Safety, tolerability, pharmacokinetics (PK), and antiviral activity of the 3rd generation capsid inhibitor AB-836 in healthy subjects (HS) and subjects with chronic hepatitis B (CHB)

E Gane[1], A Jucov[2], L Kolomiichuk[3], A Leerapun[4], E Sripariwuth[5], P Tangkijvanich[6], SI Strasser[7], T Suttichaimongkol[8], C Cooper[9], M Elkhashab[10], Y-S Lim[11], T Eley[12], J Brown[12], Y King[12], T Varughese[12], E Medvedeva[12], M Chernyakhovskyy[12], N Mani[13], AG Cole[13], S Kultgen[13], R Pamulapati[13], EP Thi[13], T Harasym[13], R Dugyala[13], S Chaudhari[13], M Sofia[13], M Child[12], G Picchio[12], KD Sims[12], MF Yuen[14]

[1] Auckland Clinical Studies, New Zealand, [2] Arensia Exploratory Medicine, Moldova, [3] Arensia Exploratory Medicine, Ukraine, [4] Maharaj Nakhon Chiang Mai Hospital, Thailand, [5] Naresuan University Hospital, Thailand, [6] King Chulalongkorn Memorial Hospital, Thailand, [7] Royal Prince Alfred Hospital, Australia, [8] ACRO Khon Kaen University, Thailand, [9] Ottawa Hospital Research Institute, Canada, [10] Toronto Liver Centre, Canada, [11] Asan Institute for Life Science, South Korea, [12] Arbutus Biopharma Clinical Development, Warminster PA, USA, [13] Arbutus Biopharma Discovery and Research, Warminster, PA , USA [14] Queen Mary Hospital, Hong Kong

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Arbutus BIOPHARMA *Curing Chronic Hepatitis B*

BACKGROUND

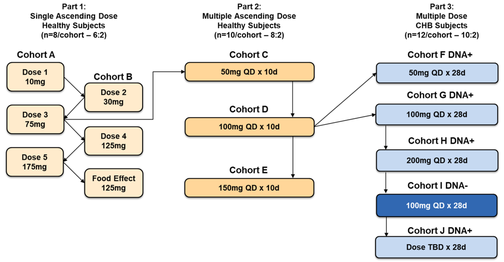
- Current therapies for chronic hepatitis B (CHB) slow or prevent the development of HBV-related liver complications, but do not typically lead to a cure.[1,2,3] Thus, there is an unmet medical need for new HBV therapies that have the potential to provide a functional cure for CHB.
- AB-836 is a low molecular weight, small-molecule (Class II) inhibitor of HBV pgRNA encapsidation resulting in empty capsids via its primary mechanism of action. At higher concentrations AB-836 has a secondary mechanism of action *via* interfering with the uncoating step post viral entry thereby inhibiting *de novo* infection of hepatocytes.[4]
- AB-836 is a potent, highly selective inhibitor of HBV replication in HBV cell culture models with no significant activity against unrelated viruses. *In vitro*, AB-836 showed activity against HBV genotypes A through H (pan-genotypic) and no cross-resistance with nucleos(t)ide analog (NA)-resistant HBV variants. Dual combination of AB-836 with NAs or the investigational GalNAc-siRNA agent AB-729 showed additive antiviral activity.
- AB-836-001 is an ongoing 3-part study evaluating safety, PK and antiviral activity of AB-836 in HS (Parts 1 and 2) and CHB subjects (Part 3). Here we report data from Parts 1, 2 and preliminary data from the first 3 cohorts of Part 3.

OBJECTIVES

- Evaluate the safety and tolerability of AB-836 following oral administration of single and multiple doses to healthy subjects and CHB subjects
- Evaluate the change in HBV DNA and other virologic parameters in CHB subjects over 28 days of dosing of AB-836
- Characterize the single dose and steady-state PK of AB-836 in healthy subjects and CHB subjects

MATERIALS AND METHODS

Figure 1: AB-836-001 Study Design



- Key eligibility criteria used for healthy subjects included
  - Males or females aged 18 to 45 years; Body mass index (BMI) ≥18 kg/m^2 and ≤32 kg/m^2
  - No history of clinically significant GI, hematologic, renal, hepatic, bronchopulmonary, neurological, psychiatric, or CV disease
  - No clinically significant abnormalities in laboratory test results, ECGs or vital sign measurements
- Key eligibility criteria used for DNA+ subjects with CHB included
  - Males or females aged 18 to 65 years; Body mass index (BMI) ≥18 kg/m^2 and ≤35 kg/m^2
  - Baseline HBV DNA ≥ 2000 IU/mL
  - No evidence of cirrhosis, advanced fibrosis or HCC via Fibroscan (<10 kPa) and ultrasound
  - ALT or AST ≤5 × upper limit of normal
- Safety and tolerability were monitored throughout the study *via* collection of treatment-emergent adverse events (TEAEs), physical examinations, vital signs, ECGs and clinical laboratory testing
- Serial and Ctrough blood samples were collected for noncompartmental PK analysis. Serial collection for CHB subjects was truncated to 6 hours post-dose.
- Plasma AB-836 was quantified via a validated LC/MS/MS assay
- HBV DNA was quantified by Roche Cobas 6800 (LLOQ 10 IU/mL)
  - HBV DNA samples <LLOQ were assigned a value of 5 IU/mL

RESULTS

Table 1: Healthy Subjects Baseline Characteristics

Baseline Measure	Cohort A N = 9	Cohort B N = 8	Cohort C 50mg QD N = 8	Cohort D 100mg QD N = 8	Cohort E 150mg QD N = 8	Pooled Placebo N = 6
Age (years) [Mean (SD)]	29.1 (8.4)	27.9 (3.4)	29.1 (4.6)	27.9 (3.4)	25.8 (5.6)	32.2 (5.6)
BMI (kg/m^2) [Mean (SD)]	24.7 (3.3)	24.6 (2.5)	24.9 (3.1)	24.7 (2.9)	24.2 (3.2)	25.4 (3.5)
Male Gender [n (%)]	9 (100)	8 (100)	8 (100)	8 (100)	8 (100)	6 (100)
Race [n (%)]						
Asian	3 (33)	1 (12)	2 (25)	0	2 (25)	0
White	5 (56)	4 (50)	1 (13)	6 (75)	5 (63)	6 (100)
Black/African American	0	0	1 (13)	0	0	0
Pacific Islander/Native Hawaiian	0	0	0	0	1 (13)	0
Other	1 (11)	3 (38)	4 (50)	2 (25)	0	0

One subject in Cohort A withdrew consent after one of the dosing periods and was replaced

Table 2: CHB Subjects Baseline Characteristics

Baseline Measure	Cohort F* 50mg QD N = 12	Cohort G^ 100mg QD N = 13	Cohort H# 200mg QD N = 13	Total N = 38
Age (years) [Mean (SD)]	41.5 (6.6)	42.5 (11.0)	38.8 (7.6)	40.9 (8.6)
BMI (kg/m^2) [Mean (SD)]	23.0 (4.9)	24.8 (2.8)	23.9 (3.3)	23.9 (3.7)
Male Gender [n (%)]	7 (58)	10 (77)	9 (69)	26 (68)
Race [n (%)]				
Asian	6 (50)	8 (62)	10 (77)	24 (63)
White	5 (42)	5 (38)	2 (15)	12 (32)
Other	1 (8)	0	1 (8)	2 (5)
Genotype [n (%)]				
A	0	0	1 (7.7)	1 (2.6)
B	2 (16.7)	4 (30.8)	3 (23.1)	9 (23.7)
C	4 (33.3)	2 (15.4)	6 (46.2)	12 (31.6)
D	5 (41.7)	6 (46.2)	2 (15.4)	13 (34.2)
Not Determined	1 (8.3)	1 (7.7)	1 (7.7)	3 (7.9)
HBeAg+ [n (%)]	4 (33)	4 (31)	4 (31)	12 (32)
ALT [Mean (SD)]	76.5 (176.8)	45.1 (20.4)	63.9 (58.9)	61.4 (102.1)
HBV DNA (Log_{10} IU/mL) [Mean (SD)]	4.96 (1.53)	6.28 (2.10)	5.76 (1.77)	5.69 (1.85)
HBsAg (Log_{10} IU/mL) [Mean (SD)]	3.45 (0.52)	3.88 (1.05)	3.79 (0.60)	3.71 (0.77)

*One subject in Cohort F was withdrawn from the study due to an asymptomatic HBV flare noted on the pre-dose Day 1 labs and will be replaced
^One subject in Cohort G had discordant HBeAg status between screening (HBeAg+) and Day -1 (HBeAg-); one additional HBeAg+ subject enrolled
#Two subjects in Cohort H were withdrawn due to inability to comply with study visits (COVID-19 and instability in Ukraine); 1 replacement was enrolled

Figure 3: Single Dose AB-836 Concentration vs Time

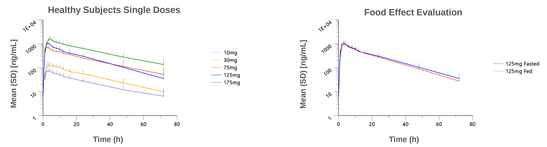
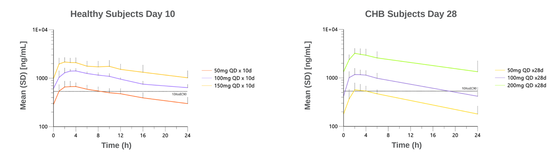


Table 4: AB-836 Single Dose Pharmacokinetics

SAD Dose	N	Cmax [ng/mL] Geometric Mean (CV%)	AUC∞ [ng*h/mL] Geometric Mean (CV%)
10mg capsule	6	75 (26)	1760 (39)
30mg capsule	6	129 (28)	3292 (33)
75mg tablet	6	770 (19)	15516 (59)
125mg tablet	6	1093 (17)	18620 (29)
125mg tablet fed	6	994 (30)	17705 (24)
175mg tablet	6	1773 (21)	39575 (40)

- AB-836 Tmax generally ranged from 2-4 h post dose and mean T-half from 15-20 h
- Cmax and AUC were largely dose proportional for the tablet formulation
- Food effect appears negligible

Figure 4: Multiple Dose AB-836 Concentration vs Time



For Figure 4, plasma concentrations at steady state in CHB subjects at 24 hours post-dose were assumed to be equivalent to pre-dose

Table 5: AB-836 Multiple Dose Pharmacokinetics

Treatment Group	N	Steady State PK Parameter							
		Cmax [ng/mL]		AUC(0-6h) [ng*h/mL]		AUCtau [ng*h/mL]		Cmin [ng/mL]	
		Geometric Mean	CV%	Geometric Mean	CV%	Geometric Mean	CV%	Geometric Mean	CV%
50mg QD HS	8	747	18	3536	22	10987	22	284	35
50mg QD CHB	9	620	27	2741	26	ND	--	162	43
100mg QD HS	8	1518	7	7349	12	22898	11	629	17
100mg QD CHB	10	1258	27	6051	25	ND	--	364	53
150mg QD HS	8	2312	19	11318	24	35250	30	950	39
200mg QD CHB	10	3340	26	15746	28	ND	--	1067	65

ND = not determined; HS = Healthy Subjects; CHB = CHB Subjects

- At the same dose, AB–836 Cmax, AUC(0-6h) were comparable on Day 1 (not shown) but generally lower in CHB subjects relative to HS at steady state
- In CHB subjects at 100mg QD and 200mg QD, plasma Cmin is approximately 7x and 20x, the serum shifted (protein adjusted) EC90, respectively, for 1° mechanism for WT [53ng/mL, HepDE19 cells]
- In CHB subjects at 100mg QD and 200mg QD, plasma Cmin is >1.5x and >5x the ssEC90, respectively, for 2° mechanism for WT [198ng/mL, PHH]

Figure 2: Log_{10} Change from Baseline HBV DNA

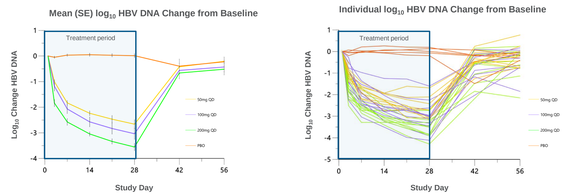


Table 3: Day 28 HBV DNA Response by Cohort

Dose Level	N	Mean (SE) Day 28 HBV DNA log_{10} change	Subjects > 3.0 log_{10} decline in HBV DNA	Subjects <LLOQ at Day 28
Cohort F 50mg QD	9	-2.66 (0.17)	4	1
Cohort G 100mg QD	11	-3.04 (0.21)	6	0
Cohort H 200mg QD	10	-3.55 (0.14)	9	3
Placebo	5	0.01 (0.06)	0	0

- Individual HBV DNA responses suggest that any baseline mutations in these cohorts, if present (data pending), did not affect response
- Individual log_{10} change in HBV DNA at Day 28 largely correlated with Cmin
- There were no meaningful changes in HBsAg over 28 days of dosing; HBV RNA data are pending

Healthy Subject Safety Summary (Parts 1 and 2)

- AB-836 was well tolerated in HS; there were no deaths or SAEs.
- One HS (50mg QD) discontinued on Day 13 (last dose Day 10) due to an TEAE of agitation.
- All but 3 TEAEs in HS were Grade 1 (Grade 2 headache, agitation, and bronchitis).
- Only 1 TEAE was considered related (Grade 1 rash) and occurred in a subject receiving placebo.
- There were no clinically significant changes in ECGs, vital signs or physical exams in any subject.

Table 6: Adverse Events – Part 3 (CHB)

Subjects, n	Cohort F 50mg QD [N=12]	Cohort G 100mg QD [N=13]	Cohort H 200mg QD [N=13]	TOTAL [N=38]
Subjects with any TEAE	4	3	4	11
Maximum TEAE Severity				
Grade 1	3	3	2	8
Grade 2	0	0	0	0
Grade 3	0	0	2	2
Grade 4	1[a]	0	0	1
Related TEAEs	0	1	1	2
SAEs	0	0	0	0
Liver-related laboratory abnormalities	1	2	2	5
ALT elevation (Maximum Lab Grade)				
Grade 3	0	2	1	3
Grade 4	1	0	1	2
AST elevation				
Grade 2	0	1	1	2
Grade 3	1	0	1	2

[a] The Grade 4 ALT and Grade 3 AST elevations noted in Cohort F were due to a pre-dose HBV flare detected on dosing Day 1 (subject was discontinued). The subject's ALT/AST upon screening was a lab Grade 2.

- Three TEAEs were considered treatment-related (Grade 1 dyspepsia in Cohort G and Grade 3 ALT/Grade 2 AST elevation in 1 Cohort H subject)
- Two subjects in Cohort G had transient Grade 3 ALT elevations that resolved with continued AB-836 dosing and were not considered TEAEs
- Two subjects in Cohort H had transaminase elevations on the last day of dosing (Day 28) that returned to baseline levels no later than Day 56 (reported as TEAEs and listed in liver related lab abnormalities above)
- All subjects with transaminase elevations were asymptomatic and none had changes in bilirubin or met DILI criteria
- No other clinically significant lab abnormalities, ECG or vital sign changes have been observed

CONCLUSIONS

- Single doses of AB-836 up to 175mg and multiple doses of 50mg, 100mg and 150mg QD for 10 days in HS and 50mg, 100mg and 200mg QD for 28 days in CHB subjects have been generally safe and well-tolerated
- AB-836 demonstrated potent inhibition of HBV replication with mean declines in HBV DNA at Day 28 of 3.04 and 3.55 log_{10} at 100mg QD and 200mg QD, respectively
- AB-836 plasma Cmin values were >1.5-fold and >5-fold over the ssEC90 for the 2nd mechanism for WT virus at 100mg and 200mg QD, respectively.
- Study AB-836-001 is being amended to add treatment arms assessing 12 weeks of AB-836 coadministration with NA in suppressed CHB subjects
- Outcomes from these new treatment arms may support combination with other agents, including the GalNAc-siRNA AB-729

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CONTACT INFORMATION

Timothy Eley, Ph.D., Executive Director, Compound Development Lead and Clinical Pharmacology
Arbutus Biopharma Inc., 701 Veterans Circle, Warminster, PA, USA 18974
Email: teley@arbutusbio.com
Tel: +1-267-422-1320

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