FINAL RESULTS OF A PHASE 1B 28-DAY STUDY OF ABI-H0731, A NOVEL CORE INHIBITOR, IN NON-CIRRHOTIC VIREMIC SUBJECTS WITH CHRONIC HBV

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CORE INHIBITORS BLOCK VIRAL REPLICATION AND cccDNA ESTABLISHMENT

Conversion of rcDNA to cccDNA

Packaging of pgRNA into nucleocapsids

Core inhibition
- Unlike Nucs, Core Inhibitors block both production of new virus and trafficking of incoming nucleocapsid to nucleus, preventing establishment of new cccDNA
- Core Inhibitors have potential to be additive or synergistic with polymerase inhibitors
ABI-H0731: A POTENT CLINICAL STAGE CORE INHIBITOR

ABI-H0731 Preclinical Profile

- Potent and selective antiviral activity against all major HBV genotypes (A-E)
- Clean safety profile in animal studies (safety pharmacology, genotoxicity, reproductive and chronic toxicity studies)
- Excellent hepatocyte stability, minimal metabolism allowing QD dosing
- 20-30x liver/plasma ratio in primates

- >150 subjects dosed to date across all studies
PHASE 1b STUDY (101B) DESIGN: 28-DAY DOSING

**Treatment (28 days)**

- **100 mg (n=10 + 2 PBO)**
- **200 mg (n=10 + 2 PBO)**
- **300 mg (n=10 + 2 PBO)**
- **400 mg (n=2)**

**Objectives**

**Primary**
- Dose-related safety and tolerability

**Secondary**
- Steady state human PK
- Dose-related antiviral effects
  - HBV DNA/RNA
  - HBsAg and HBeAg
  - Pre-existing and emergent resistance

**Once-daily oral dosing**
**HBeAg Pos and Neg patients (stratified 7:5)**
# Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ABI-H0731 QD Dosing</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg (N=10)</td>
</tr>
<tr>
<td>Male, n</td>
<td>9</td>
</tr>
<tr>
<td>Age, median yr</td>
<td>42</td>
</tr>
<tr>
<td>White, n</td>
<td>0</td>
</tr>
<tr>
<td>Asian, n</td>
<td>8</td>
</tr>
<tr>
<td>BMI, median kg/m²</td>
<td>24</td>
</tr>
<tr>
<td>Median Baseline ALT (IU/mL)</td>
<td>27</td>
</tr>
</tbody>
</table>

*One subject of mixed background*
## BASELINE VIROLOGY CHARACTERISTICS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>100 mg</th>
<th>200 mg</th>
<th>300 mg</th>
<th>400 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HBeAg (n)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean HBV DNA (Log(_{10}) IU/mL)</td>
<td>8.5</td>
<td>4.6</td>
<td>8.1</td>
<td>4.5</td>
<td>7.7</td>
</tr>
<tr>
<td>Mean HBsAg (Log(_{10}) IU/mL)</td>
<td>4.6</td>
<td>2.9</td>
<td>4.3</td>
<td>3.6</td>
<td>4.0</td>
</tr>
<tr>
<td><strong>HBV RNA(^a) (Log(_{10}) copies/mL)</strong></td>
<td>7.3</td>
<td>2.8</td>
<td>7.1</td>
<td>4.9(^b)</td>
<td>6.4</td>
</tr>
<tr>
<td><strong>Genotype, n</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>C</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>E</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>A</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\)LOQ 4.04 Log\(_{10}\) copies/mL; \(^b\)\(n=2/5\) subjects detectable at Baseline; \(^c\)\(n=2/4\) detectable at Baseline; \(^d\)1 subject was misstratified
OVERALL CLINICAL SAFETY SUMMARY

- ABI-H0731 was generally well tolerated, with no SAEs or dose limiting toxicities reported
- No dose related increases in number of AEs
- All but one TEAE was Grade 1 (mild)
- No treatment emergent clinical chemistry, hematology or coagulation abnormalities deemed treatment related/clinically significant

**Summary of all Treatment-Emergent Adverse Events**

<table>
<thead>
<tr>
<th>Adverse Event Grade</th>
<th>Subjects with at least 1 TEAE, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg (N=10)</td>
</tr>
<tr>
<td>Grade 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9 (90%)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>0</td>
</tr>
<tr>
<td>Grade 3</td>
<td>0</td>
</tr>
</tbody>
</table>

*Single Grade 3 AE was maculopapular in subject dosed at 400 mg; rash resolved following treatment discontinuation with no additional medical intervention required*
## ABI-H0731 PLASMA EXPOSURE LEVELS

<table>
<thead>
<tr>
<th>QD Dose</th>
<th>Steady State</th>
<th>Fold Accumulation*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean $C_{\text{max}}$ (ng/mL)</td>
<td>Mean $C_{\text{min}}$ (ng/mL)</td>
</tr>
<tr>
<td>100 mg (n=10)</td>
<td>1,270</td>
<td>389</td>
</tr>
<tr>
<td>200 mg (n=10)</td>
<td>2,930</td>
<td>1,020</td>
</tr>
<tr>
<td>300 mg (n=10)</td>
<td>4,320</td>
<td>1,310</td>
</tr>
<tr>
<td>400 mg (n=2)</td>
<td>5,390</td>
<td>1,510</td>
</tr>
</tbody>
</table>

*Steady state $C_{\text{max}}$/Day 1 $C_{\text{max}}$

- All patients exhibited good plasma exposure levels
- Minimal accumulation (<2-fold) observed
- Similar exposures between Caucasian and Asian patients (*data not shown*)
POTENT REDUCTIONS IN HBV DNA

- Dose responsive declines; Reductions of up to 4.1 logs at 300 and 400 mg PO QD
- All subjects rebounded post therapy

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>N</th>
<th>Mean (Range)</th>
<th>N</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>6</td>
<td>1.3 (0.8 - 1.7)</td>
<td>4</td>
<td>2.2 (0.7 - 3.6)</td>
</tr>
<tr>
<td>200 mg</td>
<td>5</td>
<td>1.9 (1.0 - 2.6)</td>
<td>5</td>
<td>2.4 (1.5 - 3.8)</td>
</tr>
<tr>
<td>300 mg</td>
<td>6</td>
<td>2.9 (1.8 - 3.9)</td>
<td>3*</td>
<td>2.5* (0.8 - 4.1)</td>
</tr>
<tr>
<td>400 mg</td>
<td>0</td>
<td>NA</td>
<td>2</td>
<td>3.9 (3.9 - 4.0)</td>
</tr>
</tbody>
</table>

*Excludes subject with known resistance at baseline
PARALLEL REDUCTIONS IN HBV RNA LEVELS

- HBV RNA reductions (1-2 logs) seen at all dose levels, and correlated with HBV DNA reductions (p <0.001)
- Mechanism-based reduction in viral RNA levels is a differentiating feature of Core inhibitors

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>N</th>
<th>Mean Copies/ uL (Range)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 mg</td>
<td>6</td>
<td>1.2 (0.7 - 1.6)</td>
</tr>
<tr>
<td>200 mg</td>
<td>5</td>
<td>1.7 (1.1 - 2.2)</td>
</tr>
<tr>
<td>300 mg</td>
<td>6</td>
<td>2.3 (1.7 – 2.6)</td>
</tr>
<tr>
<td>400 mg</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

*Internal HBV RNA RT-qPCR assay, for HBeAg positive: LOQ = 10 copies/µL

HBeAg Neg patients

- RNA levels were lower at baseline and more difficult to quantitate
- All subjects with detectable RNA at baseline had RNA declines on treatment
VIRAL ANTIGENS AND FLARES

- No new flares developed on or post study
- Among patients with abnormal liver function tests, most remained stable or showed improvement on therapy
- No significant changes seen in HBeAg or HBsAg levels, except in a single patient who was found to have a flare at baseline (ALT 399 U/L; pre-Dose)
- HBeAg positive patient (200 mg cohort) with Grade 3 ALTs at Baseline
  - Subject closely monitored
  - LFTs declined on treatment
  - Multi-log decline in HBV DNA and RNA levels
  - HBsAg declined ~0.5 log on treatment and then rebounded along with HBV DNA and RNA after therapy stopped
NO EMERGENCE OF NEW RESISTANCE VARIANTS

- All Baseline and end of treatment samples genotyped for pre-existing and emerging resistance mutations
- **No new resistant mutants found to emerge over 28-day monotherapy**
- Pre-existing resistant variants were identified
  - Single HBeAg neg patient (300 mg cohort) harbored a T109M substitution at Baseline, representing 70% of the viral population
  - T109M **enriched to 100%** by Day 8 in both the DNA and RNA populations
    - *The enrichment in RNA suggests evolution of cccDNA pools in < 1 wk*
    - HBV DNA levels declined 1-log despite ~150-fold reduction in susceptibility
  - Three patients with Y38F substitution that enriched on treatment
    - No significant phenotypic resistance or correlation with clinical outcomes
SUMMARY AND CONCLUSIONS

- ABI-H0731 is a novel Core inhibitor with selective and potent activity against all major HBV genotypes
- Four dose levels (100, 200, 300 and 400 mg) of ABI-H0731 were tested in CHB patients
- ABI-H0731 was generally safe and well tolerated, with no SAEs or dose-limiting toxicities identified
  - All TEAEs were observed to be minor (Grade 1), with exception of isolated Grade 3 Rash that resolved rapidly without intervention other than treatment discontinuation
- All dose levels yielded potent antiviral activity, with overall Mean Maximal HBV DNA reductions of $2.8 \log_{10} \text{IU/mL}$ at 300 mg, and maximal declines of up to $4.0 \log_{10} \text{IU/mL}$
- Where measurable, reductions in HBV RNA correlated with HBV DNA decreases
- To date > 150 Healthy volunteers and patients with CHB have been dose with ABI-H0731

ABI-H0731 is currently undergoing Phase 2a clinical POC studies exploring 300 mg QD in combination with Nuc therapy
ACKNOWLEDGMENTS

The Patients!

The Clinical Study teams
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• Monash Health Australia
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