Key findings leading to the discontinuation of a Capsid Inhibitor (CI), AB-506, in Healthy Subjects (HS) and Chronic Hepatitis B (CHB) Subjects

#O17

Arbutus BIOPHARMA
Curing Chronic Hepatitis B

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BACKGROUND

- HBV capsid inhibitors (CI) are being intensively studied as potential components of new combination regimens for the treatment of chronic hepatitis B (CHB) infection.
- Mechanistically, CI inhibit HBV replication by preventing the encapsidation of pre-genomic RNA and replenishment of the cccDNA pool.
- Distinguishing between host-induced ("good") and drug- or viral-induced ("bad") transaminase flares is challenging considering the natural history of CHB infection.
- Multiple dose studies in healthy subjects (HS) are rarely conducted longer than 7-14 days to assess the potential for drug toxicity before dosing the target population.
- AB-506 is an oral, class II, selective HBV CI for the treatment of CHB with activity against genotypes A-H and nucleos(t)ide resistant variants *in vitro* which, until recently, was in clinical development for the treatment of CHB.
- No transaminase elevations were noted in 28-day or 90-day toxicology studies.
- Here we report data from the first-in-human study of AB-506 (AB-506-001) and a follow-on study to evaluate potential safety observations (AB-506-003)

OBJECTIVES

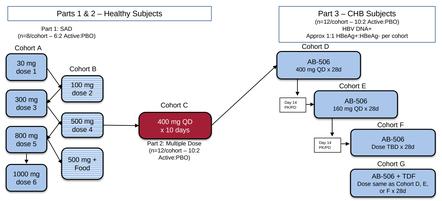
Key Objectives for Study AB-506-001

Primary:
- Safety and tolerability of single and multiple doses of AB-506 in HS (10 days) and DNA+ CHB Subjects (28 days)

Secondary/Exploratory:
- Changes in HBV-DNA and other virologic parameters in DNA+ CHB Subjects
- Characterize PK of AB-506 in HS and CHB Subjects
- Changes in immune biomarkers during and after treatment
- Changes in cytokines during treatment
- Evaluate baseline resistance and the emergence of viral resistance during and after treatment

METHODS

Figure 1: AB-506-001 Study Design



Key Eligibility Criteria, Study AB-506-001

All Subjects:
- Capable of giving signed informed consent, able to understand and comply with protocol requirements, instructions, and protocol-related restrictions, and likely to complete the study as planned

Healthy Subjects:
- Healthy 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 gastrointestinal, hematologic, renal, hepatic, bronchopulmonary, neurological, psychiatric, or cardiovascular disease
- No clinically significant abnormalities in laboratory test results, ECGs or vital sign measurements

CHB Subjects:
- Healthy males or females aged 18 to 65 years
- Body mass index (BMI) ≥18 kg/m^2 and ≤38 kg/m^2
- Documented chronic HBV infection (HBsAg positive > 6 months and negative HBcAb-IgM)
- HBV-DNA ≥2,000 IU/mL (HBeAg-negative) or ≥20,000 IU/mL (HBeAg-positive); HBsAg ≥250 IU/mL
- HBV genotype A, B, C, or D
- No evidence of cirrhosis, advanced fibrosis or HCC via Fibroscan (<10 kPa) and ultrasound
- ALT or AST ≤5 × upper limit of normal (AASLD criteria for ALT)

RESULTS

Table 1: Healthy Subject Baseline Characteristics

Baseline Measure	Cohort A Single Doses (N=11)	Cohort B Single Doses (N=10)	Cohort C Multiple Dose (N=12)	Overall (N=33)
Age (years) [Mean (SD)]	26.2 (6.7)	27.5 (6.5)	24.8 (4.3)	26.1 (5.8)
BMI (kg/m^2) [Mean (SD)]	25.2 (2.2)	26.4 (3.4)	24.1 (2.4)	25.2 (2.8)
Male Gender [n (%)]	11 (100)	10 (100)	12 (100)	33 (100)
Race [n]				
Asian	0	2	1	3
White	7	4	7	18
Pacific Islander	0	2	0	2
Other	4	2	4	10
Baseline ALT [Mean (SD)]	18.5 (4.1)	27.5 (9.3)	19.1 (8.6)	21.5 (8.5)

Table 2: CHB Subject Baseline Characteristics

Baseline Measure	Cohort D 400 mg QD (N=10)	Cohort E 160 mg QD (N=10)	Pooled PBO (N=4)
Age (years) [Mean (SD)]	41.7 (9.5)	41.3 (12.4)	40.8 (9.3)
Male Gender [n (%)]	5 (50)	5 (50)	0
BMI [Mean (SD)]	23.4 (3.5)	25.5 (5.6)	25.8 (2.4)
Race [n (%)]			
Asian	8	5	2
White	1	5	2
Pacific Islander	1	0	0
Other	0	0	0
Genotype [n, (%)]			
A	0	0	0
B	2	0	0
C	7	5	2
D	1	5	2
HBV eAg Positive [n, %]	3	7	2
ALT (U/L) Mean (SD)]	37.1 (20.3)	27.9 (17.2)	28.1 (11.6)
HBV DNA (Log_{10} IU/mL) [Mean (SD)]	6.99 (2.11)	5.21 (1.43)	5.40 (2.18)
HBV RNA (Log_{10} IU/mL) [Mean (SD)]	5.90 (2.12)	4.68 (1.29)[a]	5.37 (1.99)[b]
HBsAg (Log_{10} IU/mL) [Mean (SD)]	4.23 (0.66)	3.62 (0.56)	3.52 (0.60)

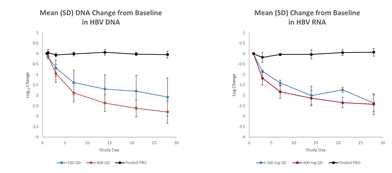
[a] 3 subjects TND; [b] 2 subjects TND

Table 3: Log_{10} Change from Baseline at Day 28/EOT

Cohort	Cohort D 400 mg QD[a]			Cohort E 160 mg QD			Pooled PBO
HBeAg Status [Treated]	HBeAg+ [N=7]	HBeAg- [N=3]	ALL [N=10]	HBeAg+ [N=3]	HBeAg- [N=7]	ALL [N=10]	ALL [N=4]
HBV DNA (Log_{10} IU/mL) [Mean (SD)]	-2.9 (0.58)	-2.5[b] (0.23)	-2.8 (0.57)	-2.2 (0.39)	-2.0 (1.1)	-2.1 (0.91)	-0.045 (0.16)
HBV RNA (Log_{10} IU/mL) [Mean (SD)]	-2.4 (0.50)	All[c] <LLOQ	-2.4 (0.50)	-2.5[d] (0.54)	-2.22[e]	-2.37 (0.40)	0.066 (0.19)
HBsAg (Log_{10} IU/mL) [Mean (SD)]	0.116 (0.208)	0.107 (0.001)	0.113 (0.176)	-0.0213 (0.029)	-0.0214 (0.082)	-0.0213 (0.069)	0.006 (0.07)

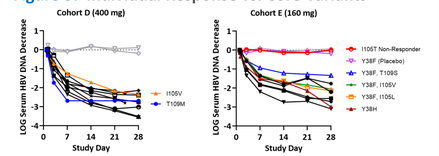
[a] 2 subjects DC for ALT excluded; [b] 1 subject <LLOQ; [c] 1 <LLOQ at baseline; [d] N=2 (1 <LLOQ by Day 28); [e] N=1 (5 <LLOQ at baseline, 1 <LLOQ by Day 28)

Figure 2: Mean (SD) Log_{10} Change from Baseline



NOTE: Grade 4 ALT Subjects in Cohort D (400 mg QD) excluded post-DC at Days 23 and 24

Figure 3: Individual Response vs. Core Variants



- Baseline substitutions at Y38, I105, and T109 were noted in 5, 4 and 2 of the 24 subjects respectively
- 1 of 20 subjects did not respond to AB-506 treatment; correlated with pre-existing I105T variant
- I105T point mutation resulted in a 19-fold increase in EC50 *in vitro*

Table 4: Frequency of Pre-Existing HBV Core Variants

Variant[1]	Observed Cases (n)	Observed Frequency (%)	Frequency in HBVdb[2] (%)
Y38F	13	25	3.1
Y38H	2	3.8	1.2
I105T	4	7.7	0.6
I105V	7	13	1.1
I105L	5	9.6	0.7
T109S	2	3.8	0.1
T109M	3	5.8	0.7

NOTE: Observed frequency in 52 CHB subjects screened for AB-506-001

Safety Summary AB-506-001 HS:

- No deaths, SAEs or AEs leading to discontinuation were observed. One subject withdrew consent in the 400 mg QD panel.
- Most AEs were assessed as unrelated to study drug; all but two AEs were Grade 1/mild.
- The two Grade 2/moderate AEs were headache and ligament strain which were also assessed as unrelated.
- No dose-related trends in AE frequency or severity were observed.
- No clinically significant abnormalities in laboratory tests, ECGs, or vital signs were noted.

Safety Summary AB-506-001 CHB Subjects:

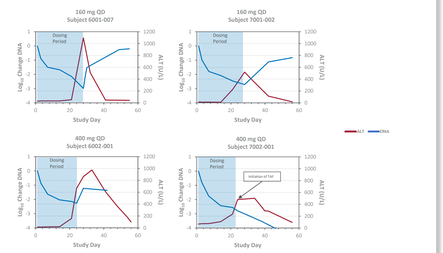
Table 5: Adverse Events AB-506-001 CHB Subjects

Parameter	Cohort D 400 mg QD (n=10)	Cohort E 160 mg QD (n=10)	Placebo (n=4)
# subjects with AE	7	8	3
Worst Reported Grade AE [n,%]			
Grade 1	4 (40)	4 (40)	1 (25)
Grade 2	1 (10)	2 (20)	2 (50)
Grade 3	0	1 (10)[a]	0
Grade 4	2 (20)	1 (10)[a]	0
SAEs	0	0	0
D/C due to AE	2[b]	1[c]	0
Total # Subjects with Grade ≥2 ALT Elevation[d]	2	4	0
Grade 2	0	2	0
Grade 3	0	0	0
Grade 4	2	2	0

(a) ALT and/or AST elevations; (b) transaminase elevations; (c) Grade 1 rash;
(d) based on 2015 AASLD ALT normal range (<30 and <19 U/L for male and female, respectively)

- Grade 4 ALT subjects were from South Korea (2) or Hong Kong (2) sites.
- Grade 2 ALT subjects were from Hong Kong (1) or Thailand (1) sites.
- No other clinically significant abnormalities in laboratory tests, ECGs, or vital signs were noted.

Figure 4: Grade 4 ALT vs HBV DNA to FU Day 28

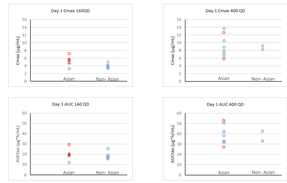


- These subjects had normal bilirubin, INR and liver synthetic function.
- ALT elevations rapidly resolved post-discontinuation of AB-506.
- One subject with Grade 4 ALT (7002-001) had remarkable and sustained antiviral responses during/after ALT normalization (see Table 6).

Table 6: HBV Viral Markers vs Time Subject 7002-001

Viral Marker	HBV DNA* (IU/mL)	HBsAg (IU/mL)	HBV RNA (c/mL)	HBeAg (PEI U/mL)	HBsAb (IU/mL)	HBeAb
Log_{10} BL (Day 1) value	8.01	4.34	7.07	2.98	<LLOQ	N/A
Log_{10} Change from BL Day 302	-7.01	-2.23	-3.10	-2.67	N/A	N/A
Actual Value Day 302	<LLOQ	130	9433	2.05	3.88	Negative

Figure 5: AB-506 AUC and Cmax vs ALT Elevation

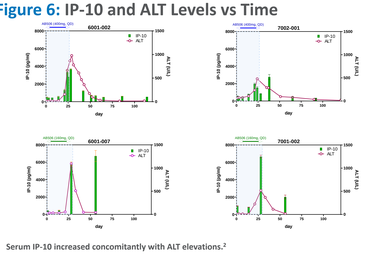


NOTES:
Red symbols indicate subjects with ALT elevation
Circle = Grade 4; Triangle = Grade 2

- Frequency/Severity of ALT elevation in CHB Subjects did not correlate with AB-506 Dose, Cmax or AUC at Day 1 (all subjects shown).
- C_{trough} and limited Day 28 PK (not shown) also did not correlate with ALT elevations.

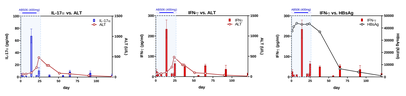
Cytokine Profiling AB-506-001 Grade 4 ALTs:

Figure 6: IP-10 and ALT Levels vs Time



- Serum IP-10 increased concomitantly with ALT elevations.[2]
- No other CHB subjects had these simultaneous increases in IP-10 and ALT.

Figure 7: T cell activation markers, HBsAg and ALT Levels over Time - Subject 7002-001



- IFN-γ and IL-17α spikes preceded ALT rise.
- HBsAg levels declined after IFN-γ spike, suggesting potential beneficial immune component to ALT flare.

Safety Findings and Next Steps:

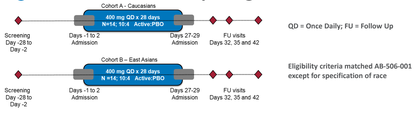
- ALT elevations were noted in a subset of CHB subjects after the 10-day dosing period studied in HS and do not appear dose related.
- Grade 4 elevations only occurred in subjects of East Asian ancestry.
- Conduct 28-day study in Asian and Caucasian HS at 400 mg (or PBO) QD
  - Study AB-506-003

AB-506-003

Primary Objective:

- To evaluate the safety and tolerability of AB-506 following oral administration of once daily multiple doses for 28 days to HS

Figure 8: AB-506-003 Study Design



QD = Once Daily; FU = Follow Up

Eligibility criteria matched AB-506-001 except for specification of race

AB-506-003 Demography:

- Cohort A (Caucasian) contained 8 (57%) males and mean (SD) age, BMI and baseline ALT were 26.1 (5.2) years, 21.9 (1.7) kg/m^2, and 15.9 (7.0) U/L.
- Cohort B (Asian) contained 9 (64%) males and mean (SD) age, BMI and baseline ALT were 27.6 (7.7) years, 23.1 (2.6) kg/m^2, and 16.7 (6.6) U/L.

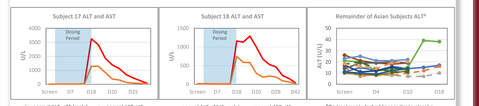
Table 7: Safety Summary AB-506-003 (Healthy Subjects)

Parameter	Cohort A (Caucasian) n=10	Cohort B (Asian) n=10	Pooled PBO n=8
# subjects with AE, n (%)	8 (80)	6 (60)	6 (75)
Worst Reported Grade AE, n(%)			
Grade 1	8 (80)	3 (30)	6 (60)
Grade 2	0	1 (10)	0
Grade 3	0	0	0
Grade 4	0	2 (20)[a]	0
SAEs, n (%)	0	2 (20)	0
D/C due to AE, n (%)	0	3 (30)[b]	0
Total # Subjects with Grade ≥2 ALT Elevation[c]	0	2 (20)	0
Grade 2	0	0	0
Grade 3	0	0	0
Grade 4	0	2 (20)	0

(a) hepatitis, transaminase elevation; (b) Gr 2 rash, hepatitis, transaminase elevation;
(c) based on 2018 AASLD ALT normal range (<35 and <25 U/L for male and female, respectively)

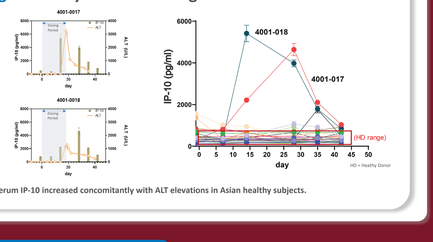
- Most AEs were Grade 1/mild and assessed as unrelated.
- No other clinically significant abnormalities in laboratory tests, ECGs, or vital signs were noted.

Figure 9: Grade 4 ALT Abnormalities AB-506-003



- These subjects had normal bilirubin and INR values.
- ALT elevations rapidly resolved post-discontinuation of AB-506.

Figure 10: Cytokine Profiling AB-506-003 Grade 4 ALTs



- Serum IP-10 increased concomitantly with ALT elevations in Asian healthy subjects.

CONCLUSIONS

- AB-506 demonstrated potent inhibition of HBV replication with mean declines in HBV DNA and HBV RNA of 2.8 and 2.4 log_{10}, respectively.
- One CHB subject harboring a resistant variant (I105T) at baseline had complete non-response to AB-506 monotherapy which underscores the importance of conducting molecular epidemiology studies to determine the prevalence of potentially-resistant CI variants
- AB-506 was associated with reversible transaminase increases after Day 20 of dosing in a subset of Asian CHB subjects.
  - One CHB subject with transaminase flares has had persistent HBeAg (>2.6 log_{10}) and HBsAg (>2.2 log_{10}) declines from baseline 9-10 months post-flare and was the only subject with increases from baseline in IFN-γ and IL-17-α preceding ALT flare.
  - The remaining Asian CHB subjects only experienced increases in IP-10 at the time of the flare and no meaningful declines in HBs or HBe antigen.
- A 28-day study (AB-506-003) in Asian and Caucasian HS demonstrated that the transaminase elevations observed in a subset of Asian CHB subjects ≥ Day 14 were also drug-related.
  - Transaminase elevations in Asian HS were associated with increases in serum IP-10.
- The development of AB-506 underscores the importance of taking the necessary steps to fully characterize the occurrence of transaminase flares.
- Further development of AB-506 has been discontinued but we remain committed to advancing an improved next-generation capsid inhibitor.

REFERENCES

(1) Data acquired via next generation sequencing of plasma HBV DNA genome using Illumina®; (2) The HBV knowledge database (https://hbvdb.ibcp.fr/);
(3) Data acquired via multiplex assay using Luminex™

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