Safety and pharmacodynamics of the GalNAc-siRNA AB-729 in subjects with chronic hepatitis B infection

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- A therapeutic expert and pioneering clinical researcher leading numerous studies on novel antiviral and immunomodulatory agents for the treatment of chronic hepatitis B virus infection

- Research includes prevention, natural history, virology, treatment of chronic hepatitis B and C and hepatocellular carcinoma and is actively involved with cutting-edge research on novel markers for hepatitis B infection and occult hepatitis B infection

- One of the top international researchers in the field of hepatitis B, with more than 450 papers published in world-renowned medical journals
Disclosures

MFY acted as a consultant for AbbVie, Arbutus Biopharma, Bristol-Myers Squibb, Dicerna Pharmaceuticals, GlaxoSmithKline, Gilead Sciences, Janssen, Merck Sharp and Dohme, Clear B Therapeutics, Springbank Pharmaceuticals and Assembly Biosciences, and received grant/research support from Assembly Biosciences, Arrowhead Pharmaceuticals, Bristol-Myers Squibb, Fujirebio Incorporation, Gilead Sciences, Merck Sharp and Dohme, Springbank Pharmaceuticals, Sysmex Corporation.
AB-729 GalNAc-siRNA Therapeutic

- Single trigger RNA interference agent administered subcutaneously
- Proprietary liver targeting technology based on GalNAc ligand interaction with ASGPr
- Inhibits HBV replication, reduces all HBV transcripts, and lowers all HBV antigens
- Pan-genotypic activity across HBV genotypes
AB-729-001 Study Overview

**Presentation includes data available through 06-Oct-2020**

### Part 1: Single Ascending Dose in Healthy Subjects

- **Dose 1 (60 mg)**
  - n=6; 4 active : 2 placebo
  - (≥ Day 15 Safety)

- **Dose 2 (180 mg)**
  - n=6; 4 active : 2 placebo
  - (≥ Day 15 Safety)

- **Dose 3 (360 mg)**
  - n=6; 4 active : 2 placebo

### Part 2: Single Doses in Chronic Hepatitis B Subjects (open-label)

- **Cohort A: 180 mg**
  - HBV DNA -
  - n=4
  - (≥ Day 15 Safety)

- **Cohort B: 60 mg**
  - HBV DNA -
  - n=6
  - (≥ Day 15 Safety)

- **Cohort C: 90 mg**
  - HBV DNA -
  - n=6

### Part 3: Repeat Doses in Chronic Hepatitis B Subjects (open-label)

- **Cohort D: 90 mg**
  - HBV DNA +
  - n=6

- **Cohort E: 60 mg Q4W**
  - HBV DNA -
  - n=7

- **Cohort F: 60 mg Q8W**
  - HBV DNA -
  - n=7

- **Cohort G: 90 mg Q8W**
  - + TDF: HBV DNA +
  - n=7

- **Cohort I: 90 mg Q8W**
  - HBV DNA -
  - n=7

- **Cohort J: 90 mg Q12W**
  - HBV DNA -
  - n=7

**HBV:** Hepatitis B Virus  |  **TDF:** tenofovir disoproxil fumarate
Key Inclusion Criteria

- **Cohorts A, B, C and E**
  - Age 18 – 65 years old
  - At least 6 months of stable nucleos(t)ide analogue (NA) therapy (ETV, TDF, TAF) prior to Screening
  - HBeAg positive or negative
  - HBV-DNA < LLOQ and HBsAg ≥ 250 IU/mL at Screening
  - Non-cirrhotic, Fibroscan® result of ≤10 kPa
  - ALT/AST at Screening:
    - Part 2 (Cohorts A, B, and C): ≤ 5x ULN
    - Part 3 (Cohort E): ≤ 2x ULN
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Baseline Measure</th>
<th>Cohort A 180 mg (N=4)</th>
<th>Cohort B 60 mg (N=6)</th>
<th>Cohort C 90 mg (N=6)</th>
<th>Cohort E 60 mg Q4Wk (N=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (range)</td>
<td>42.8 (35-53)</td>
<td>48.2 (33-56)</td>
<td>54.8 (47-62)</td>
<td>45.1 (33-63)</td>
</tr>
<tr>
<td>Male gender, n (%)</td>
<td>3 (75%)</td>
<td>3 (50%)</td>
<td>6 (100%)</td>
<td>4 (57%)</td>
</tr>
<tr>
<td>BMI, mean (SD)</td>
<td>23.7 (3.62)</td>
<td>26.6 (3.23)</td>
<td>25.2 (1.96)</td>
<td>27.7 (5.01)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>3 (50%)</td>
<td>6 (100%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>White</td>
<td>4 (100%)</td>
<td>3 (50%)</td>
<td>0</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>ALT (U/L), mean (SD)</td>
<td>39.3 (35.36)</td>
<td>20.0 (6.52)</td>
<td>25.5 (9.23)</td>
<td>22.4 (10.52)</td>
</tr>
<tr>
<td>HBV eAg negative, n (%)</td>
<td>3 (75%)</td>
<td>6 (100%)</td>
<td>6 (100%)</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>HBsAg (IU/mL), mean (range)</td>
<td>8577 (4720 – 10,289)</td>
<td>2095 (405 – 5110)</td>
<td>822 (261 – 1400)</td>
<td>5372 (584 – 11761)</td>
</tr>
</tbody>
</table>

- All subjects were virologically suppressed on an NA (ETV, TDF or TAF) with HBV DNA < LLOQ (20 IU/mL)
- HBV genotype was not determined
Single doses of AB-729 result in comparable mean HBsAg declines at Week 12 followed by a sustained plateau phase

AB-729 60 mg single dose (N=6)*

Week 12 mean (SE): -0.99 (0.24)

3/6 HBsAg <100 IU/mL
1/6 HBsAg <10 IU/mL

AB-729 90 mg single dose (N=6)**

Week 12 mean (SE): -1.23 (0.18)

5/6 HBsAg <100 IU/mL
1/6 HBsAg <10 IU/mL

AB-729 180 mg single dose (N=4)#

Week 12 mean (SE): -1.10 (0.15)

0/4 HBsAg <100 IU/mL

*N=5 at Week 10, 14, 18, 22, 28, and 32
**N=4 at Week 14 and 16; N=3 at Weeks 18 – 24
#N=3 after Week 12; nominal visits ± 7 days
Repeat dosing of AB-729 60 mg every 4 weeks results in continuous HBsAg declines beyond Week 12

Mean (SE) Week 12: -1.10 (0.15)
Mean (SE) Week 16: -1.44 (0.18)
Mean (SE) Week 20: -1.73 (0.12) [N=3]

Repeat dosing of AB-729 60 mg every 4 weeks results in continuous HBsAg declines beyond Week 12.
AB-729 reduces HBV RNA to the limits of quantification or detection in most subjects; HBcrAg also declines

Maximum reductions shown through Week 12 in subjects with quantifiable data at baseline

LLOQ = lower limit of quantitation; TND = target not detected; SD = single dose
HBcrAg samples <LLOQ (3.0 log_{10} IU/mL) assigned a value of 2.9 log_{10} IU/mL
HBV RNA samples <LLOQ (1.65 log_{10} IU/mL) or target not detected assigned a value of 1.64 log_{10} IU/mL
AB-729 was safe and well tolerated after single and repeat doses

- No SAEs or discontinuations due to AEs
- No treatment-related Grade 3 or 4 AEs or laboratory abnormalities
- 1 subject (Cohort A) with rapid decline in HBsAg of ~2.0 log_{10} IU/mL had an unrelated Gr 2 AE of food poisoning resulting in unrelated transient Grade 3 AEs of ALT/AST elevation (without bilirubin changes)
- Injection site TEAEs were mild (erythema, pain, pruritis, bruising) or moderate (pain) and transient
- No clinically meaningful changes in ECGs or vital signs

<table>
<thead>
<tr>
<th>Subjects, n (%)</th>
<th>Cohort A (180 mg) N=4</th>
<th>Cohort B (60 mg) N=6</th>
<th>Cohort C (90 mg) N=6</th>
<th>Cohort E (60 mg Q4Wk) N=7</th>
<th>Total N=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects with any TEAE</td>
<td>4 (100)</td>
<td>4 (67)</td>
<td>5 (83)</td>
<td>4 (57)</td>
<td>17 (74)</td>
</tr>
<tr>
<td>Subjects with related TEAEs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>3 (75)</td>
<td>2 (33)</td>
<td>5 (83)</td>
<td>3 (43)</td>
<td>13 (57)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>1 (25)</td>
<td>2 (33)</td>
<td>2 (33)</td>
<td>2 (29)</td>
<td>7 (30)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (50)</td>
<td>0</td>
<td>3 (50)</td>
<td>1 (14)</td>
<td>6 (26)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Most common related TEAEs (in ≥ 2 subjects):</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Injection site pain</td>
<td>0</td>
<td>0</td>
<td>5 (83)</td>
<td>0</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Injection site erythema</td>
<td>0</td>
<td>1 (17)</td>
<td>0</td>
<td>2 (29)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>ALT elevation</td>
<td>2 (50)</td>
<td>0</td>
<td>0</td>
<td>3 (43)</td>
<td>5 (22)</td>
</tr>
<tr>
<td>AST elevation</td>
<td>1 (25)</td>
<td>0</td>
<td>0</td>
<td>1 (14)</td>
<td>2 (9)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (50)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (9)</td>
</tr>
</tbody>
</table>

Grading criteria based on Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1., July, 2017

ALT and AST elevations were all Grade 1 excepting one Grade 2 ALT, all were asymptomatic without bilirubin changes

† 4/5 subjects from same site; 2 Gr 2 TEAEs had AB-729 dose erroneously split into 2 injections, all TEAEs lasted <1 hour
‡ n, % is number of events out of 54 total AB-729 doses administered
Key Take-Aways

- Across all single-dose cohorts, mean HBsAg concentrations continuously declined up to Week 12 before reaching a plateau
  - No clear dose response was observed based on HBsAg decline at Week 12; however the duration of the plateau phase may be dose dependent
  - This finding supports dosing of AB-729 less frequently than every 4 weeks
- The kinetics of HBsAg decline were similar between the single dose and repeat dose cohorts up to Week 12
- Upon repeat dosing, HBsAg continued to steadily decline beyond Week 12 with no plateau in response observed to date
- HBV RNA and HBcrAg declined upon AB-729 administration
- The doses and dose frequencies of AB-729 explored were generally safe and well tolerated
We express our gratitude to the patients who participated in this study as well as investigators, study site staff, Andreas Kroemer and the Novotech team, Covance, DDL, PharStat Inc., and Mark Anderson and Gavin Cloherty of Abbott Diagnostics for their contributions to this study. The authors also thank other Arbutus staff, including Michael Child, Maksym Chernyakhovskyy, Deana Antonello, Joanne Brown, Julia Williams, Laura Maile as well as the AB-729 Discovery team.