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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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 \textit{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/m² and ≤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/m² and ≤32 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)

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**Study Design:**

**Part 1:** SAD (n=8/cohort – 6:2 Active:PBO)
- Cohort A: 30 mg dose 1
- Cohort B: 300 mg dose 3
- Cohort C: 800 mg dose 5
- Cohort D: 1000 mg + Food

**Part 2: Multiple Dose** (n=12/cohort – 10:2 Active:PBO)
- Cohort A: 500 mg dose 2
- Cohort B: 300 mg dose 3
- Cohort C: 500 mg dose 4
- Cohort D: 400 mg dose 4
- Cohort E: 100 mg dose 5
- Cohort F: 30 mg dose 1
- Cohort G: 800 mg dose 5

**Part 3: CHB Subjects** (n=12/cohort – 10:2 Active:PBO)
- Cohort A: 500 mg dose 2
- Cohort B: 300 mg dose 3
- Cohort C: 500 mg dose 4
- Cohort D: 400 mg dose 4
- Cohort E: 100 mg dose 5
- Cohort F: 30 mg dose 1
### Healthy Subject Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Measure</th>
<th>Cohort A (N=11)</th>
<th>Cohort B (N=10)</th>
<th>Cohort C (N=12)</th>
<th>Overall (N=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [Mean (SD)]</td>
<td>26.2 (6.7)</td>
<td>27.5 (6.5)</td>
<td>24.8 (4.3)</td>
<td>26.1 (5.8)</td>
</tr>
<tr>
<td>BMI (kg/m²) [Mean (SD)]</td>
<td>25.2 (2.2)</td>
<td>26.4 (3.4)</td>
<td>24.1 (2.4)</td>
<td>25.2 (2.8)</td>
</tr>
<tr>
<td>Male Gender [n (%)]</td>
<td>11 (100)</td>
<td>10 (100)</td>
<td>12 (100)</td>
<td>33 (100)</td>
</tr>
</tbody>
</table>

- **Race [n]**
  - Asian: 0
  - White: 7
  - Pacific Islander: 0
  - Other: 4

- **Baseline ALT [Mean (SD)]** | 18.5 (4.1) | 27.5 (9.3) | 19.1 (8.6) | 21.5 (8.5) |

### CHB Subject Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Measure</th>
<th>Cohort D 400 mg QD (N=10)</th>
<th>Cohort E 160 mg QD (N=10)</th>
<th>Pooled PBO (N=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years) [Mean (SD)]</td>
<td>41.7 (9.5)</td>
<td>41.3 (12.4)</td>
<td>40.8 (9.3)</td>
</tr>
<tr>
<td>Male Gender [n (%)]</td>
<td>5 (50)</td>
<td>5 (50)</td>
<td>0</td>
</tr>
<tr>
<td>BMI [Mean (SD)]</td>
<td>23.4 (3.5)</td>
<td>25.5 (5.6)</td>
<td>25.8 (2.4)</td>
</tr>
</tbody>
</table>

- **Race [n]**
  - Asian: 0
  - White: 1
  - Pacific Islander: 1
  - Other: 0

- **Genotype [n (%)]**
  - A: 0
  - B: 2
  - C: 7
  - D: 1

- **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) | 5.37 (1.99) |

- **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

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

<table>
<thead>
<tr>
<th>Variant</th>
<th>Observed Cases (n)</th>
<th>Observed Frequency(^1) (%)</th>
<th>Frequency in HBVdb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y38F</td>
<td>13</td>
<td>25</td>
<td>3.1</td>
</tr>
<tr>
<td>Y38H</td>
<td>2</td>
<td>3.8</td>
<td>1.2</td>
</tr>
<tr>
<td>I105T</td>
<td>4</td>
<td>7.7</td>
<td>0.6</td>
</tr>
<tr>
<td>I105V</td>
<td>7</td>
<td>13</td>
<td>1.1</td>
</tr>
<tr>
<td>I105L</td>
<td>5</td>
<td>9.6</td>
<td>0.7</td>
</tr>
<tr>
<td>T109S</td>
<td>2</td>
<td>3.8</td>
<td>0.1</td>
</tr>
<tr>
<td>T109M</td>
<td>3</td>
<td>5.8</td>
<td>0.7</td>
</tr>
</tbody>
</table>

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

### Adverse Events in CHB Subjects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort D 400 mg QD (n=10)</th>
<th>Cohort E 160 mg QD (n=10)</th>
<th>Placebo (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td># subjects with AE</td>
<td>7</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Worst Reported Grade AE [n, %]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>4 (40)</td>
<td>4 (40)</td>
<td>1 (25)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (10)</td>
<td>2 (20)</td>
<td>2 (50)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>1 (10)*</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>2 (20)</td>
<td>1 (10)*</td>
<td>0</td>
</tr>
<tr>
<td>SAEs</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D/c due to AE</td>
<td>2b</td>
<td>1c</td>
<td>0</td>
</tr>
<tr>
<td>Total # Subjects with Grade ≥2 ALT Elevation</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

- 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)

<table>
<thead>
<tr>
<th>Viral Marker</th>
<th>HBV DNA* (IU/mL)</th>
<th>HBsAg (IU/mL)</th>
<th>HBV RNA (c/mL)</th>
<th>HBeAg (PEI U/mL)</th>
<th>HBsAb (IU/mL)</th>
<th>HBeAb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log₁₀ BL (Day 1) value</td>
<td>8.01</td>
<td>4.34</td>
<td>7.07</td>
<td>2.98</td>
<td>&lt;LLOQ</td>
<td>N/A</td>
</tr>
<tr>
<td>Log₁₀ Change from BL Day 302</td>
<td>-7.01</td>
<td>-2.23</td>
<td>-3.10</td>
<td>-2.67</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Actual Value Day 302</td>
<td>&lt;LLOQ</td>
<td>130</td>
<td>9433</td>
<td>2.05</td>
<td>3.88</td>
<td>Negative</td>
</tr>
</tbody>
</table>

*DC and Initiation of TAF Day 23

NOTE: Log₁₀ Change axis truncated at -4.0 log₁₀
Cytokine Profiling in Serum for Grade 4 ALT Subjects

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

Investigated cytokines:

- EGF
- FGF-2
- Eotaxin
- TGFα
- G-CSF
- FR-3L
- GM-CSF
- Fractalkine
- IFNa2
- IL-10
- IL-1α
- IL-3
- IL-4
- IL-5
- IL-6
- IL-7
- IL-8
- IL-9
- IL-12P40
- IL-12P70
- IL-15
- GRO
- MCP-3
- IL-1RA
- PDGF-AA
- IL-2
- MIP-1α
- IL-3
- MIP-1b
- IL-4
- RANTES
- IFNα2
- PDGF-AB/BB
- IL-5
- TNFβ
- VEGF

- IFN-γ and IL-17α spikes preceded ALT rise.
- HBsAg levels declined after IFN-γ spike, suggesting potential beneficial immune component to ALT flare.
Study AB-506-003 (28 day dosing in Healthy Subjects)

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

- 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.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Cohort A (Caucasian) n=10</th>
<th>Cohort B (Asian) n=10</th>
<th>Pooled PBO n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td># subjects with AE, n (%)</td>
<td>8 (80)</td>
<td>6 (60)</td>
<td>6 (75)</td>
</tr>
<tr>
<td>Worst Reported Grade AE, n(%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>8 (80)</td>
<td>3 (30)</td>
<td>6 (60)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>1 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>2 (20)</td>
<td>0</td>
</tr>
<tr>
<td>SAEs, n (%)</td>
<td>0</td>
<td>2 (20)</td>
<td>0</td>
</tr>
<tr>
<td>D/C due to AE, n (%)</td>
<td>0</td>
<td>3 (30)</td>
<td>0</td>
</tr>
<tr>
<td>Total # Subjects with Grade ≥2 ALT Elevation</td>
<td>0</td>
<td>2 (20)</td>
<td>0</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>2 (20)</td>
<td>0</td>
</tr>
</tbody>
</table>

(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*
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.