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

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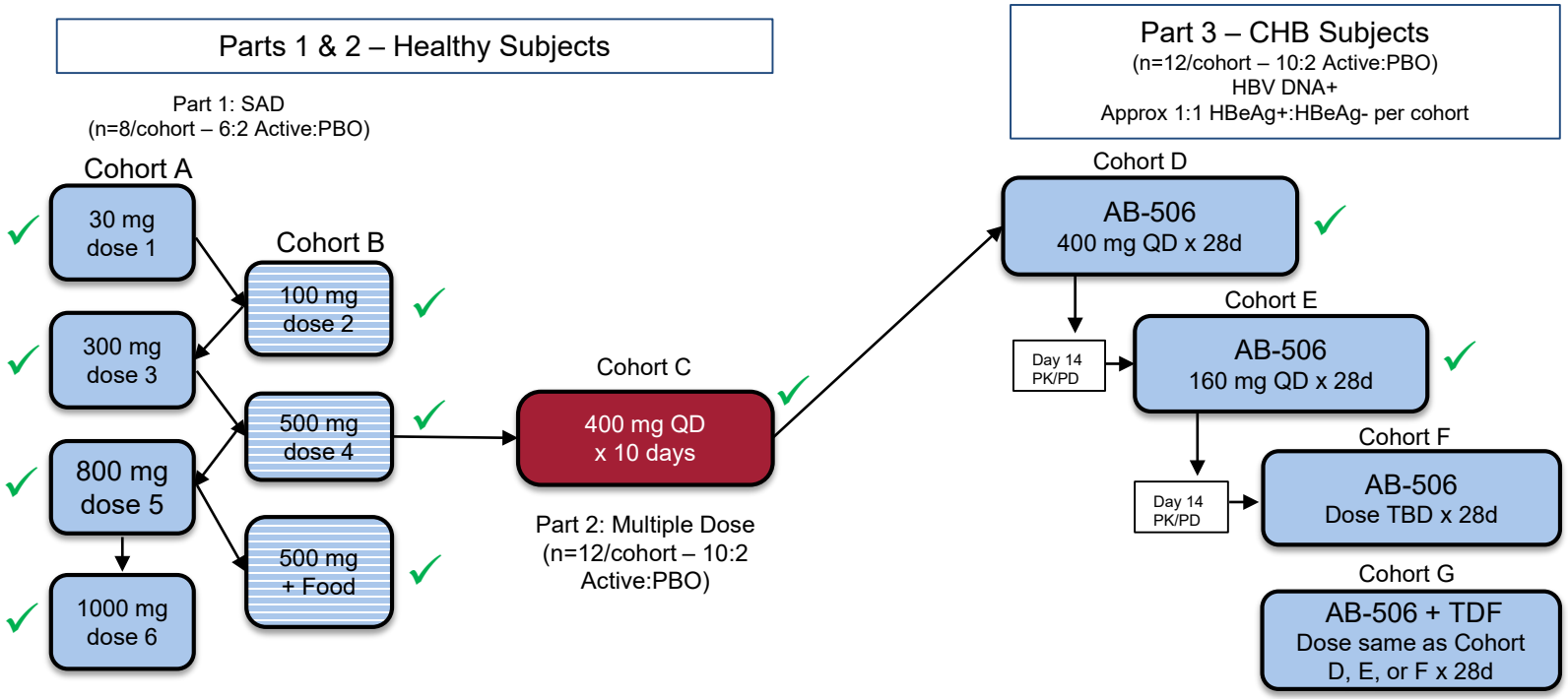
# Introduction

- HBV capsid inhibitors (CI) are being 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.
- In the context of HBV drug development, 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
- This presentation summarizes one year of AB-506 clinical development and underscores the importance of taking the necessary steps to fully characterize the occurrence of transaminase flares

# Background

- No transaminase elevations were noted in 28-day or 90-day AB-506 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).

# Study AB-506-001: Study design and inclusion criteria




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

**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/m2and ≤32 kg/m2
- 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/m2and ≤38 kg/m2
- 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)

# Study AB-506-001: Baseline characteristics

## 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) |

## CHB Subject Baseline Characteristics

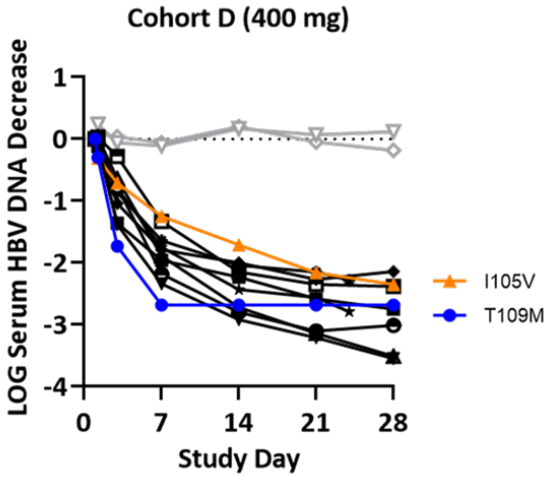
| Baseline Measure | Cohort D 400 mg QD (N=10) | Cohort E 160 mg QD (N=10) | Pooled PBO (N=4) |
|---|---|---|---|
| Age (years) [Mean (SD)] | 41.7 (9.5) | 41.3 (12.4) | 40.8 (9.3) |
| Male Gender [n (%)] | 5 (50) | 5 (50) | 0 |
| BMI [Mean (SD)] | 23.4 (3.5) | 25.5 (5.6) | 25.8 (2.4) |
| Race [n (%)] | | | |
| 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) |

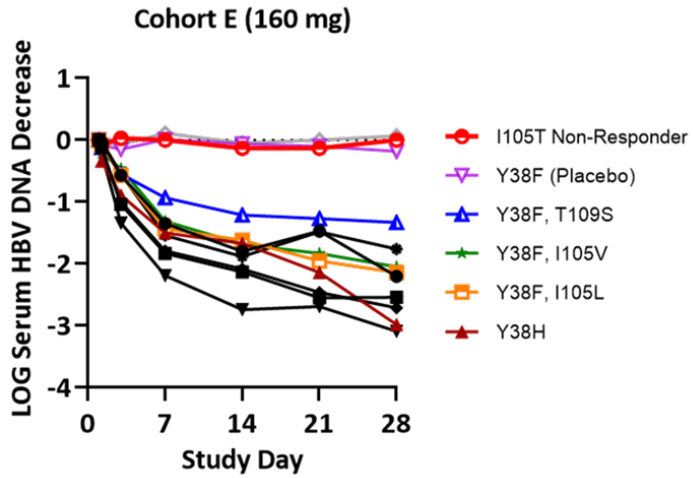
[(a)] 3 subjects TND; [(b)] 2 subjects TND

# HBV DNA, HBV RNA and HBsAg changes at day 28

| 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)




- 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 $EC_{50}$ *in vitro*

# Study AB-506-001: Frequency of baseline HBV Core variants observed

| Variant | Observed Cases (n) | Observed Frequency[1] (%) | Frequency in HBVdb (%) |
|---|---|---|---|
| **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 |

[1]Frequency in 52 CHB subjects screened for study AB-506-001 compared to frequency in HBVdb, the HBV knowledge database (https://hbvdb.ibcp.fr/)

# Study AB-506-001: Safety findings in CHB Subjects

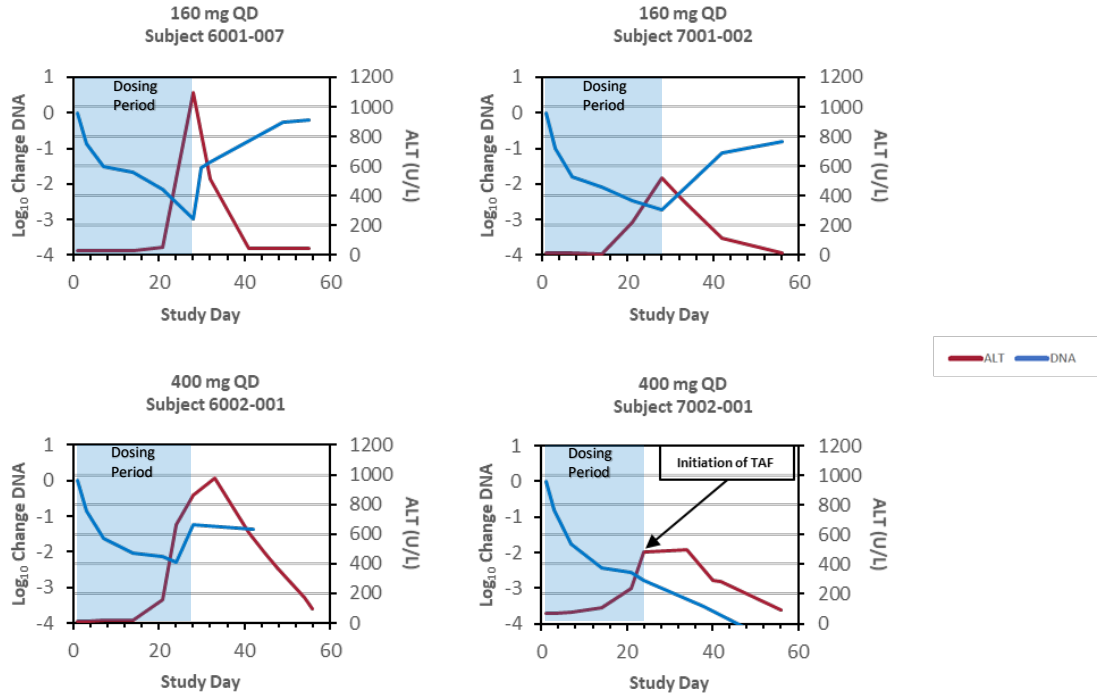
## Adverse Events in CHB Subjects

| 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.

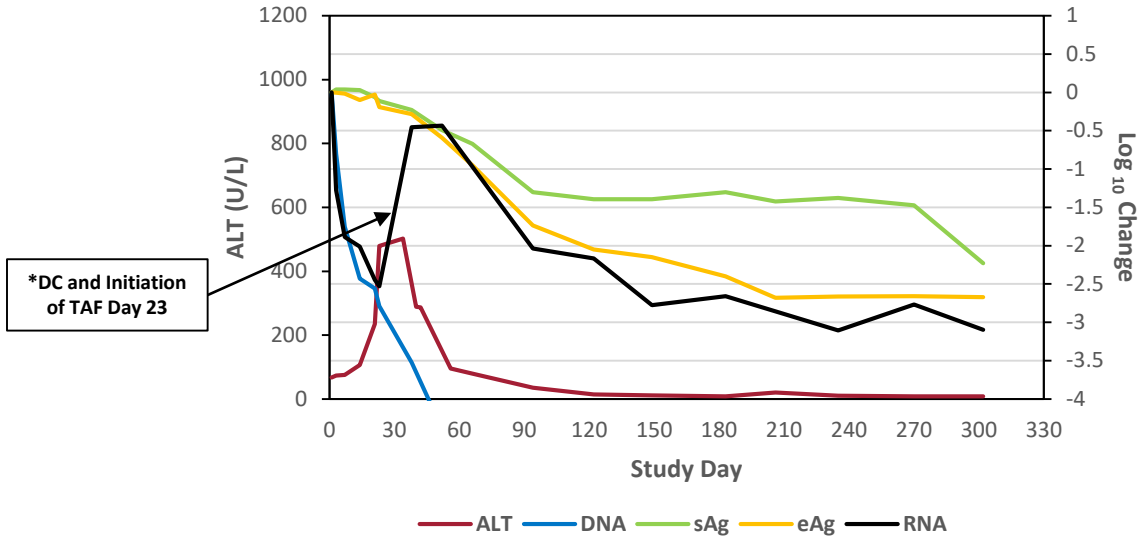
## Grade 4 ALT vs HBV DNA to FU Day 28




- 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

**Frequency/Severity of ALT elevation in CHB Subjects did not correlate with AB-506 Dose, Cmax or AUC at Day 1**

# ALT and HBV viral markers vs time – Subject 7002-001 (Grade 4 ALT)

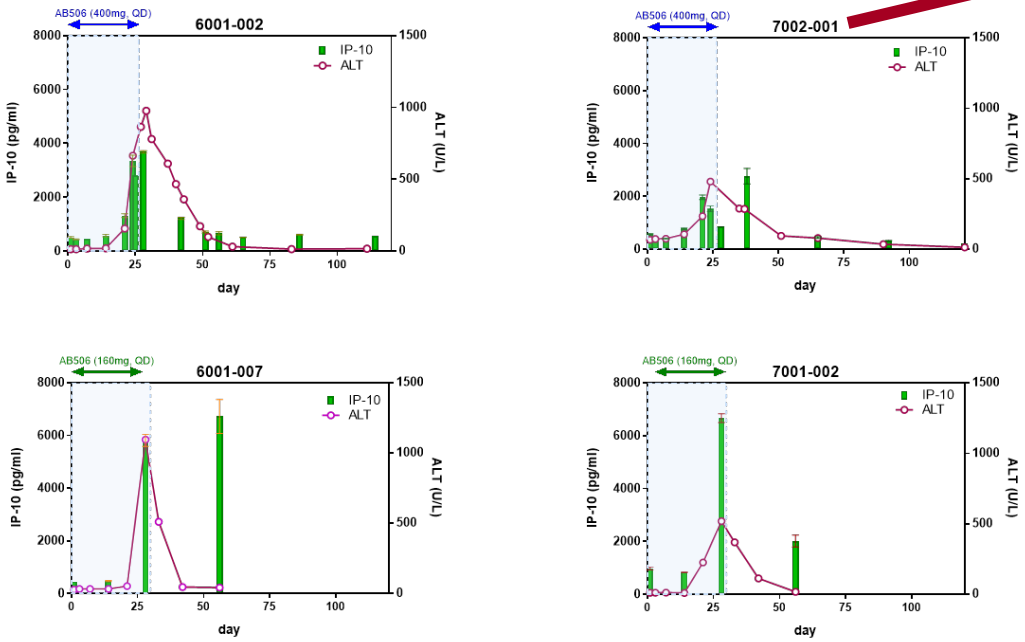



NOTE: $Log_{10}$ Change axis truncated at -4.0 $log_{10}$

| 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 |

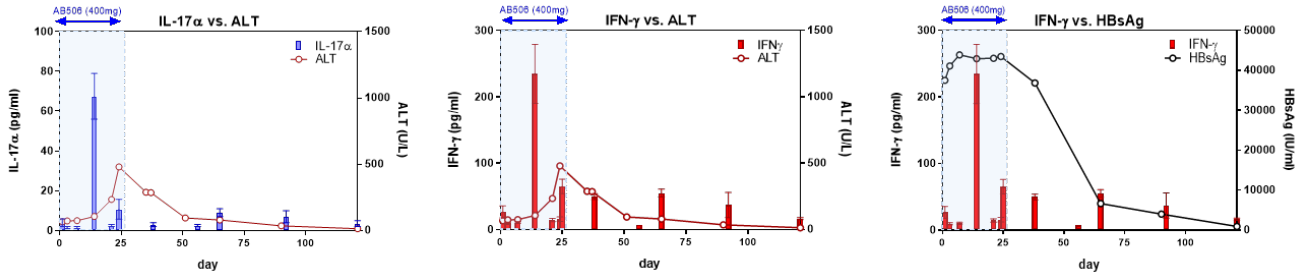
# Cytokine Profiling in Serum for Grade 4 ALT Subjects

## IP-10 and ALT Levels vs Time




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

## T cell activation markers, HBsAg and ALT Levels over Time - Subject 7002-001

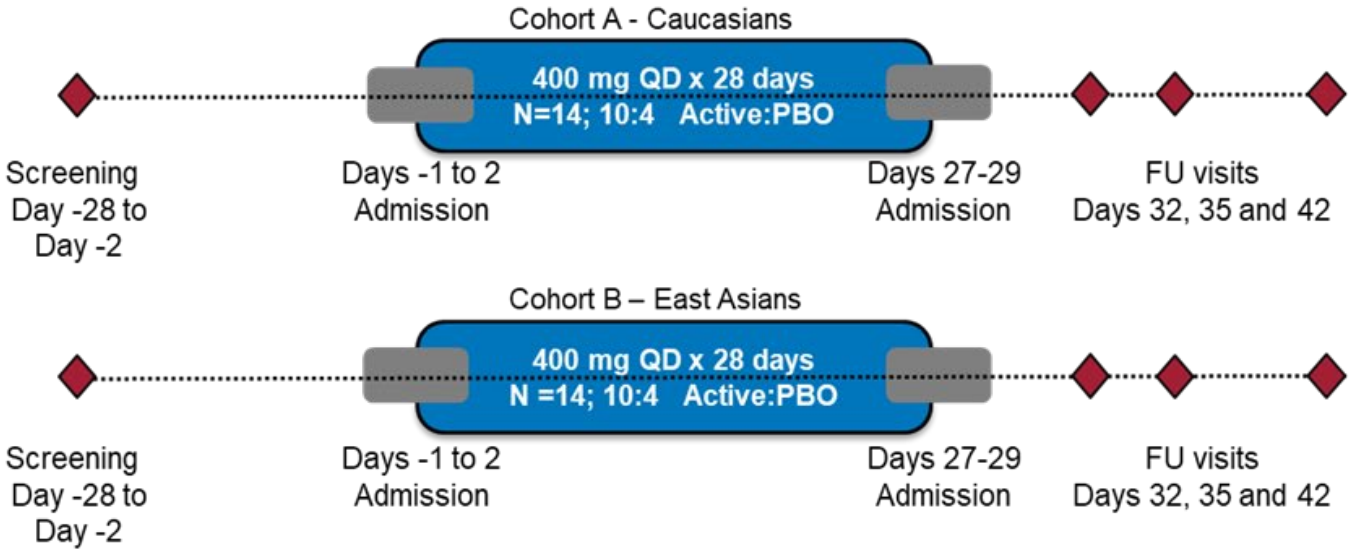



- IFN-γ and IL-17α spikes preceded ALT rise.
- HBsAg levels declined after IFN-γ spike, suggesting potential beneficial immune component to ALT flare.

## Investigated cytokines

| | | | |
|---|---|---|---|
| EGF | GRO | sCD40L | IL-6 |
| FGF-2 | IL-10 | IL-1RA | IL-7 |
| Eotaxin | MCP-3 | IL-1a | IL-8 |
| TGFa | IL-12P40 | IL-9 | IL-15 |
| G-CSF | IL-12P70 | IL-1b | MCP-1 |
| Flt-3L | PDGF-AA | IL-2 | MIP-1a |
| GM-CSF | IL-13 | IL-3 | MIP-1b |
| Fractalkine | PDGF-AB/BB | IL-4 | RANTES |
| IFNa2 | | IL-5 | TNFb |
| | | | VEGF |

# Study AB-506-003 (28 day dosing in Healthy Subjects)




QD = Once Daily; FU = Follow Up

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

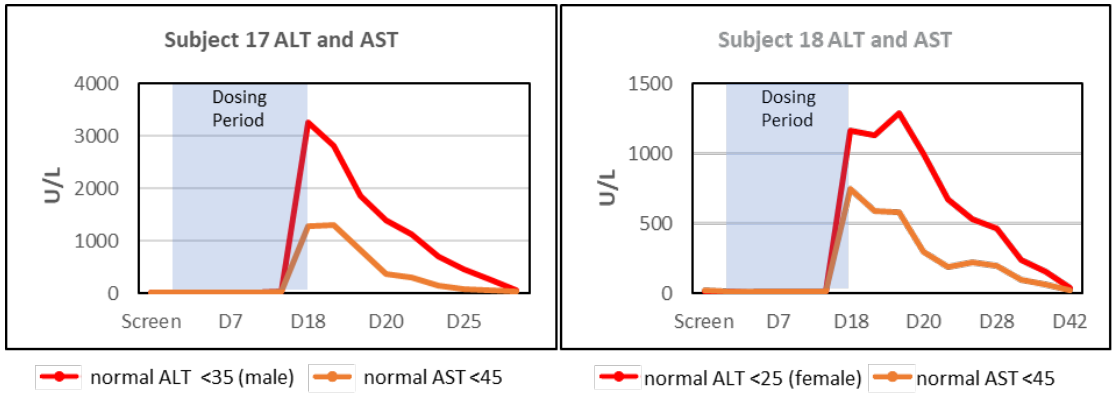
**AB-506-003 Demography:**

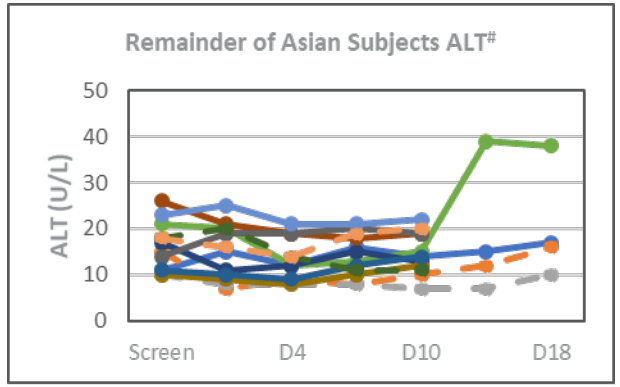
- **Cohort A (Caucasian) contained 8 (57%) males and mean (SD) age, BMI and baseline ALT were 26.1 (5.2) years, 21.9 (1.7) kg/m2, and 15.9 (7.0) U/L.**
- **Cohort B (Asian) contained 9 (64%) males and mean (SD) age, BMI and baseline ALT were 27.6 (7.7) years, 23.1 (2.6) kg/m2, and 16.7 (6.6) U/L.**

# Study AB-506-003: Safety Summary

| 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)



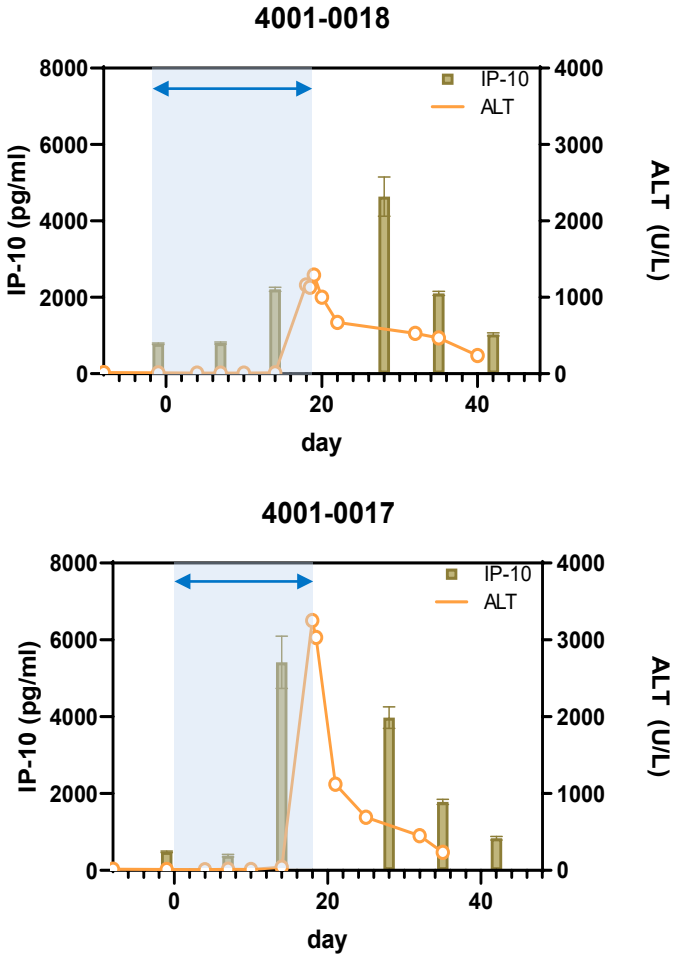



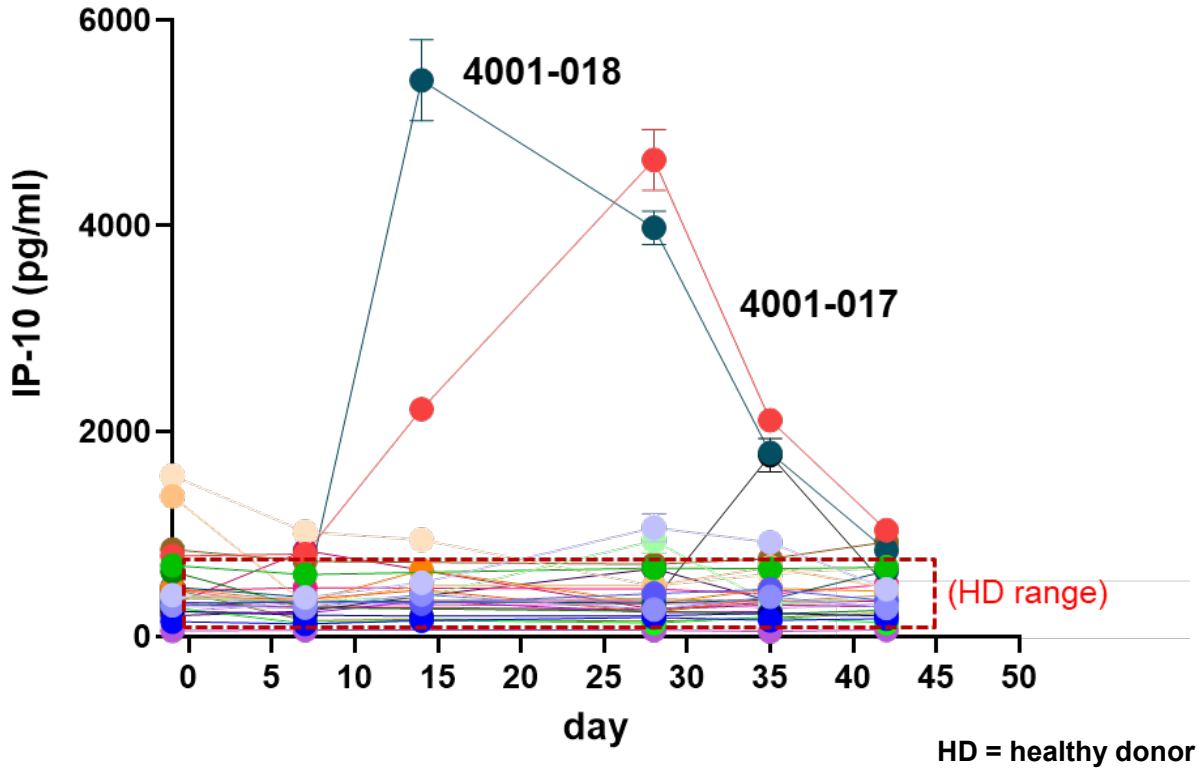

#On treatment; dashed lines indicate placebo

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

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

# Serum IP-10 increased concomitantly with ALT elevations in Asian healthy subjects (Study AB-506-003)



# 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
- 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 drug-related.
- Further development of AB-506 has been discontinued but we remain committed to advancing an improved next-generation capsid inhibitor.