inhibitor, In Healthy Volunteers

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INTRODUCTION

- Chronic hepatitis B infection remains a major cause of morbidity and mortality worldwide. Approximately 257 million people worldwide are infected and are at risk of developing chronic liver diseases, such as hepatitis, fibrosis, cirrhosis, and hepatocellular carcinoma.[1,2] Despite broad implementation of hepatitis B virus (HBV) vaccination programs, new cases of infection are still common
- Standard of care nucleos(t)ide HBV polymerase inhibitors can maintain on-treatment viral DNA suppression to the limits of quantitation but are not able to fully suppress viral replication or prevent establishment of covalently closed circular DNA (cccDNA).[3,4] Viral suppression is rarely sustained after treatment withdrawal
- Core protein inhibitors (CIs) represent a novel approach that targets multiple aspects of the viral life cycle with a small molecule direct-acting antiviral. CIs can inhibit formation of new infectious virions, as well as prevent trafficking of incoming nucleocapsids to the nucleus and block establishment of cccDNA. CIs are being developed for the treatment of patients with chronic HBV infection
- Here we report phase 1a results from the ongoing first-in-human phase 1a/1b dose-ranging study of ABI-H2158

BACKGROUND

- ABI-H2158 is a novel second-generation CI with activity against all genotypes tested [A-E], favorable pharmaceutical and pharmacokinetic (PK) properties in preclinical models, and potent antiviral activity against HBV replication (EC_{90} of 69 ng/mL) in primary human hepatocyte systems. Additionally, in vitro mechanism-based assays show that ABI-H2158 exhibits potent activity to melt preexisting viral capsids[5] and prevent cccDNA generation

Cell System	Primary Human Hepatocytes				HepG2- NTCP		
Biomarker	Viral DNA	HBeAg	HBsAg	pgRNA	Biomarker	Capsid Melting	cccDNA
EC_{90}, ng/mL	69	242	262	288	EC_{50}, ng/mL	276	163

EC_{90}, 90% maximal effective concentration. EC_{90}, 90% maximal effective concentration.

KEY OBJECTIVES

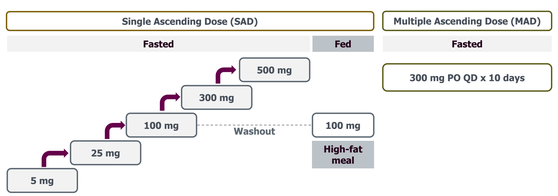
Primary

- To assess the dose-related safety and tolerability of orally administered ABI-H2158 in healthy volunteers following single (Part 1) and multiple (Part 2) oral doses

Secondary

- To evaluate the PK of ABI-H2158 in plasma following single doses and 10-day multiple doses in healthy volunteers (Parts 1 and 2)

STUDY DESIGN



Key Inclusion/Exclusion Criteria

- Able and willing to provide informed consent prior to screening
- Male or female between 18 and 55 years of age, BMI ≥ 18, and ≤ 34 kg/m^2 with a minimum weight of 45 kg
- No positive serology for HIV, hepatitis C virus, hepatitis B surface antibody, and/or hepatitis B core antibody at screening
- In good health, in the judgement of the investigator, as determined by clinical and laboratory assessments (no clinically significant abnormalities at screening)
- No ongoing illness at time of screening or within 30 days prior to study start
- No medical condition that may interfere with the absorption, distribution, or elimination of study drug or with the clinical and laboratory assessments in this study
- No participation in a study of another investigational agent in the last 60 days

METHODS

- Eight healthy volunteers per cohort were randomized (6 to active, 2 to placebo) to receive single or multiple doses of ABI-H2158 or in fasted (or fed) state
- Safety assessments included physical examinations, vital signs, 12-lead electrocardiograms (ECGs), collection of adverse events, and laboratory safety tests
- Serial PK plasma samples were drawn at prespecified intervals in both single ascending dose (SAD) and multiple ascending dose (MAD) cohorts
- Plasma concentrations of ABI-H2158 were determined using a validated liquid chromatography tandem mass spectrometry method
- PK parameters were determined by noncompartmental analysis using Phoenix WinNonLin
- A safety monitoring committee reviewed safety and PK prior to each dose escalation

Demographics

	Demographics							
	SAD					MAD		
ABI-H2158 Dose	5 mg n = 6	25 mg n = 6	100 mg n = 6	300 mg n = 6	500 mg n = 6	300 mg n = 6	Combined Active n = 36	Pooled Placebo n = 12
Mean age (min, max), y	34 (22, 50)	30 (21, 43)	26 (21, 29)	29 (21, 43)	25 (21, 31)	34 (21, 48)	29 (21, 50)	26 (19, 49)
Male, n (%)	4 (67)	6 (100)	6 (100)	6 (100)	6 (100)	5 (83)	33 (92)	9 (75)
Mean BMI (min, max), kg/m^2	25 (21, 27)	26 (21, 29)	23 (19, 27)	24 (20, 34)	24 (22, 28)	25 (22, 28)	24 (19, 34)	24 (21, 27)
Race, n (%)								
Caucasian	4 (66)	5 (83)	2 (33)	6 (100)	5 (83)	4 (66)	26 (72)	9 (75)
Asian	1 (17)	1 (17)	2 (33)	0	0	1 (17)	5 (14)	2 (17)
Others	1 (17)	0	2 (33)	0	1 (17)	1 (17)	5 (14)	1 (8)

Disposition: One volunteer in the 100-mg fasted cohort elected to not return for a fed cohort. Otherwise, all volunteers completed study dosing as assigned, with no premature discontinuations or treatment modifications.

PHARMACOKINETICS

Pharmacokinetic Parameters

PK Parameters	SAD						MAD	
Dose (fed/fasted)	5 mg (fasted) n = 6	25 mg (fasted) n = 6	100 mg[a] (fasted) n = 6	100 mg[a] (fed) n = 5	300 mg (fasted) n = 6	500 mg (fasted) n = 6	300 mg QD (fasted) Day 1 n = 6	300 mg QD (fasted) Day 10 n = 6
C_{max} ± SD, µg/mL	0.17 ± 0.043	0.57 ± 0.17	2.0 ± 0.5	2.0 ± 0.21	3.7 ± 0.92	6.8 ± 2.3	3.5 ± 2.3	5.3 ± 3.8
C_{24} ± SD, µg/mL	0.023 ± 0.0097	0.12 ± 0.046	0.5 ± 0.2	0.56 ± 0.17	0.99 ± 0.33	2.4 ± 1.3	0.97 ± 0.73	1.9 ± 1.5
T_{max} ± SD, h	1.3 ± 0.61	1.7 ± 0.82	1.3 ± 0.52	2.4 ± 1.1	2.7 ± 1.2	4.0 ± 1.1	2.3 ± 1.2	2.7 ± 1.0
$T_{1/2}$ ± SD, h	9.8 ± 2.9	13 ± 2.9	14 ± 2.3	16 ± 4.5	21 ± 7.3	16 ± 4.3	14 ± 2.5	18 ± 6.2
AUC_{-24} ± SD, h•µg/mL	1.3 ± 0.43	5.9 ± 1.2	23 ± 5.9	25 ± 3.2	43 ± 13	92 ± 34	41 ± 30	72 ± 51
CL/F ±SD, L/h	3.5 ± 1.4	3.2 ± 0.95	3.3 ± 1.3	2.7 ± 0.53	4.9 ± 1.8	4.3 ± 2.4	–	–
Vz/F ± SD, L	46 ± 9.5	58 ± 11	68 ± 26	61 ± 13	140 ± 47	89 ± 32	–	–

[a]5 of 6 volunteers from the 100-mg fasted cohort returned to clinic following a 7-day washout and were re-dosed 30 min after a standardized high-fat meal.

Anticipated Exposures in Excess of In Vitro EC_{90}

PK Parameters	SAD						MAD	
Dose (fed/fasted)	5 mg (fasted) n = 6	25 mg (fasted) n = 6	100 mg[a] (fasted) n = 6	100 mg[a] (fed) n = 5	300 mg (fasted) n = 6	500 mg (fasted) n = 6	300 mg QD (fasted) Day 1 n = 6	300 mg QD (fasted) Day 10 n = 6
C_{24} ± SD, µg/mL	0.023 ± 0.0097	0.12 ± 0.046	0.5 ± 0.2	0.56 ± 0.17	0.99 ± 0.33	2.4 ± 1.3	0.97 ± 0.73	1.9 ± 1.5
$C_{24} > EC_{90}$ (antiviral)[b]	–	+	+	+	+	+	+	+
$C_{24} > EC_{90}$ (cccDNA)[b]	–	–	+	+	+	+	+	+

[a]5 of 6 volunteers from the 100-mg fasted cohort returned to clinic following a 7-day washout and were re-dosed 30 min after a standardized high-fat meal.
[b]In vitro.

PK Summary

- ABI-H2158 exposures increased in a roughly dose-proportional fashion between 5 mg and 500 mg
- In the MAD cohort, steady-state concentrations were achieved quickly, with an accumulation ratio of ≈ 1.5-fold at steady state
- No significant change in exposure was seen when ABI-H2158 was administered with a standardized high-fat meal
- Half-life ranged between 10 and 18 hours, supporting QD dosing

Mean Time-Versus-Concentration Profiles

Figure 1. SAD

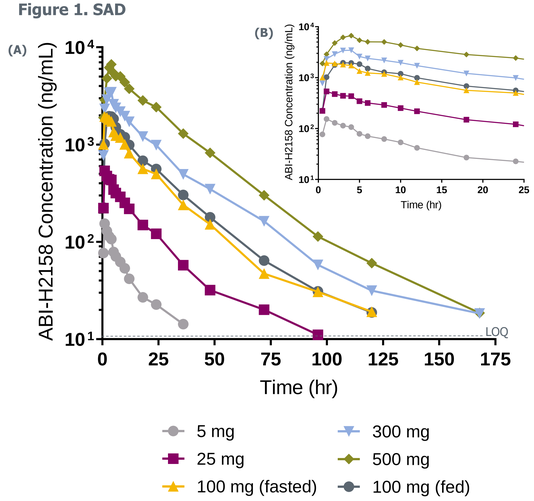


Figure 2. MAD

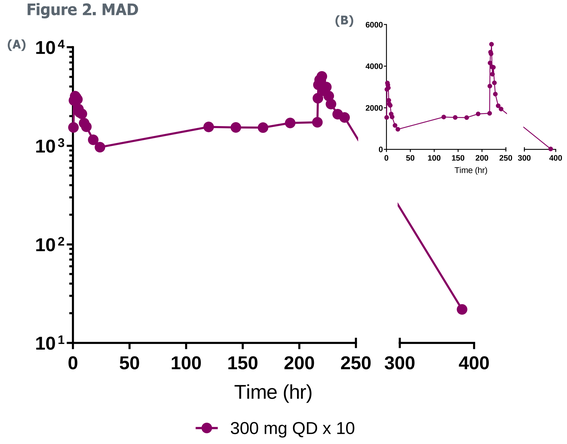


Figure 1. ABI-H2158 concentrations over time in the SAD cohort over the full time course (A) and over the first 24 hours (B)
Figure 2. ABI-H2158 concentrations over time in the MAD cohort on the log (A) and linear (B) scale

CLINICAL SAFETY

Clinical Safety Overview

- All treatment-emergent adverse events (TEAEs) were mild (grade 1)
  - There were no treatment-emergent moderate, severe, or serious AEs reported in any cohort
  - Only 3 of 48 subjects had any TEAE evaluated as "possibly" related
  - There was no increase in TEAE frequency or severity associated with dose or duration
  - The most common TEAE was headache (n = 7 in total)
- Most treatment-emergent laboratory abnormalities were mild (grade 1)
  - 3 volunteers had transient grade 2 treatment-emergent laboratory abnormalities assessed as not clinically significant (glucose [n = 1], increased cholesterol [n = 2])
- No treatment-related clinically significant ECG, vital signs, physical exam, or laboratory test abnormalities were observed in any cohort

TEAE[a] in ≥ 2 Volunteers Overall (regardless of relatedness)

TEAEs[b]	SAD, n (%)						MAD, n (%)	
AE (preferred term)	5 mg n = 6	25 mg n = 6	100 mg n = 6	300 mg n = 6	500 mg n = 6	Placebo Combined n = 10	300 mg n = 6	Placebo n = 2
Headache, grade 1	1 (17)	0	0	1 (17)	0	1 (10)	2 (33)	2 (100)
Arthralgia, grade 1	0	0	0	0	0	2 (20)	0	0
Disturbance of attention, grade 1	0	0	0	1 (17)	0	0	1 (17)	0
Nausea, grade 1	1 (17)	2 (33)	0	0	0	0	0	0
Constipation, grade 1	0	1 (17)	1 (17)	0	0	0	0	0
Oropharyngeal pain, grade 1	0	1 (17)	0	0	0	0	0	1 (17)

n, number of unique events.
[a]A TEAE is defined as an adverse event that occurred or worsened following the first administration of study drug (MedDRA version 21.1).
[b]TEAEs belonging to general disorders and administration (eg, intravenous site and ECG site reactions) and to injury (abrasions and insect bites) were excluded from the table.

CONCLUSIONS

- In this phase 1a dose-ranging study of ABI-H2158 in healthy human volunteers, ABI-H2158 was safe and well tolerated following single ascending doses of 5 mg, 25 mg, 100 mg (fasted and fed), 300 mg, and 500 mg PO QD (SAD) and 300 mg PO QD × 10 (MAD)
- No significant food effect was seen when ABI-H2158 100 mg was administered with a standardized high-fat meal
- There was no increase in the number or severity of TEAEs with increase in dose, and no pattern of clinical safety or laboratory abnormalities was observed within or across any cohorts
- Human PK parameters suggested low to moderate volunteer-to-volunteer variability
- Trough liver concentration are projected to achieve exposures in excess of the in vitro EC_{90} levels needed to inhibit both HBV replication and cccDNA establishment with QD administration
- A phase 1b dose-ranging study is currently ongoing in patients with HBV

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DISCLOSURES

ME, ER, KA, SL, and UL are employees of Assembly Biosciences. EJG is an advisor and/or speaker for Gilead, AbbVie, Janssen, and Roche. CS has no disclosures.

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