926

Phase 1a Safety and Pharmacokinetics (PK) of ABI-H0731, a Novel Core Protein Allosteric Modifier (CpAM)

Edward Gane[1,2], Christian Schwabe[2], Kayshap Patel[3], Patrick Smith[3], Sandy Liaw[4], Eric Ruby[4], Kelvin Chan[4], Leping Li[4], Richard Colonno[4] and Uri Lopatin[4]

[1]New Zealand Liver Transplant Unit, Auckland City Hospital, Auckland, New Zealand; [2]Clinical Trial Unit, Auckland Clinical Studies, Auckland, New Zealand; [3]Certara Inc, Princeton, NJ, USA; [4]Assembly Biosciences, Inc., San Francisco, CA USA

AASLD THE LIVER MEETING 2017 WASHINGTON, DC OCTOBER 20-24

assembly biosciences

Introduction

- Approximately 240 million people worldwide are chronically infected with Hepatitis B virus (HBV) and are at risk of developing chronic liver diseases, such as hepatitis, fibrosis, cirrhosis and hepatocellular carcinoma (HCC)[1]. Currently approved treatments for chronic HBV include nucleos(t)ide analogs (Nucs) such as entecavir (ETV) and tenofovir, and interferons (IFN and PEG-IFN). While Nucs are highly effective at inhibiting HBV replication for prolonged periods, cures – defined as HBsAg loss, and sustained (off treatment) clearance of viremia with normalization of transaminases – only occur in <10% of treated patients. New classes of anti-HBV molecules are needed to significantly improve cure rates in chronic HBV patients.
- HBV core protein (Cp) is involved in multiple steps of the HBV life cycle, including formation and amplification of cccDNA levels. A novel class of direct acting HBV antivirals, Core Protein Allosteric Modifiers (CpAMs), have been discovered and developed to target HBV core protein. ABI-H0731 is a potent and selective orally available CpAM, capable of inhibiting both new virion formation and the establishment of new cccDNA in cell-based assays[2].
- As previously reported, ABI-H0731 retains activity in Primary Human Hepatocytes and exhibits antiviral potency against all HBV genotypes tested (A,B,C and D) as well as nucleoside resistant mutants[2,3]. In addition, ABI-H0731 possesses highly favorable DMPK properties, such as metabolic stability and PK[3]. This overall profile supported clinical evaluation of ABI-H0731 in healthy volunteers and HBV-infected patients.
- Here we report the first clinical data on ABI-H0731 in healthy adult volunteers in a Phase 1a study evaluating the safety and pharmacokinetics of orally administered ABI-H0731.

Phase 1a Study Objectives

Primary Objective

- Assess the dose-related safety and tolerability of ABI-H0731 after single and multiple oral doses of ABI-H0731 in healthy human volunteers

Secondary Objectives

- Assess ABI-H0731 human pharmacokinetics following single and multiple oral doses in healthy volunteers
- Assess the systemic PK profile of ABI-H0731 in healthy, human volunteers when administered with and without food (i.e., with fed and fasted dosing)

Key Inclusion/Exclusion Criteria

1. Able and willing to give informed consent
2. Male or female between 18 and 65 years of age, BMI 18-32 kg/m^2
3. No history of chronic or recurrent medical conditions requiring frequent medical interventions
4. No clinically significant abnormalities at time of screening
5. No clinically significant abnormalities in the 12-lead ECG at time of screening
6. No ongoing illness at time of screening or within 30 days prior to study start
7. No medical condition that may interfere with the absorption, distribution or elimination of study drug (ABI-H0731), or with the clinical and laboratory assessments in this study
8. No participation in a study of another investigational agent in the last 60 days

Study Design/Methods

- Eight healthy volunteers/cohort randomized 6:2 (ABI-H0731:Placebo) to receive single or multiple PO doses of ABI-H0731. Initial single-dose cohorts were: A1 (100 mg Fasted), A2 (300 mg Fasted) and A6 (300 mg Fed). As a preliminary food assessment, Cohort A2 subjects returned following a 7-day washout and were re-dosed 30 min after a standardized medium fat meal. Subsequently, Cohorts A4 (600 mg Fed) and A5 (1,000 mg Fed) were dosed 30 min after a standardized medium fat meal. Multiple-dose cohorts A7 (800 mg QD) and A8 (800 mg BID) were dosed for 7 days, with all doses taken 30 min following standardized moderate fat meals.
- Serial PK plasma were drawn pre-dose in single ascending dose (SAD) cohorts at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24, 30, 36, 48, 72 and 168 hr post dose. For multiple ascending dose (MAD) Cohorts A7 and A8, plasma serum samples were drawn pre-dose, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12 and 18 hr post dose. Pre-dose day 2, 3, 4 and 7, and 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24 and 168 hr post the Day 7 dose. Cohort A8 excluded the 18-hr sample collection.
- Plasma concentrations of ABI-H0731 were determined using a validated liquid chromatography mass spectrometry method.
- PK parameters were determined by non-compartmental methods, using Phoenix WinNonLin.
- Descriptive statistics of adverse events and laboratory abnormalities were evaluated prior to each successive cohort.

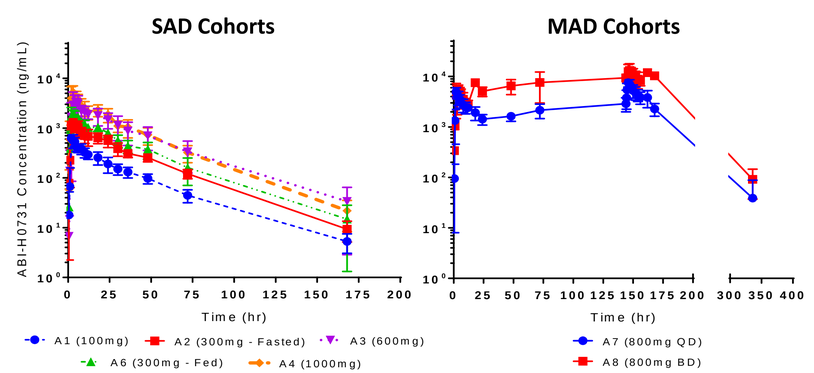
Demographics and Subject Disposition

Demographics: 48 healthy subjects enrolled (8/cohort), 24 Males, 24 Females, 33 Caucasian, 8 Asian, 7 Other
Disposition: All subjects completed study with no premature discontinuations or treatment modifications

PK Parameters

	Cohort	Dose (Fed/Fasted)	N	C_{max} ± SD (ng/mL)	C_{min} ± SD (ng/mL)[c]	T_{max} (hr, range)[b]	$T_{1/2}$ ± SD (hr)	AUC_{0-24} ± SD (ng.hr/mL)	Cl/F ±SD (L/hr)	VZ/F ± SD (L)
SAD	A1	100 mg (Fasted)	6	654 ± 115	191 ± 35	2 (2-4)	28.4 ± 3	7,500 ± 1,430	6.9 ± 1.4	279 ± 56
	A2*	300 mg (Fasted)	6	1,340 ± 185	559 ± 27	3 (2-5)	24.8 ± 4	17,600 ± 4,110	8.3 ± 1.3	297 ± 71
	A6*	300 mg (Fed)	6	2,180 ± 326	800 ± 20	2.5 (2-6)	23.9 ± 5	27,300 ± 4,040	5.8 ± 1.3	196 ± 33
	A3	600 mg (Fed)	6	3,740 ± 1,690	1,483 ± 35	3.5 (3-6)	25.4 ± 6	46,100 ± 17,000	6.9 ± 2.8	235 ± 56
	A4	1,000 mg (Fed)	6	5,650 ± 2,250	1,871 ± 31	2.5 (2-4)	23.5 ± 4	61,600 ± 17,700	9.2 ± 3.3	322 ± 175
MAD	A7	800 mg QD (Fed) Day 1	6	5,190 ± 983	1,425 333	2.5 (2-4)	--	58,200 ± 989	--	--
	A7	800 mg QD (Fed) Day 7	6	8,175 ± 1,090	2,895[c] ± 28	2.5 (2-5)	--	105,000 ± 25,200	--	--
	A8	800 mg BD (Fed) Day 1	6	6,160[a] ± 1,780	2,770[a] ±589	4[a] (2-4)	--	85,200[a] ± 17,700	--	--
	A8	800 mg BD (Fed) Day 7	6	14,800[a] ± 3,960	9,398[c] ± 15	3[a] (2-5)	--	252,000[a] ± 55,000	--	--

[a]T_{max}, C_{max} and C_{min} for BID samples analyzed only over 1st 12 hr; AUC_{0-24} = 2x AUC_{0-12}; [b]Median; [c]C_{min}= C_{24} for SAD and Day 1 of MAD, and pre-dose trough for Day 7 MAD
*Cohort A6 consisted of subjects from Cohort A2 who returned to clinic following a 7-day washout and were re-dosed 30 min following a standardized medium fat meal



Clinical Safety and Tolerability Overview

Treatment-emergent laboratory abnormalities

- **No TE lab abnormalities were deemed clinically significant**
- There were no treatment-emergent hematology or coagulation results ≥ Grade 1; Treatment emergent clinical chemistry abnormalities were low grade and/or deemed either spurious or not clinically significant
- Lab abnormalities were scattered with no apparent target body system pattern
- Within the limitations of the small study size, no clear relationship was seen between clinical laboratory abnormalities and treatment (ABI-H0731 vs. Placebo) or dose

Treatment emergent adverse events (TEAEs)

- Most TEAEs occurred as single events
- **All TEAE (N = 46) were Grade 1 (mild),** except for single 1 grade 2 AE of back pain not attributed to study drug
- With possible exception of Grade 1 rashes seen in cohorts A7 and A8, no relationship was seen between ABI-H0731 dose and AEs
- Three post-treatment rashes were noted between days 8 and 11 of follow up; all rashes were assessed as Grade 1 (mild) by the Principal Investigator, were not associated with other systemic signs nor pattern of lab abnormalities, and resolved within 3-4 days

Clinical Safety and Tolerability

Treatment Emergent AEs with >1 Reported, Regardless of Relatedness

	Cohort (doses, mg)							
Preferred Term	Overall with AE	A1 (1) N = 6 100 QD	A2/A6 (2) N = 6* 300 QD	A3 (1) N = 6 600 QD	A4 (1) N = 6 1,000 QD	A7 (7) N = 6 800 QD	A8 (14) N = 6 800 BID	Placebo N = 12
Headache	9	2	1	0	0	2	3	1
Light-Headedness	5	2	0	0	1	0	1	1
Rash/Generalized Rash	3	0	0	0	0	1	2	0
Bruise at Cannulation Site	2	0	1	1	0	0	0	0
Abdominal Discomfort	2	0	2	0	0	0	0	0
Treatment Emergent AEs Considered Possibly or Probably Related to Study Drug								
Rash/Generalized Rash	3	0	0	0	0	1	2	0
Headache	2	0	0	0	0	2	0	0
Epigastric Pain	1	0	0	0	0	1	0	0
Light-headedness	1	0	1	1	0	0	1	0
Bloating	1	0	0	1	0	0	0	0
Skin Photosensitivity	1	0	1	0	0	0	0	0

Treatment emergent AEs with single occurrences included abdominal cramps, anorexia, bloating, constipation, discomfort at cannulation site, bruise at attempted cannulation site, epigastric pain, epistaxis, eye fatigue, fatigue, heat rash, intermittent abdominal discomfort, intermittent dry cough, intermittent muscular twitching in legs, lumbar back pain, lump at venipuncture site (left arm), mouth ulcer, nausea, petechiae upper arms, skin photosensitivity, sore throat and widespread mosquito bites

Conclusions

- ABI-H0731 is a novel CpAM with selective and potent activity against all major HBV genotypes in cell based infection assays
- The Phase 1a dose ranging study in healthy human volunteers demonstrated the safety and tolerability of single and multiple doses ranging from 100 mg PO QD (SAD) through 1,600 mg (given 800 mg PO BD in a 7-day MAD cohort)
- Administration with food resulted in a ~45% increase in AUC
- No clear pattern of clinical or laboratory abnormalities were observed, with the possible exception of mild (Grade 1) reversible rashes in a subset of MAD subjects
- Human PK parameters suggested low subject-to-subject variability and the potential to attain therapeutic plasma and liver levels in HBV infected patients with once daily administration
- A Phase 1b dose-ranging study is currently ongoing in HBV patients

References

1. EASL 2017 Clinical Practice Guidelines on the management of HBV infection. Journal of Hepatology 2017 vol. 67 j 370–398
2. Huang, Qi et al. AASLD 2016 Blockade of HBV Virus Replication and Inhibition of cccDNA establishment by Core Protein Allosteric Modifiers (CpAMs) Poster 1897, AASLD 2016
3. Huang, Qi et al. Preclinical characterization of potent core protein assembly modifiers for the treatment of chronic hepatitis B. Poster 104 EASL 2016

Disclosures

This study was funded by Assembly Biosciences. UL, RC, LL, SL, ER and KC are employees of Assembly Biosciences. These authors may own stock or stock options in Assembly Biosciences. KP and PS are employees of Certara. EG is an advisor or on Speakers Bureau for AbbVie, Alios, Arbutus, Gilead Sciences, Janssen, Merck, Assembly Biosciences and Roche. CS has no declared conflict of interest

Contact: Uri Lopatin, MD: uri@assemblybio.com