Evaluation of relationships between AB-506 related ALT elevations and AB-506 pharmacokinetics (PK), metabolite concentrations and plasma bile acids

Poster #26

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BACKGROUND

- HBV capsid inhibitors are being developed as potential components of new combination regimens for the treatment of chronic hepatitis B (CHB) infection.
- AB-506 is an oral, class II, selective HBV capsid inhibitor for the treatment of CHB.
- The AB-506 program was discontinued due to transaminase elevations following treatment ≥ 14 days that were initially observed in Asian subjects with CHB [Study AB-506-001] that were subsequently replicated in healthy subjects [Study AB-506-003].
- Here we present exploratory *post hoc* analyses searching for associations between the incidence and severity of transaminase elevation with possible predictors that could be influenced by race/ethnicity.

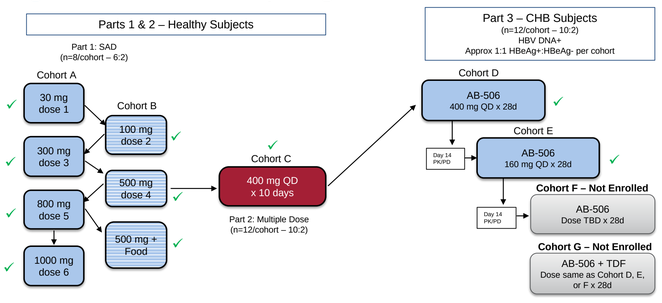
OBJECTIVES

- Explore potential associations between PK of AB-506, its metabolites and plasma bile acids with the occurrence and severity of ALT abnormalities observed in both healthy subjects (HS) and subjects with CHB

MATERIALS AND METHODS

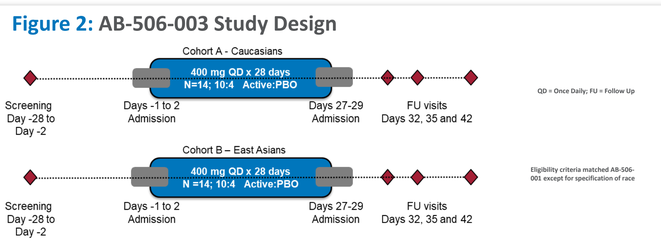
- The design for Study AB-506-001 is presented in Figure 1.

Figure 1: AB-506-001 Study Design



- The design for Study AB-506-003 is presented in Figure 2.

Figure 2: AB-506-003 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 used for subjects with CHB included
  - 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)
  - No evidence of cirrhosis, advanced fibrosis or HCC via Fibroscan (<10 kPa) and ultrasound
  - ALT or AST ≤5 × upper limit of normal (AASLD criteria used for ALT)
- Safety and tolerability were monitored throughout the study via collection of adverse events (AEs), physical examinations, vital signs, ECGs and clinical laboratory testing.
- Antiviral activity was assessed in subjects with CHB (previously reported).[1,2]
- Serial and C_{trough} blood samples were collected in both studies for noncompartmental PK analysis [Phoenix 8.2, Certara, Princeton, NJ, USA]. Serial collection for subjects with CHB was truncated.
- In the 400 mg QD CHB cohort, C_{trough} samples were further utilized for metabolite and bile acids assessment.
- Plasma AB-506 was quantified via a validated LC/MS/MS assay [QPS LLC, Newark, DE, USA].
- Plasma bile acids were quantified via a commercially available validated LC/MS/MS assay [Covance Laboratories Inc, Salt Lake City, UT, USA].
- Plasma AB-506 metabolites were assessed semi-quantitatively via in-house LC/MS/MS.

RESULTS

Table 1: Baseline Demographic Characteristics

Baseline Measure	Study AB-506-001				Study AB-506-003	
	Cohorts A, B and C Overall (N=33)	Cohort D 400 mg QD (N=10)	Cohort E 160 mg QD (N=10)	Pooled CHB Placebo (N=4)	Cohort A Caucasian (N=14)	Cohort B East Asian (N=14)
Age (years) [Mean (SD)]	26.1 (5.8)	41.7 (9.5)	41.3 (12.4)	40.8 (9.3)	26.1 (5.2)	27.6 (7.7)
BMI (kg/m^2) [Mean (SD)]	25.2 (2.8)	23.4 (3.5)	25.5 (5.6)	25.8 (2.4)	21.9 (1.7)	23.1 (2.6)
Male Gender [n (%)]	33 (100)	5 (50)	5 (50)	0	8 (57)	9 (64)
Race [n]						
Asian	3	8	5	2	0	14
White	18	1	5	2	14	0
Pacific Islander	2	1	0	0	0	0
Other	10	0	0	0	0	0
ALT [Mean (SD)]	21.5 (8.5)	37.1 (20.3)	27.9 (17.2)	28.1 (11.6)	15.9 (7.0)	16.7 (6.6)

- In AB-506-001, healthy subjects (Cohorts A, B and C) were primarily White/Caucasian Male and CHB subjects were primarily Asian.
- East Asian and Caucasian healthy subjects in AB-506-003 were comparable in terms of Age and BMI to those in AB-506-001 and each other.

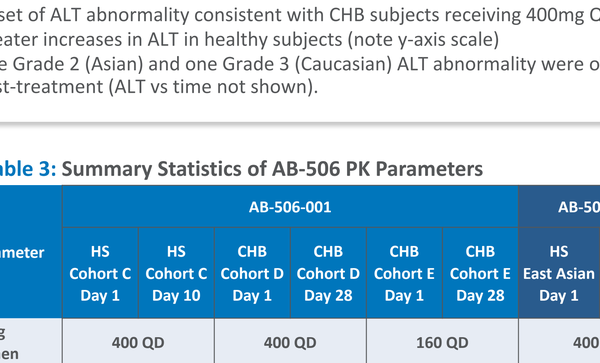
Table 2: Safety Summary AB-506-001 and AB-506-003

Parameter	Study AB-506-001			Study AB-506-003		
	Cohort D CHB 400 mg QD (n=10)	Cohort E CHB 160 mg QD (n=10)	CHB Pooled PBO (n=4)	Cohort A Caucasian (n=10)	Cohort B East Asian (n=10)	HS Pooled PBO (n=8)
# subjects with AE	7	8	3	8	6	6
Worst Reported Grade AE [n,%]						
Grade 1	4 (40)	4 (40)	1 (25)	8 (80)	3 (30)	6 (60)
Grade 2	1 (10)	2 (20)	2 (50)	0	1 (10)	0
Grade 3	0	1 (10)[a]	0	0	0	0
Grade 4	2 (20)	1 (10)[a]	0	0	2 (20)[a]	0
SAEs	0	0	0	0	2	0
D/C due to AE	2[b]	1[c]	0	0	3[b]	0
Total # Subjects with Grade ≥2 ALT Elevation[d]	2	4	0	0	2	0
Grade 2	0	2	0	0	0	0
Grade 3	0	0	0	0	0	0
Grade 4	2	2	0	0	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); D/C =discontinued; PBO = placebo

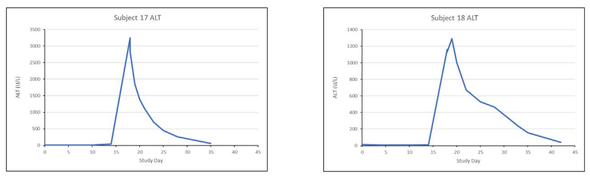
- Other than ALT abnormalities as shown in Table 2, safety was unremarkable.
- All Grade 4 On-Treatment ALT abnormalities at 400mg QD [Figures 3 and 4] and two Grade 2 abnormalities at 160mg QD in CHB subjects were Asian subjects.
- All ALT elevations were transient and reversible upon treatment discontinuation. Bilirubin and INR values remained normal in all subjects; none met DILI criteria.

Figure 3: AB-506-001 Grade 4 On-Treatment ALT Abnormality vs Time



- Data suggested onset of ALT abnormality was earlier with 400 mg QD.
- Severity did not appear to correlate with dose in CHB subjects.
- Two Grade 2 ALT abnormalities at 160 mg QD not shown

Figure 4: AB-506-003 Grade 4 On-Treatment ALT Abnormality vs Time



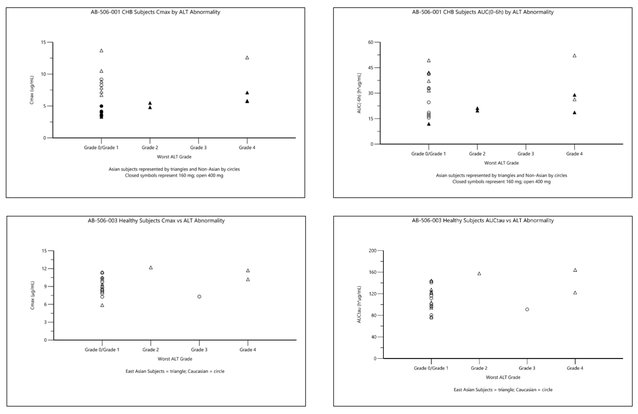
- Onset of ALT abnormality consistent with CHB subjects receiving 400mg QD
- Greater increases in ALT in healthy subjects (note y-axis scale)
- One Grade 2 (Asian) and one Grade 3 (Caucasian) ALT abnormality were observed post-treatment (ALT vs time not shown).

Table 3: Summary Statistics of AB-506 PK Parameters

Parameter	AB-506-001						AB-506-003	
	HS Cohort C Day 1	HS Cohort C Day 10	CHB Cohort D Day 1	CHB Cohort D Day 28	CHB Cohort E Day 1	CHB Cohort E Day 28	HS East Asian Day 1	HS Caucasian Day 1
Dosing Regimen	400 QD		400 QD		160 QD		400 QD	
N	10	9	10	5	10	7	10	10
Cmax [ng/mL] Geo Mean (CV%)	6919 (20)	8057 (20)	8770 (28)	10711 (8)	4521 (26)	5031 (30)	9739 (19)	8667 (15)
Tmax (h) Med (min-max)	3.0 (2.0-6.0)	3.0 (2.0-4.0)	2.5 (1.0-6.0)	2 .0 (1.0-4.0)	2.5 (1.0-6.0)	3.0 (1.0-4.0)	4.0 (2.0-4.0)	4.0 (2.0-4.0)
AUC(0-6h) [ng*h/mL] Geo Mean (CV%)	28827 (25)	35273 (25)	37978 (21)	50834 (13)	18782 (25)	22086 (30)	44015 (20)	39438 (18)
AUCtau [ng*h/mL] Geo Mean (CV%)	81391 (27)	88470 (33)	NA	NA	NA	NA	120769 (22)	103061 (22)
Accumulation Index Mean (SD)	NA	1.17 (0.28)	NA	1.39 (0.25)	NA	1.2 (0.26)	NA	NA

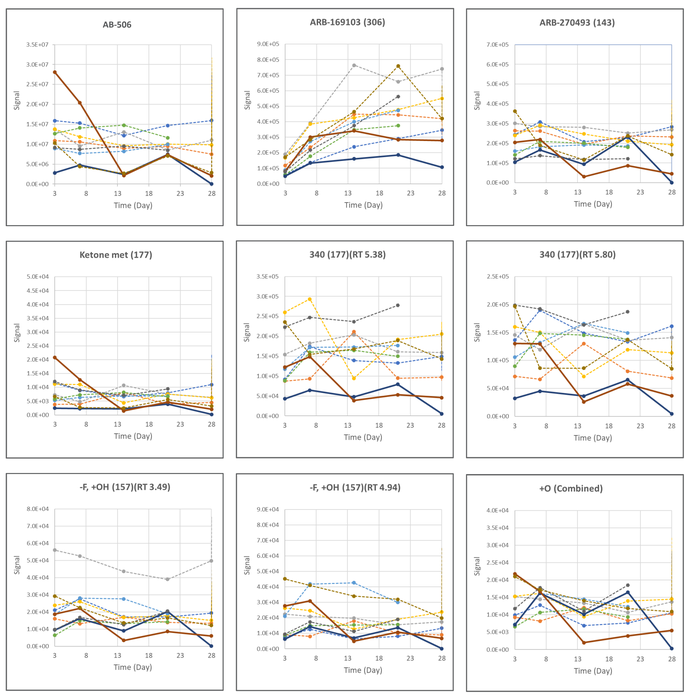
- Minimal accumulation of AB-506 at steady state supported PK vs ALT exploration using Day 1 Serial PK; Day 28 was unavailable for all discontinued subjects.

Figure 5: AB-506-001 and AB-506-003 ALT Grade vs AB-506 Cmax & AUC



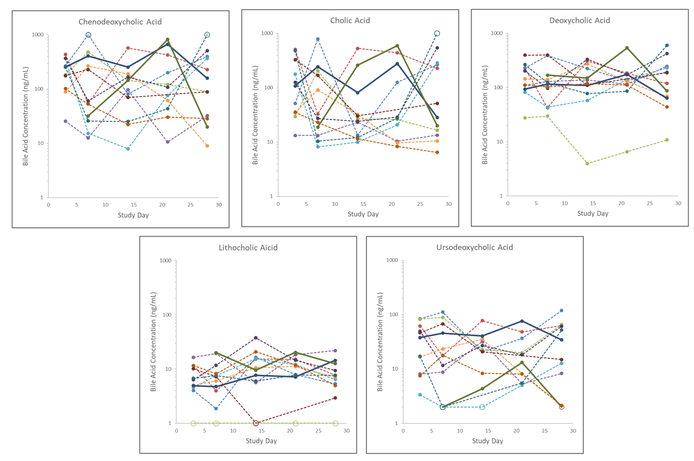
- There were no obvious trends between Day 1 AB-506 Cmax or AUC and the incidence or severity of ALT elevation in either healthy subjects or CHB subjects. C_{trough} values also showed no trends (not shown).
- There were no obvious PK differences between Asians and Non-Asians.

Figure 6: AB-506 Metabolite C_{trough} over 28 Days CHB 400 mg QD



- Actual quantification not performed; interpretation based on MS signal strength
- Based on differential y-axes, signal strength for metabolites appears to be generally 2 orders of magnitude lower than AB-506 (upper left), suggesting very low metabolite concentrations relative to AB-506
- CHB subjects with Grade 4 ALT abnormality (solid lines) did not appear to differ from other actively treated subjects for any metabolite evaluated.
  - Lower concentrations at Day 28 were post treatment discontinuation.

Figure 7: Plasma Bile Acids over 28 Days in CHB Subjects 400 mg QD



NOTE: open symbols represent values above the ULOQ or below the LLOQ

- CHB subjects with Grade 4 ALT abnormality (solid lines) did not appear to differ from other actively treated subjects for any bile acid quantified.
- No evidence of a trend toward cholestasis in treated subjects
- No evidence that bile acid trafficking in plasma could predict events
- Consistent with absence of concurrent bilirubin elevation in subjects with ALT abnormality

CONCLUSIONS

- Safety of AB-506 was largely unremarkable other than ALT elevation.
- A novel 28-day study in healthy subjects confirmed ALT elevations were drug-related and not disease-related, leading to program discontinuation.
- Evaluation of AB-506 PK in healthy and CHB subjects and metabolite MS signal as a surrogate for concentration in CHB subjects showed no clear differences with ALT abnormality.
- Evaluation of plasma bile acid concentrations showed no clear differences in CHB subjects with ALT abnormality and no apparent trends with duration of treatment.
- Although sample size was small for non-Asians at the 400 mg dose level in CHB subjects, AB-506 metabolites and bile acid data showed no clear differences between Asians and non-Asians.
- Further exploratory work is ongoing.

REFERENCES

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